University of Szeged

Faculty of Pharmacy

Department of Pharmaceutical Technology

Head: Prof. Dr. Habil. Piroska Szabó-Révész Ph.D., D.Sc.

Ph.D. Thesis

THE IMPORTANCE OF MAGNESIUM STEARATE IN PHARMACEUTICAL INDUSTRY AND IN THE PREFORMULATION STUDIES OF MEDICATED CHEWING GUMS

by

Imre Jójárt

Pharmacist

Supervisor:

Prof. Dr. Habil. Klára Pintye-Hódi Ph.D., D.Sc.

Szeged

2014

PUBLICATIONS:

I. Kása P jr, **Jójárt I**, Hódi K:
Régi-új gyógyszerforma, avagy a gyógyszeres rágógumi főnix-effektusa
Gyógyszerészet, 53, pp. 527-535 (2009)

II. **Jójárt I.**, Sovány T., Pintye-Hódi K., Kása P. jr:
Study of the behaviour of magnesium stearate with different specific surface areas on the surface of particles during mixing. Journal of Adhesion Science and Technology, 26; 2737-2744 (2012) IF: 0.900

III. Kása P. jr., **Jójárt I.**, Kelemen A., Pintye-Hódi K.:
Formulation study of directly compressible chewable polymers containing ascorbic acid. Pharmaceutical Development and Technology, 1-6 (2012) IF: 1.333

IV. **Jójárt I.**, Kelemen A., Pintye-Hódi K., Kása P jr.:
Tracking of the post-compressional behaviour of chewing gum tablets
Composites: Part B 49, 1–5 (2013) IF: 2.143

V. **Jójárt I.**, Kása P. jr., Kelemen A., Pintye-Hódi K.:
Study of the compressibility of chewing gum and its applicability as an oral drug delivery system.
(manuscript is sent for review)

PRESENTATION:

I. **Jójárt Imre**, Vágó Magdolna, ifj. Kása Péter, Hódi Klára
A fajlagos felület befolyásának vizsgálata röntgen-fluoriméterrel magnézium-sztearát esetében
XVI. Országos Gyógyszertechnológiai Konferencia, Siófok (2010).

CONTENTS

1 INTRODUCTION 1

2 AIMS 1

3 LITERATURE SURVEY 2

3.1 MAGNESIUM STEARATE 2

3.2 CALCULATION OF THE SPREADING COEFFICIENT 2

3.3 ENERGY DISPERSIVE X-RAY MICROANALYSIS 3

3.4 MEDICATED CHEWING GUMS 4

4 SECTION I - THE EFFECTS OF MAGNESIUM STEARATE 7

4.1 MANUFACTURING PROBLEMS IN PHARMACEUTICAL INDUSTRY 7

4.1.1 Background: Process validation, general descriptions 7

4.1.2 Product I details 8

4.1.2.1 Short display, magnesium stearate related parameters 8

4.1.2.2 Materials 8

4.1.2.3 Methods 8

4.1.2.3.1 Qualified equipments used for manufacturing 8

4.1.2.3.2 Brief Description of manufacturing process 9

4.1.2.4 Description and the solving of the manufacturing problem 9

4.1.3 Product II details 11

4.1.3.1 Short display, magnesium stearate related parameters 11

4.1.3.2 Materials 11

4.1.3.3 Methods 11

4.1.3.3.1 Qualified equipments used for manufacturing 11

4.1.3.3.2 Brief Description of manufacturing process 12

4.1.3.4 Description and the solving of the manufacturing problem 12

4.1.4 Product III details 15

4.1.4.1 Short display, magnesium stearate related parameters 15

4.1.4.2 Materials 15

4.1.4.3 Methods 16

4.1.4.3.1 Qualified equipments used for manufacturing 16

4.1.4.3.2 Brief description of manufacturing process 16

4.1.4.4 Description and the solving of the manufacturing problem 16

4.1.4.4.1 Investigation 19

4.2 INVESTIGATION THE EFFECT OF MAGNESIUM STEARATE 23

4.2.1 Materials 23

4.2.2 Methods 23
4.2.2.1 Blending 23
4.2.2.2 X-ray fluorescence analysis 23
4.2.2.3 Morphological study 24
4.2.2.4 Measurement of contact angle 24
4.2.3 Results and discussion 25
5 SECTION II - FORMULATION STUDY OF MEDICATED CHEWING GUM AND THE EFFECT OF MAGNESIUM STEARATE 28
5.1 MATERIALS 28
5.2 METHODS 29
5.2.1 Preparation of mixtures 29
5.2.2 Flow properties and moisture content 30
5.2.3 Tableting 30
5.2.4 Friability test 31
5.2.5 Deformability test 32
5.2.6 Geometrical parameters measurement 32
5.2.7 Surface free energy 32
5.2.8 Dissolution tests 32
5.2.9 Microscopic study 33
5.2.10 Porosity 33
5.3 EXPERIMENTAL RESULTS OF PHARMAGUM CHEWING GUM TABLETS 33
5.3.1 Compressibility tests 33
5.3.2 Chewability test 35
5.3.3 Dissolution test 36
5.4 EXPERIMENTAL RESULTS OF CAFOSA CHEWING GUM TABLETS 36
5.4.1 Investigation of elastic recovery of tablets 36
5.4.2 Formulation study of Cafosa-based chewing gum and its applicability as an oral drug delivery system 40
5.4.2.1 Formulation tests 40
5.4.2.2 Dissolution tests 45
5.4.3 Evaluation of results 46
6 CONCLUSIONS, PRACTICAL USEFULNESS 49
REFERENCES
ACKNOWLEDGEMENTS
APPENDIX

1 INTRODUCTION

Solid dosage forms such as tablets and capsules are the most popular drug delivery systems. Tablet and capsule dosage forms mainly contain active pharmaceutical ingredients and excipients [1]. The excipients may be diluents, binders, disintegrants, glidants and lubricants; lubricants are usually added in the final stages of mixing of the formulation components, prior to compression or encapsulation. Both tablets and capsules require lubricants in their formulations in order to reduce the friction between the powder and metal surfaces. The main function of lubricants is to prevent the adhesion of compacts to the surface of the punches, dyes or encapsulating tools used in pharmaceutical manufacture [2-4].

Magnesium stearate is the most widely used lubricant during tablet compaction and capsule filling operations in the pharmaceutical industry. It is preferred because of its low cost, high lubrication potential, relatively high melting point and chemical stability.

In industry, a number of problems arise in this context. It is important to investigate and resolve these problems. This is especially important in case of relatively new drug delivery systems, because there is not too much experience about their formulation. Medicated chewing gum has recently been included in the Pharmacopeias as a separate drug dosage form. New method of its production is not widespread yet. (Ph. Eur.) [5-7]

2 AIMS

There are two main parts of this study. In the first part of my thesis I will present manufacturing problems which can be bound to the magnesium stearate (MgSt), and ways of solving them, discussing the composition of the products, the machines used and the technologies employed. Furthermore I will present my experiments with magnesium stearate, and the conclusions derived from the results.

The second part of my dissertation is a formulation study of directly compressible chewing gum. That's not a widespread way of preparing a medicated chewing gum, and there are relatively few data and experience about this method. The role of MgSt is also very important in case of this drug form. This part includes all of the experimental results and the conclusions will be presented.

3 LITERATURE SURVEY

3.1 Magnesium stearate

Magnesium stearate is a mixture of plant or animal origin, various magnesium salts of fatty acids. The fatty acid components are mainly stearic acid and palmitic acid; minor proportions are of other fatty acids. The fatty acid fraction contains at least 40.0% stearic acid. Magnesium stearate is the most widely used lubricant. In the pharmaceutical industry it is one of the most popular lubricants because relatively cheap. It has high lubricating capacity, relatively high melting point (117 – 150 °C) and it is chemically stable [8]. The effect of lubricant is well known: it has extremely small particle size therefore is able to form semicontinuous layer on the surface of the larger particles [9-11]. The effects as compared to other metallic salts of fatty acids derived from the fact that the metallic polar part of the molecule binds to the surface of particles, as a consequence of the apolar hydrocarbon molecules away from the surface of the dust is located in [12]. Consequently, a non-polar layer is formed between the particles and the various devices, such as crimping tools and capsules. Advantages and disadvantages of the use of magnesium stearate arising from the the non-polar layer can be experienced during compression and encapsulation. The hydrophobic nature frequently prevent the fluid ingress among to ingredients of capsule, so after the capsule shell dissolves in the gastrointestinal fluid, a capsule-shaped stopper often remains back, particularly if the capsule filling materials have been compressed by encapsulating machine [2]. Because of the described negative properties the minimum effective concentration is used: generally 0.5 - 3%.

3.2 Calculation of the spreading coefficient

The lubrication effect is influenced by the mixing time and speed, the specific surface area and the spreading coefficient of the magnesium stearate. The spreading coefficient can be calculated via the free surface energy [13, 14], which is widely assessed indirectly from wettability measurements [15-17]. In the method of Wu and Brzozowski [18], the surface free energy is taken as the sum of the dispersive and the polar components. The surface free energies of solid materials can be determined by means of contact angle measurements, using two liquids with known polarities, which involve the solution of an equation with two unknowns:

$$(1+\cos\Theta)\gamma_l = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \qquad (1)$$

where Θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension. If the surface free energies of the solid materials are known, the spreading

coefficient (S) may be computed and the interactions between the two materials may be predicted. S is calculated as the difference between the adhesion work and the cohesion work. The two materials which interact can be two powders, a powder and a liquid (e.g. a core and a layering fluid), or any material and the equipment.

The spreading coefficient (S_{12}) of one material (1) over the surface of another material (2) can be determined according to the following equation [19]:

$$S_{12} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2}\right] \qquad (2)$$

If the spreading of the layering material on the surface of the core is insufficient, the efficiency of layering and the properties of the layer formed may be restricted.

3.3 Energy dispersive X-ray microanalysis

Using X-ray microanalysis by them energetic properties it is possible to detect qualitatively and quantitively the elements in the samples. Its use spread to various areas of the industry, particularly in microelectronics, but recently studies in pharmaceutical technology shows that it can be applied equally suitable for the detection of contaminating elements and examine the distribution of elements as well.

In thisstudy a compact table-top energy dispersive X-ray fluorimeter (Figure 1) was used for the elemental analysis of magnesium. This technique is suitable for the direct measurement in drugs of the elements ranging from sodium to uranium [10, 20].

Figure 1: Energy dispersive X-ray fluorimeter

When a material is irradiated by the beam from an X-ray tube, its constituent atoms are excited. This causes them to emit X-ray fluorescence. Each element in the sample emits its own uniquely characteristic fluorescent radiation, with an intensity directly related to the concentration of that element in the material. This phenomenon is the basis of X-ray fluorescence spectrometry. (Figure 2)

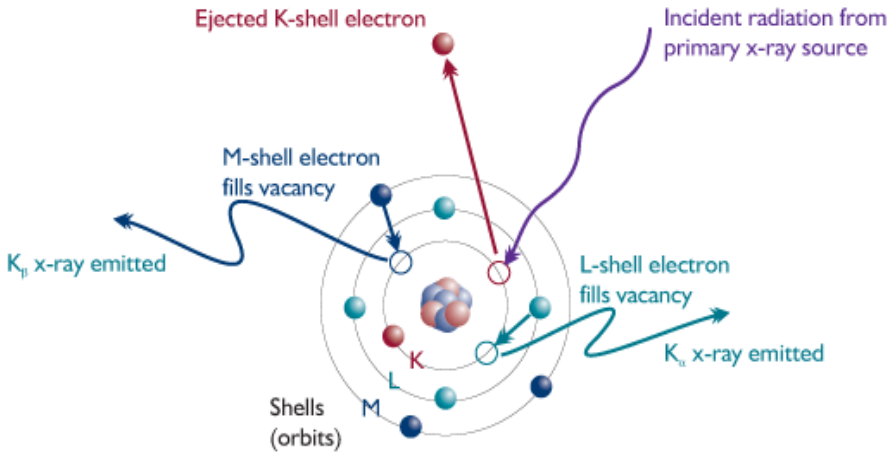


Figure 2: Fluorescence phenomena [21]

The fluorescence comprises discrete X-ray photons emitted at various (characteristic) energy levels. Photons of all energies are received simultaneously by the detector of the spectrometer and converted into a series of electrical signals, which are electronically amplified, processed and transformed into digital values. The digital values are stored in a multichannel analyzer, which separates them according to the photon energy levels. The result is the spectrum for the sample, which is further processed by the software to deliver a result calculated directly in terms of element concentrations [21].

The aim of this study was to investigate the properties of magnesium stearate such as to test the effects of various parameters on the distribution of magnesium stearate on the surface of particles in mixtures.

3.4 Medicated Chewing Gums

Chewing gum has been used world-wide since ancient times when man experienced the pleasure of chewing a variety of gum-like substances, such as tree resins, leaves, waxes and animal skins. Chewing gum has long been utilized. The eosin of the Sapodilla tree was used by the Mayan Indians for 1000 years, and after the Second World War the first synthetic chewing gums were developed [22-27].

The dosage form or delivery system is critical for the success of a pharmaceutical or a food product. Today, chewing gum is undergoing new consideration as a drug delivery system; it provides patient benefit and compliance, and has new competitive advantages from technological and marketing aspects. The active pharmaceutical ingredients (API) can be easily released from chewing gum into the salivary fluid within few minutes of chewing. Local and systemic effect can be reached by using this type of dosage form. The drug can be

absorbed through the oral mucosa or swallowed (gastrointestinal absorption). These absorption pathways are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. Drug can be easily permeated (e.g. BCS class I) from oral mucosa by the pressure created by the chewing action and absorbed directly via the buccal membrane avoids metabolism in the G.I tract and the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum compared to other oral delivery system. Therefore, ultimately patients will get quick relief. [5, 28-41]

Medical chewing gums are official as drug delivery systems in the Pharmacopoeias (e.g.:Ph.Eur. (1991) and USP). Medicated chewing gums are solid, single-dose preparations that have to be chewed but not swallowed. Chewing gums contain one or more active pharmaceutical ingredients (APIs) that are released by chewing (Ph.Eur.) [42]. Medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded. Chewing gum consists basically of a neutral and tasteless masticatory gum base and several non-masticatory ingredients, such as fillers, softeners, sweeteners, flavoring and texture regulating agents [42-43]. The gum bases currently used are mostly of synthetic origin and comprised of elastomers, resins, waxes, fats and emulsifiers. The elastomers are styrene–butadiene copolymers mixed with polyisobutene. The addition of rosin esters and polyvinyl acetate improves the texture, allows longer-lasting flavor and reduces the tendency of the gum to stick to the teeth. Other agents, such as glycerol monostearate and lecithin, act as emulsifiers and promote the uptake of saliva during chewing [44]. Powdered sugar and corn syrup were originally used as bulk sweeteners; nowadays, a mixture of sorbitol, xylitol, mannitol and aspartame is more commonly used in sugarfree, non-cariogenic gums and medicinal products [45-46]. Unfortunately, the thermal instability of many active ingredients (vitamins, vegetable extracts, etc.) precludes traditional chewing gum production methods because the temperature profiles associated with this type of production may reach 90°C [47].

Chewing gums can be manufactured through melting processes, extrusion or direct compression. Recently, chewing gums produced by direct compression have been proposed [48-49]. This method has only been possible since the direct compressible gum-based products have appeared on the market (e.g. Health-in-Gum® [50]). Direct compression is a popular method in tablet manufacturing because it involves a comparatively short processing time, low labour costs, a small number of manufacturing steps, little demand for equipment and relatively simple process validation. With this conventional tablet compression technology, these chewing gums can include higher levels of active ingredients than in

traditional extruded gums; the lower temperature protects sensitive bioactive and phytochemical components and the lower moisture content improves the shelf-life of active molecules.

However, the most common drawback in direct compression of the gum base is that it sticks to the punches of the tableting equipment. This is due to the adhesive nature of the gum, the main component of the formulation; for this reason, the procedure is difficult and needs lower production speed and cooling operations in order to prevent tableting machine damage. Sticking and friction can be minimized through the use of lubricants, such as magnesium stearate. Forms of magnesium stearate with different specific surface areas are available commercially. Their lubrication effect depends on the specific surface area. Furthermore the tableting tools are kept at temperatures below 18°C; however, it should be noted that the temperature should not be so low as to interfere with the handling of medicated gums and tableting process. Thus, the temperature should be above 10–12°C.

Of course the examination of active pharmaceutical ingredients (API) release is really important in case of chewing gum tablets as well. For investigation of the dissolution of API's from medicated chewing gum tablets, different apparatus have been developed. Till 1999 only two apparatus/methods have been available [39, 51]. Then the chewing equipment applied was developed by Erweka GmbH, and described by Kvist et al [52]. Further descriptions of dissolution and chewing gum tablet investigations have been reported by Azarmi et al [53].

The aim of this study was to examine production conditions of the medication chewing gum tablets, the compression parameters, the applicability of different type of magnesium stearates, the compressibility, the chewability and the drug release, which provide useful information for the industrial production.

4 SECTION I - THE EFFECTS OF MAGNESIUM STEARATE

4.1 Manufacturing problems in pharmaceutical industry

4.1.1 Background: Process validation, general descriptions

I work as pharmatechnologist and my main project is performing process validations. The correct validation of pharmaceuticals, that is, the method of proof in accordance with GMP (Good Manufacturing Practice) principles, which can be demonstrated that a process, procedure, device, method, activity or system actually meets the specified requirements [54-59].

Pharmaceutical Technology Department carried out with the aim of validation of a particular product: The objective of these validations is to assure that manufacturing process according to methodology described in the Manufacturing Validation Procedures (MVP) of the product is capable for reproducible manufacture of the product that complies with all in-process, validation and finished product specifications. The quality of these product conforms to the in-process (IPC), validation and final product requirements.

Typically validation process of solid dosage forms (tablets, capsules) is performed. During the tableting or encapsulation of granules speed validation is performed. These validations should be performed by prospective manner with production of at least 3 successive batches in the commercial batch size. The compression/encapsulation is started at the low speed according to MVP of product and not less than ($1/10^{th}$ of the batch) are compressed, than the high speed (the practicable highest) is set up at which the IPC tests are within the limits of acceptance criteria. Not less than ($1/10^{th}$ of the batch) are compressed / encapsulated at that speed as well. After this running the target speed optimum selected is set up and the compression / encapsulation continued. These validations mainly should be performed by prospective manner with production of at least 3 successive batches in the commercial batch size. All parameters tested should be within the limits of acceptance criteria. In example the dissolution profil of the samples must be similar to the profile of biobatch wich is the test batch used in the biostudy to demonstrate bioequivalence, or used in the biowaiver to demonstrate similarity, compared to the comparator product. The data will be evaluated to verify that the results of the total batch to be consistently within the limits, based on the samples tested. Process Validation Report is prepared by Pharmaceutical Technology Department.

During validation work of different products various dissolution problems were observed. In some cases magnesium stearate as an excipient was the cause of these problems. In case of some products the specific surface area of magnesium stearate and the homogenization time are really important parameters. We met these phenomena in case

different manufacturing techniques and different solid dosage forms. These will be explained below, covering the composition, manufacture of machinery and technology used for these problems and their solutions.

4.1.2 Product I details

4.1.2.1 Short display, magnesium stearate related parameters

This product is a film-coated tablet which is manufactured using wet granulation; compression, and then coating. Magnesium stearate is added to the granule just before final blending.

The final blending time: 5 minutes

Type of magnesium stearate applied at the beginning of the validations: with large specific surface area (6 – 10 m^2/g) (Producer: Peter Greven Nederland, Venlo, Netherlands)

The amount of magnesium stearate in the formulation: 1%

4.1.2.2 Materials

The composition of the Product I can be seen in Table 1

Table 1: Materials used for the manufacture of the Product I

Composition	
Name	**Quality**
Active pharmaceutical ingredient (API)	Ph.Eur.
Lactose monohydrate (pulvis)	Ph.Eur.
Starch pregelatinised (Starch 1500)	Ph.Eur.
Hypromellose (15 MPAS)	Ph.Eur.
Croscarmellose sodium	Ph.Eur.
Silica colloidal anhydrous	Ph.Eur.
Magnesium stearate (Peter Greven) (1%)	Ph.Eur.
Water purified	Ph.Eur.
Opadry, II 33G28707 white	in-house

4.1.2.3 Methods

4.1.2.3.1 Qualified equipments used for manufacturing

A list of equipments used for the manufacture of the product in Table 2

Table 2: Equipments

High shear mixer: LÖDIGE MGT 400
Fluidization dryer: GLATT WST CD-60
Oscillation granulator: FREWITT.
Blender/tumbler, (Flo-bin 750 litre)
Rotating compression machine with deduster, FETTE P2000/II, P2090
Metal checker
Coating equipment, GLATT GC-1250

4.1.2.3.2 Brief Description of manufacturing process

The manufacturing process is demonstrated in Figure 3.

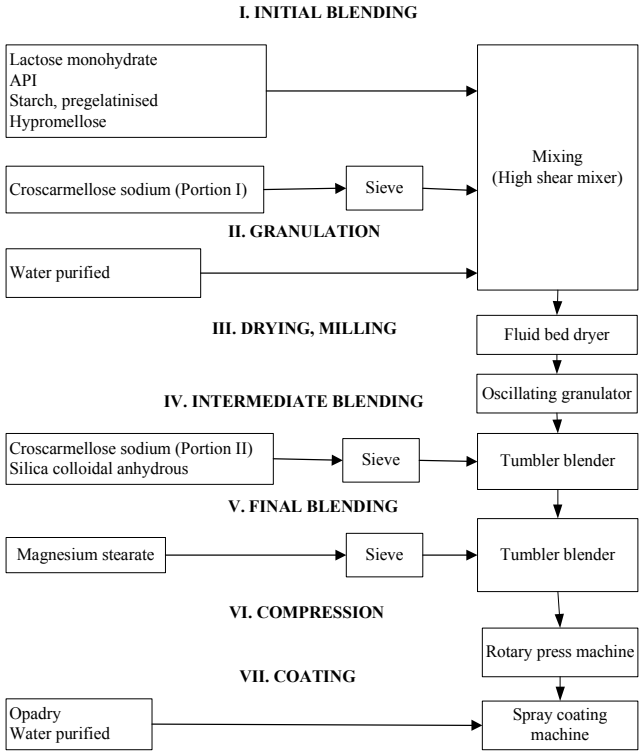


Figure 3: Flow chart – Product I

4.1.2.4 Description and the solving of the manufacturing problem

During validation process dissolution tests should be performed, including film-coated tablets and corpus case, which results must comply in the pre-defined specifications (Biobatch profile). In case of generic products in the development stage, comparative dissolution study had been carried out to confirm that generic product and the product manufactured by the originator product are in equivalence.

The dissolution tests were carried out as follows (a photometric measurement):

Table 3: Dissolution conditions

Device:	according to Ph. Eur. (paddle stirrer)
Dissolution medium:	0.1 M HCl
Dissolution medium temperature:	37 ± 0.5 ° C
Dissolution medium volume:	900 ml
Sample time point:	10, 20, 30, 45 and 60 minutes

The validation process also conducted a number of occasions for various reasons, which were mainly carried out in connection with registrations for changes. During the initial validation lower dissolution results were occurred (Figure 4), but only in few cases were out of specification result.

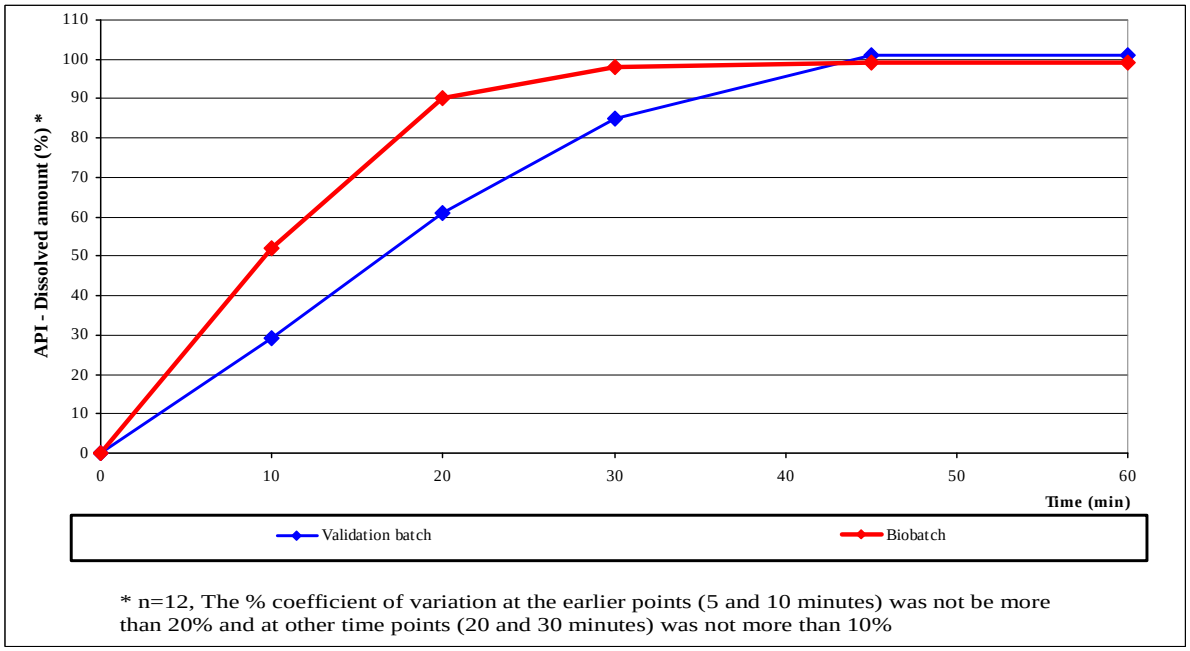


Figure 4: Dissolution profiles of the Biobatch and Validation batch

In this context, various changes were proposed in the production process. Initially, we reduced the core hardness, to decrease the disintegration time and this is abbreviated to accelerate the dissolution rate. The binder addition time and the granulation time were reduced to get “weaker” granule. The coating parameters have been also modified but mainly it was the aim to achieve better appearance. The dissolution profiles significantly did not improved due to these changes then it was decided to change the lubricant from the large surface area (6-10 m^2 / g – Peter Greven) magnesium stearate to the lower specific surface area (1.5-3.5 m^2 / g - Undesa) magnesium stearate with "coarser" particle. After this modification the dissolution profile was still not perfect, but it was not a lubricant failure, the cores have been pressed harder because continuous sticking problems. This problem has been solved by the following corrections: the granulation end point and the granulation time were modified, furthermore power end point limit was determined in the granule recipe and the loss on drying (LOD) specification of dried granule was modified.

These changes clearly show that the product quality highly depends on numerous manufacturing parameters and the properties of excipients as well.

4.1.3 Product II details

4.1.3.1 Short display, magnesium stearate related parameters

The second product is an uncoated tablets prepared by fluidization granulation. The magnesium stearate was added to the granules directly before final blending.

The final homogenization time: 1 minute

The initially used Magnesium Stearate: with high specific surface area (6-10 m^2 / g)

(Manufacturer: Peter Greven Nederland, Venlo, The Netherlands)

The amount of magnesium stearate in the formulation: 1%

4.1.3.2 Materials

The composition of the Product I can be seen in Table 4

Table 4: Materials used for the manufacture of the product

Composition	
Name	**Quality**
Active pharmaceutical ingredient (API)	Ph. Eur.
Lactose monohydrate	Ph.Eur.
Potato starch	Ph.Eur.
Povidone K 25	Ph.Eur.
Denatured alcohol	USP+BP.
Silica, colloidal anhydrous	Ph.Eur.
Magnesium stearate	Ph.Eur.

4.1.3.3 Methods

4.1.3.3.1 Qualified equipments used for manufacturing

Table 5: Equipments

GLATT Granulation suite (high shear mixer with fluid bed drier, rotating impeller with screen “cheese grater” 1.5 mm
RUSSELL vibratory sieve (30 mesh, 40 mesh)
Blender/tumbler, (Flo-bin 750 litre)
Rotating compression machine with deduster, FETTE P2000/II, P2090
Metal checker

4.1.3.3.2 Brief Description of manufacturing process

The manufacturing process is demonstrated in Figure 5.

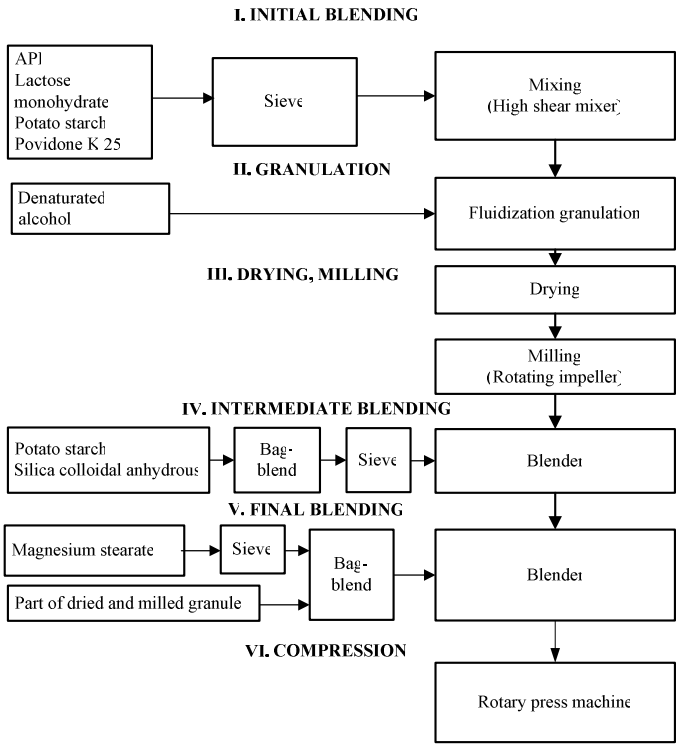


Figure 5: Flow chart – Product II

4.1.3.4 Description and the solving of the manufacturing problem

In case of one validation batch of this product we got out of specification dissolution result at 45 minutes sampling time (batch No.: Batch 6). Predetermined specification limit: not less than 90 % of the labeled amount must be dissolved within 45 minutes. This value was lower in case of this batch.

The dissolution tests were carried out as follows (a photometric measurement):

Table 6: Dissolution conditions

Device:	according to Ph. Eur. (paddle stirrer)
Dissolution medium:	Water purified
Dissolution medium temperature:	37 ± 0.5 ° C
Dissolution medium volume:	900 ml
Sample time point:	45 minutes

After the development phase in case of the first validation batch (Batch 1) similar problems were observed, but it could be eliminated by final blending time reduction with maintain adequate homogeneity. 3 minutes final blending time used for experimental validation batches and the first validation batch was reduced to 1 minute during the further manufacturing. New validation was started with manufacturing further validation batches.

Similar problem was not observed. The manufacturing was performed according to the documentation, which was approved by the developers.

Based on the review of manufacturing documents it can be stated that the API and other excipients forming the product have been weighed in appropriate quantity and quality. Using the required parameters there was no problem during fluid granulation. The drying took shorter than the planned time. The loss on drying still conformed to the specification. The homogenization times were consistent with the requirement. The manufacturing procedure did not contain extra comments on granulation phase.

The following in process parameters were measured during compression: average resistance to crushing (alias crushing strength or hardness), thickness, friability, disintegration time and average weight. The measurements were carried out in appropriate intervals and all results conformed to the pretermined acceptance criterias, although the measured disintegration times were close to the upper limit of the specification have (specification: < 10 minutes, actual: from 7 minutes 45 seconds to 9 minutes 10 seconds). The list of disintegration times is in table 4.

Validation tests (Table 7) provided for in the protocol is carried out correctly.

Table 7: Validation tests

granule physical tests:	sieve analysis
	bulk and tapped density
	flowing properties
tablet physical tests:	average weight
	resistance to crushing
	friability
	disintegration time
	assay tests

The sieve analysis results show (Table 8) that the granule has “finer grain” than in case the previous batches. Based on the validation test results (Table 9) it is concluded that the hardness values are similar to the previous two batches, and close to the lower limit of the specification. The disintegration times, although were within specification, but were higher than the results of previous batches (required: not more than 10 mins, actual: 7.8-8 minutes). The active substance contents of tablets were appropriate: 98.8%, 99.1%, and 100.4%.

Table 8: Sieve analysis results

Batches		**1st validation batch**	**2nd validation batch**	**3rd validation batch**	**4th validation batch**	**5th validation batch**	**6th validation batch**
Batch number		**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**
Sieve analysis							
Sieve size (μm)	**1000**	0.03	0.01	0.06	0.01	0.00	0.00
Sieve residue (%)	**710**	0.32	0.10	0.31	0.54	0.02	0.00
	500	1.65	1.57	1.51	1.51	1.28	1.00
	355	3.26	2.36	3.70	3.20	1.98	4.60
	250	9.42	10.21	10.03	9.53	9.00	9.60
	106	49.06	54.11	42.11	41.53	50.33	36.00
	53	30.11	25.17	27.93	31.07	25.99	20.00
	0	5.98	6.14	14.41	12.39	11.37	**28.60**
Bulk density (g/cm³)		0.663	0.648	0.667	0.699	0.639	0.650
Tapped density (g/cm³)		0.780	0.762	0.785	0.817	0.765	0.770
Flowing time (second)		2	2	2	2	2	1

Table 9: Rewiew of the main parameters in case of the first 6 validation batches

Batches	**1st validation batch**		**2nd validation batch**		**3rd validation batch**		**4th validation batch**		**5th validation batch**		**6th validation batch**	
Batch number	**Batch 1**		**Batch 2**		**Batch 3**		**Batch 4**		**Batch 5**		**Batch 6**	
Magnesium stearate Specific surface area (m^2/g)	6.8 m^2/g		7.6 m^2/g		7.6 m^2/g		7.5 m^2/g		6.2 m^2/g		8.3 m^2/g	
Drying time after fluid granulation	14 mins		9 mins		16 mins		14 mins		14 mins		13 mins	
Final blending time(min)	**3 mins**		1 min		1 min		1 min		1 min		1 min	
Dissolution (%) (sampling at 45 minutes)	**82 % (average)**		91 % (average)		92 % (average)		98 % (average)		95 % (average)		**62 % (minimum) 78 % (maximum)**	
Resistance to crushing Specification:	Compr. begin	6.6	Compr. begin	4.5	Compr. begin	4.9	Compr. begin	6.0	Compr. begin	5.5	Compr. begin	5.3
	Compr. middle	5.7	Compr. middle	5.2	Compr. middle	5.1	Compr. middle	5.8	Compr. middle	5.7	Compr. middle	4.9
Average: 5-8 kp	Compr. end	6.5	Compr. end	5.4	Compr. end	4.9	Compr. end	5.9	Compr. end	6.4	Compr. end	5.2
Disintegration time during In process tests, (min, sec.) specification: <10 minutes	**9'00" – 9'45"**		5'00" – 7'00"		5'00" – 5'30"		7'00" – 7'30"		6'00" – 7'00"		**7'45" – 9'10"**	
Disintegration time (min) during Validation tests, specification: <10 minutes	Compr. begin	**6.9**	Compr. begin	4.5	Compr. begin	3.6	Compr. begin	6.0	Compr. begin	4.0	Compr. begin	**7.8**
	Compr. middle	**6.4**	Compr. middle	4.3	Compr. middle	5.2	Compr. middle	6.1	Compr. middle	4.1	Compr. middle	**7.8**
	Compr. end	**6.3**	Compr. end	5.3	Compr. end	5.0	Compr. end	6.3	Compr. end	4.6	Compr. end	**8.0**

Based on these results, it was concluded that on the surface of relatively small granular particles the larger surface area of magnesium stearate formed a hydrophobic layer, resulting elongated disintegration time and slower dissolution of the API. The fluidized granulation is a well controlled manufacturing process, however, in routine production it can occur that "fine-grained" granules form. This phenomenon mainly comes from the properties of API. To overcome this problem, we suggested the use of a magnesium stearate with smaller specific surface area, preventing the further dissolution problems. After this modification dissolution problem was no longer occured and the disintegration time was greatly reduced. The problem was successfully solved.

4.1.4 Product III details

4.1.4.1 Short display, magnesium stearate related parameters

This product is a capsule containing 2 different API and manufactured by wet granulation. The speciality of this production technology is that the two active ingredients are in different phases. First active ingredient is in the internal phase which made by wet granulation and the other active ingredient is mixed to the materials after sieving as a part of the external phase. Application of this technology due to the moisture-sensitive active ingredient added to the external phase after wet granulation. The magnesium stearate was added directily before the final blending phase after a brief bag blending (in Polyethylene bag).

Mannitol and Cellulose are fillers in composititon to provide the necessary load mass. Povidone is binder which is often used in wet granulation. Talcum is in the composition to improve the granule flow properties, while Magnesium stearate reduces the adhesion/friction between the granule and the used equipments.

The final homogenization time: 5 minutes

The initially used Magnesium Stearate: with high specific surface area (6-10 m^2 / g)

(Manufacturer: Peter Greven Nederland, Venlo, The Netherlands)

The amount of magnesium stearate in the formulation: 1%

4.1.4.2 Materials

Table 10: Materials used for the manufacture of the product

Composition	
Name	**Quality**
Active pharmaceutical ingredient (API) I	Ph.Eur.
Active pharmaceutical ingredient (API) II	Ph.Eur.
Cellulose, microcrystalline	Ph.Eur.
Mannitol	Ph. Eur.
Povidone K30	Ph.Eur.
Talc	Ph.Eur
Magnesium Stearate	Ph.Eur.
Water purified	Ph.Eur.
Hard gelatin capsules	In house

4.1.4.3 Methods

4.1.4.3.1 Qualified equipments used for manufacturing

A list of equipments used for the manufacture of the product in table 11.

Table 11: Equipments

Granulation suite Diosna CCS600(II.): high shear mixer, fluid bed dryer, (Comil, 1.0 mm „cheese” greater)
Russell vibratory sieve (20, 40 mesh)
Blender, Tumbler (Flo-bin 750L)
Capsule Filling machine
Weight sorter
Capsule polishinig machine
Metal detector

4.1.4.3.2 Brief description of manufacturing process

The manufacturing process is demonstrated in Figure 6.

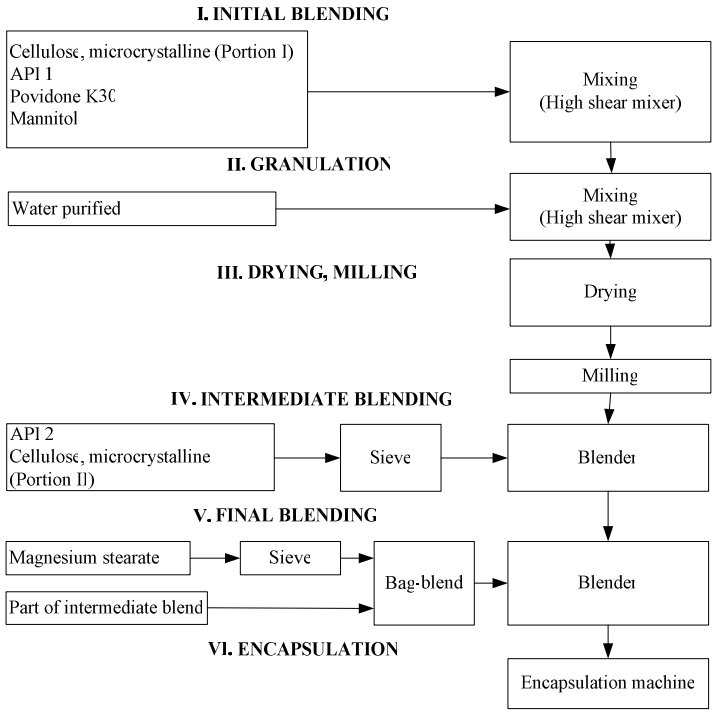


Figure 6: Flow chart – Product III

4.1.4.4 Description and the solving of the manufacturing problem

During process validation not expected dissolution problems were observed. The aim was to explore the cause of these problems and solve them, because these phenomena were not observed during development. Based on the good granule homogenity test results after the first validation batch (Batch 1) we continued the validation with the second batch manufacturing (Batch 2). The granule productions were in line with expectations. After granulation the granules has been charged in capsule, and the associated speed validation was performed. The encapsulation of the two batches was planned in same date. The

encapsulation was started at the low speed (40 300 capsules/hour) according to Manufacturing validation procedure and not less than 50,000 capsules ($1/10^{th}$ of the batch) were encapsulated, then the practicable highest speed (50 400 capsules/hour) was set up at which the IPC tests were within the limits of acceptance criteria. Not less than 50,000 capsules ($1/10^{th}$ of the batch) were encapsulated at that speed as well. After this running the target speed optimum selected were set up and the encapsulation continued. This speed was equal to the high speed (50 400 capsules / hour) value. After the in-process tests the validation and final product (release) tests had been started. The validation studies have not been finished completely because we got not conformed dissolution results which were confirmed by the results of the Chemical Control Department. The required validation tests and measured results are in table 12.

Table 12: Validation tests and results

Parameters	**Ch.: Batch 1 Validation test results**			**Specifications**
Average weight, Uniformity of mass	Not tested			Percentage deviation NMT 7.5 % from the theoretical weight
Assay -API 1 -API 2	Not tested			95,0 – 105,0 % (acceptance criteria Ph. Eur.)
Uniformity of Dosage Units(by content uniformity) - API 1 - API 2		**API 2**	**API 1**	Conforms to the current Ph.Eur AV value NMT 15,0
	Low speed	2,7	3,4	
	High speed	2,9	5,0	
	Target speed beginning	5,0	2,9	
	Target speed beginning	3,4	3,4	
	Target speed beginning	6,1	8,0	
Dissolution average (min, max) (%) - API 1 - API 2		**API 2**	**API 1**	NLT 75% (Q) of the labelled amount within 45 minutes
	Low speed	98 (96, 101)	101 (99, 102)	
	High speed	96 (91, 101)	**74 (65, 86)**	
	Target speed beginning	97 (95, 99)	**78 (74, 80)**	
	Target speed beginning	95 (91, 98)	**84 (70, 93)**	
	Target speed beginning	**65 (55, 71)**	**33 (29, 37)**	
Dissolution profile - API 1 - API 2		**API 2**	**API 1**	It must be similar to the profile of the Biobatch
	Low speed	similar	similar	
	High speed	not similar	not similar	
	Target speed beginning	not similar	not similar	
	Target speed beginning	not similar	not similar	
	Target speed beginning	not similar	not similar	

The dissolution tests were carried out as follows (a photometric measurement):

Table 13: Dissolution conditions

Device:	according to Ph. Eur. (paddle stirrer)
Dissolution medium:	Water purified
Dissolution medium temperature:	37 ± 0.5 ° C
Dissolution medium volume:	900 ml
Sample time point:	5, 10, 15, 20, 30 and 45 minutes

The samples filled at low speed show good dissolution results. The dissolution conforms to the specification. The expectation for the dissolution profile similarity with the dissolution profile of the referent product (Biobatch) also met.

The samples at high speed and the further samples showed continuously worsening results. The Figure 7 and 8 show clearly this progress.

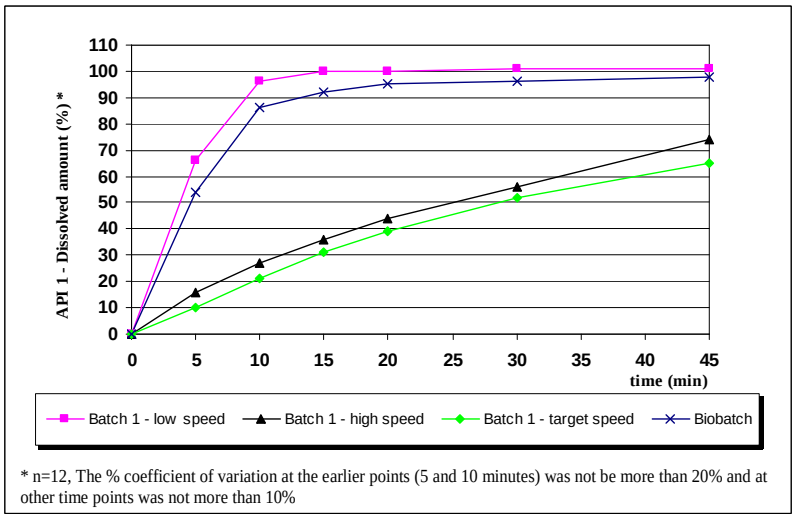


Figure 7: Dissolution profile of API 1

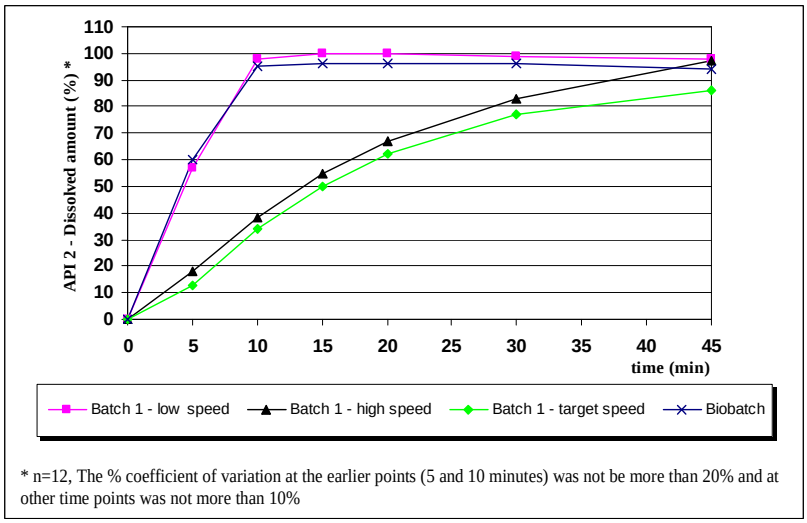


Figure 8: Dissolution profile of API 2

It can be observed that the API 1 in the internal phase shows lower dissolution than the API 2 in the external phase. This phenomenon can be explained by binding forces within the granule particles which caused the delayed release of the drug.

In case of the second batch (No.: Batch 2) we examined the low speed samples because these samples has been already showed low dissolution values. At 45-minute sampling the dissolution value was 62 % in case API 2 and 30 % in case API 1 instead of the 80 % requirement.

4.1.4.4.1 Investigation

It was observed that in case of the insufficient samples whole capsules (which do not disintegrate) remained in the dissolution vessel. The center of the capsules was not wetted (Figure 9) after loosening the capsule shell. It is assumed that the surface of the granulate particles become hydrophobic during filling, thereby inhibite dissociation of active ingredients. Hydrophobicity acting proves that the surfactant (Tween ® 20) which was added to the dissolution medium can accelerate the fluid entering the interior of filled granule so facilitate its disintegration and increase the degree of dissolution of the active ingredients.

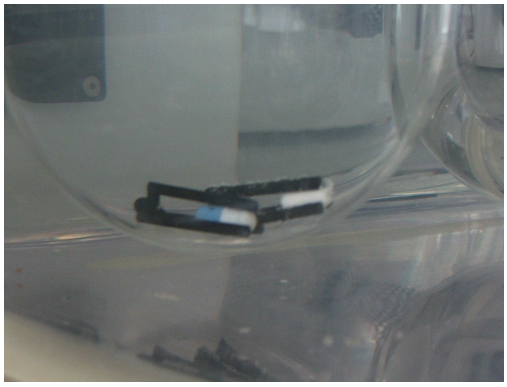


Figure 9: Whole capsule and not dissolved filled granule at the bottom of the dissolution vessel

Additional dissolution study started with capsules filled granule by hand. In the course of the experiment we modelled the granule filling strength to capsule shell. The granule has been loosely sprinkled into the capsule shells and in other case the granule was pressed into capsule shells using the greatest possible force. Using the two different charging methods the dissolution results conformed to the specification. With this evidence, the granule remained in the dissolution medium does not depend on the degree of filling strength. The release also spread over the surface of granules medium migration. The granule sprinkled on the surface of the dissolution medium also showed an appropriate dissolution results.

The granules sampled in various phases of encapsulation show different behavior if these were sprinkled on the surface of the dissolution medium. During the examination of inproper dissoluted capsule fillings it was found that the filling forms non-wettable, oily layer on the surface charge of the dissolution medium. (Figure 10)

Figure 10: Non-wettable layer on the surface

In contrast, the non-filled granules and the filling of well dissolved capsules contact solution quickly, almost instantaneously. (Figure 11) We used this test as an addititonal IPC test during further validation. Using this method it was easy to detect any change during encapsulation.

Figure 11: The behaviour of the easily dissoluted granule

The addditional test was carried out as follows:

To do this, we used a different filling of appropriate and inappropriate behavior in release capsules. The essence of the simplified test, the capsule filling of the liquid surface scattering, the visual observation of, the instrument can be approximated by numerical analysis results. The rapid test was 400 ml beaker was carried out under the following conditions:

Table 14: Dissolution conditions for visual observations

Dissolution medium:	Water purified
Dissolution medium temperature:	room temperature
Dissolution medium volume:	300 - 350 ml

If the full charge falls to the bottom of the vessel in 1 minute, and does not form a film-like layer on the surface of the medium, the value and the dissolution profile of the predicted characteristic is appropriate. When wetted (into the medium) over a period

of 1-5 minutes, the dissolution specifications are near unity, but running in a flat curve has been mentioned. If the granule is only slightly or not at all wetted (that stated for 5 min) and the medium surface to form a permanent film on the filled capsule dissolution value will not meet the requirements.

Subsequently, a granule batch was produced in a pilot scale. The granule was capsulated by two different encapsulating machines. Relative low speed was used to prevent friction.

The capsules were sampled in every 30 minutes to make the test mentioned above.

After starting encapsulation of the granules the disc temperature continued to rise and the solving after nearly 3 hours showed a deviation. Based on our experience, it was concluded that the over 26-28 º C the final blend became more hydrophobic (Table 15).

Table 15: Results of visual tests using high specific surface area MgSt

Bosch type equipment		
Solving	**Temperature (°C)**	**Comment**
conforms	24.6	start of encapsulation
not conforms	25.5	(+3 hours) visible differents
not conforms	26.0	(+ 8 hours) the granule is not solved
not conforms	25.9	(+ 12hours) stop
Macofar type equipment		
Solving	**Temperature (°C)**	**Comment**
conforms	22.5	start of encapsulation
still conforms	26.2	(+3 hours) visible differents
not conforms	28.2	(+ 8 hours) the granule is not solved
not conforms	29.8	(+ 12 hours) stop

Summarizing the experience we came to the conclusion that the high surface area of magnesium stearate used in the product need to replace a lower rate (Table 16), thus reducing the chances of particles coating by MgSt. The change has successfully solved the previous solving/dissolution problems.

Table 16: Datas of different MgSt-s based on Certificate of Analysis by the manufacturers

Specific surface are	**Magnesium Stearate (Peter Greven)**	**Magnesium Stearate (UNDESA)**
Manufacturer specifications	6 – 10 m^2/g	1,5 – 3,5 m^2/g
Actual values	9,2 m^2/g	2,5 m^2/g

According to the production technology the granulation process was performed in the same manner till the internal phase manufacturing and then it was homogenized with the external phase, using alternative types of magnesium stearate (batch number: Batch 3). The granules are also encapsulated using two different encapsulation machine. During the encapsulation at all times adequate dissolution was observed by visual observation (Table 17) and then measured from the product. (Figure 12 and 13)

Table 17: Results of visual tests using lower specific surface area MgSt

Macofar type equipment		
Solving	**Temperature (°C)**	**Comment**
conforms	20.3	start of encapsulation
conforms	26.1	(+ 4 hours) critical temperature
conforms	27.2	(+ 7 hours) stop
Bosch type equipment		
Solving	**Temperature (°C)**	**Comment**
conforms	24.6	start of encapsulation
conforms	25.3	(+ 2 hours) high speed
conforms	26.1	(+ 3 hours) critical temperature
conforms	27.6	(+ 5 hours) stop

Temperature increasing was observed as during the encapsulation of previous batch but the product quality was not gone wrong. (see on table 17)

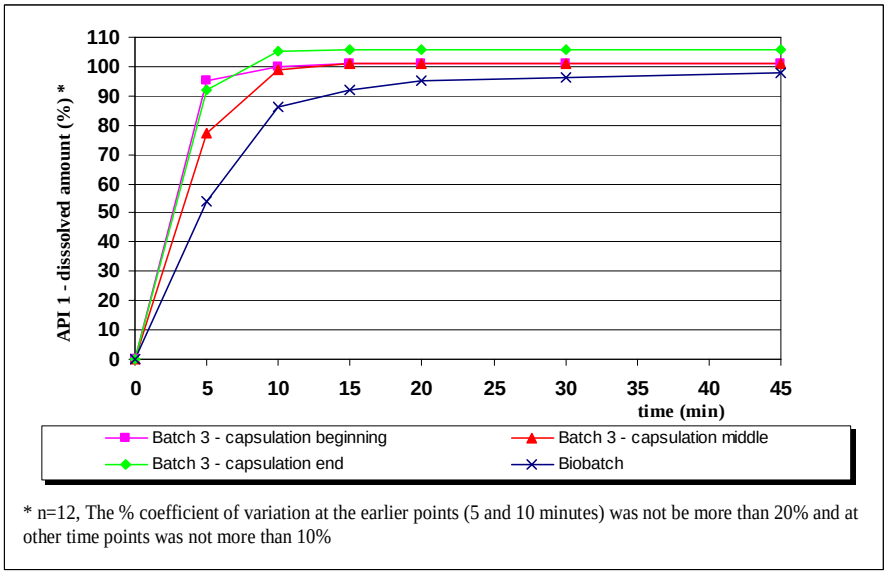


Figure 12: Dissolution profile of API 1

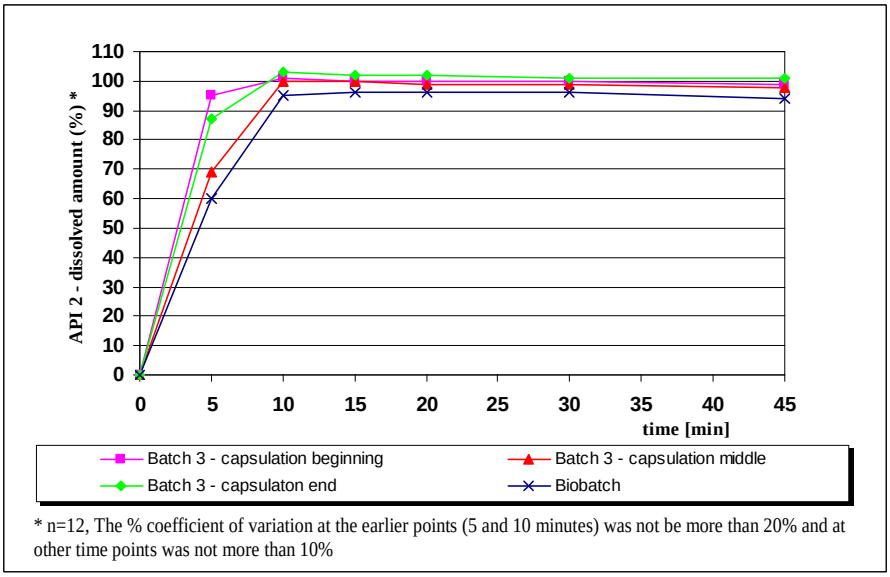


Figure 13: Dissolution profile of API 2

The dissolution problem occurred during the validation process have been succefully solved changing the type of MgSt based on the experience of experimental tests. The cause of the phenomenon is that the MgSt partially melted on the surface of the particles (which depends on the temperature, the degree of friction and the duration of encapsulation) and that made a hydrophobic layer.

4.2 Investigation the effect of magnesium stearate

Based on the experiences mentioned above (Industrial experiences) further examinations of properties of magnesium stearate were started.

4.2.1 Materials

Two types of magnesium stearate were used as lubricant, with different specific surface areas: 8-10 m^2/g (Peter Greven Nederland, Venlo, The Netherlands) and 2.5 m^2/g (Undesa, Union Derivan, S.A., Barcelona, Spain)

The other materials applied were API 1, API 2 (Ph.Eur.) and granule contained both active ingredients.

4.2.2 Methods

4.2.2.1 Blending

The granules were mixed separately with 1% of the two types of magnesium stearate in a Turbula mixer (W.A. Bachofen Maschinenfabrik, Switzerland). The two mixtures were blended in two ways to prepare samples for examinations:

(a) at a fixed blending speed of 25 rpm for various times (2, 5, 8, 10 and 15 min), or

(b) at various blending speeds (25, 50, 75 and 90 rpm) for a fixed time of 5 min.

4.2.2.2 X-ray fluorescence analysis

Measurements on the samples were made with a Philips MiniPal PW 4025 (MiniPal, Philips Analytical, Almelo, The Netherlands) energy dispersive X-ray fluorescence analyser. During the measurements, the conditions applied were 4 kV, 1000 A and 1 bar He purge. The samples were measured for 600 s and the measurements were repeated in triplicate for each sample. The concentration of Magnesium was calculated by means of linear calibration (r^2= 0.9980) from the intensities of the K shell of the detected radiation. The K value of Magnesium occurs at 1.253 keV. (Figure 14)

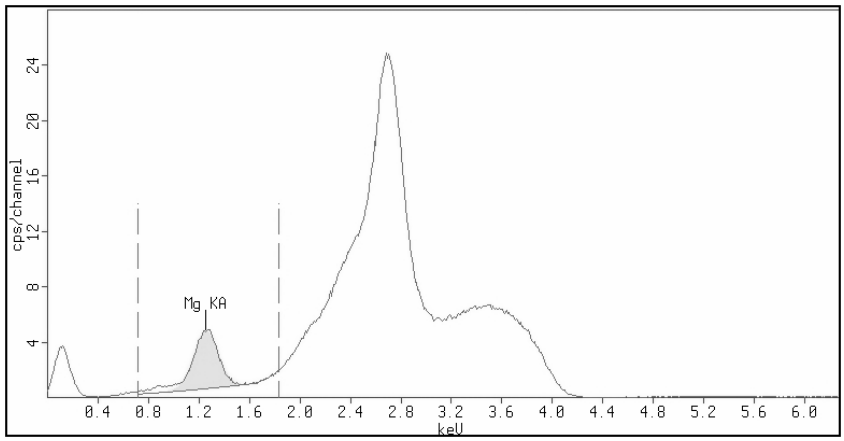


Figure 14: Energy dispersive spectrum of Mg.

4.2.2.3 Morphological study

The surfaces of the samples were tested with a scanning electron microscope (SEM) (Hitachi S4700, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A sputter coating unit (Polaron E5100, VG Microtech, UK) was used to charge the surfaces for the SEM measurements. The air pressure during the analyses was 1.3 – 13 mPa.

4.2.2.4 Measurement of contact angle

Contact angles were measured on flat comprimates 12 mm in diameter, compressed with a hydraulic press (Röltgen GmbH & Company KG, Sollingen, Germany) at 1 MPa from the bulk materials (API 1, API 2, granules and magnesium stearate).

An automatic syringe was used for the dropping, and circle fitting was applied to determine the contact angles formed on comprimates prepared from different samples. The test fluids were distilled water and diiodomethane (Merck KGaA, Darmstadt, Germany). In the case of water, the drop volume was 10 µl, while in the case of diiodomethane, it was 3 µl. The advancing contact angles were measured. According to Ström [60], the dispersion component of the surface tension is 21.8 mN/m for water and 50.8 mN/m for diiodomethane, while the polar component of the surface tension is 51.0 mN/m for water and 0.0 mN/m for diiodomethane.

4.2.3 Results and discussion

The SEM pictures showed that the magnesium stearate with the higher specific surface area (Peter Greven) (Figure 15) was evenly distributed over the granule surface, while the magnesium stearate with the lower specific surface area (Undesa) (Figure 16) exhibited enrichment on the surface of the particles. The difference in grain size between the two types of magnesium stearate was clearly visible.

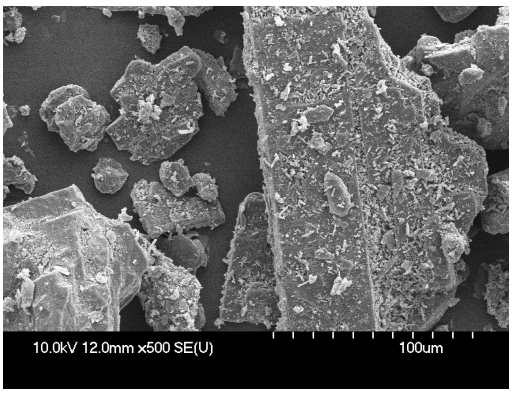


Fig. 15:Distribution of Mg-stearate with the higher specific surface area on the surface of the granules

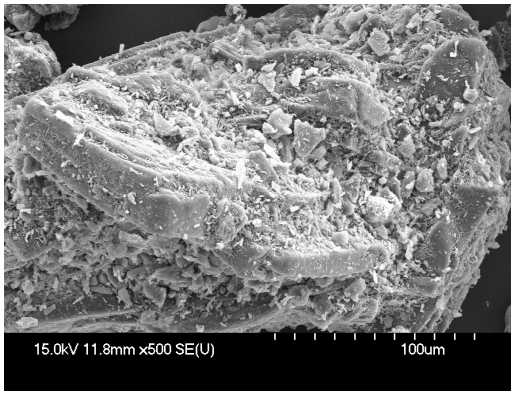
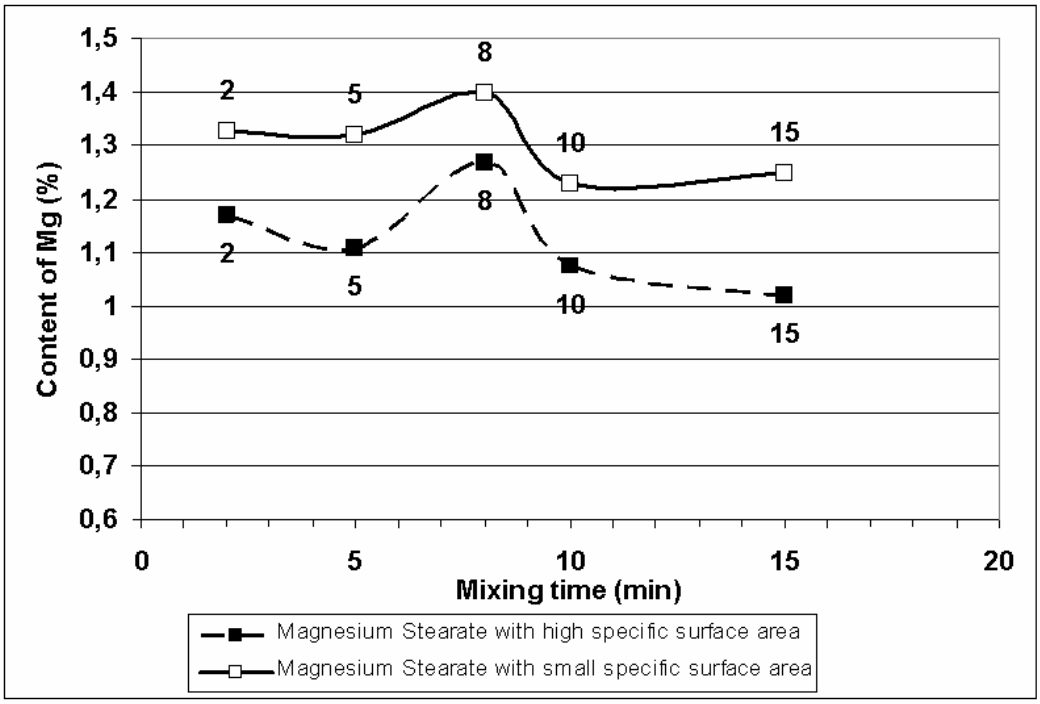


Fig. 16:Distribution of Mg-stearate with the lower specific surface area on the surface of the granules

The samples were examined by X-ray fluorimeter. At constant blending speed, with variation of the duration of blending, both type of magnesium stearate revealed magnesium concentration was the highest at a duration of 8 min (Figure 17). This phenomenon demonstrates that the covering of the particles by magnesium stearate is the highest at this time. After longer mixing time an overmixing can be observed.

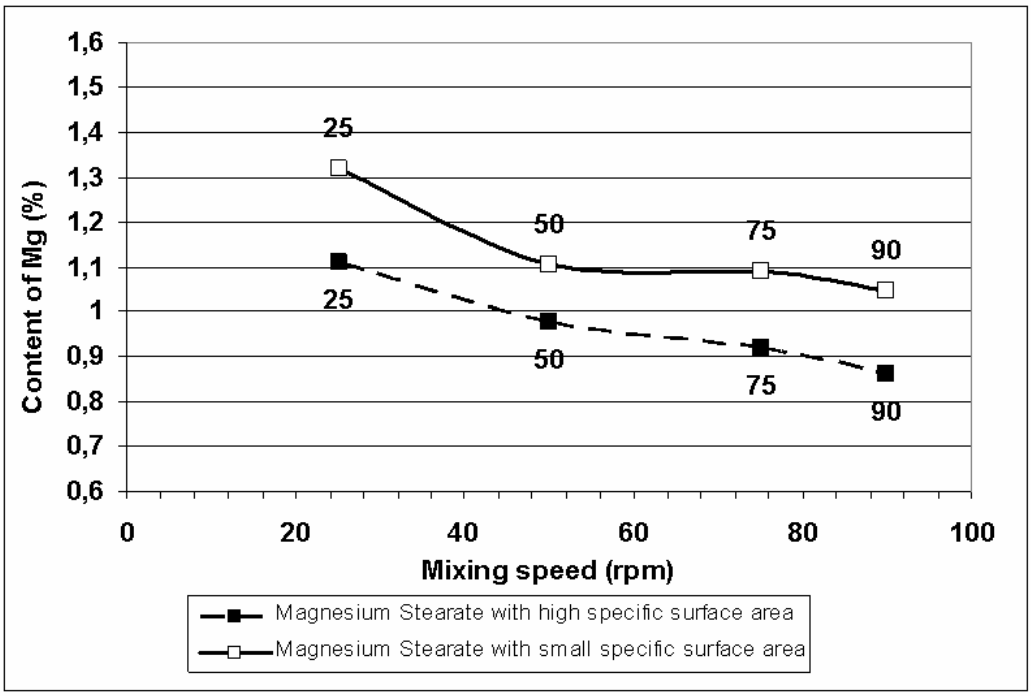
It was additionally seen, that the magnesium stearate with the lower specific surface area resulted higher magnesium concentrations. This is in accordance with the visual observations (Figs 15 and 16), that the particles containing magnesium stearate with the higher specific surface area formed a thinner, but uniform layer.

When the blending was performed for a fixed period of time at differetnt blending speeds, it was found that the highest magnesium content was measured at 25 rpm for both forms of magnesium stearate (Figure 18), higher speed again leadin to overmixing. The magnesium stearate layer was thinner, but further increase of the speed did not cause any change in the homogeneity during 5 min.



* n=2, SD: Not more than (NMT) 5 %

Figure 17: Influence of blending time at blending speed of 25 rpm on the distribution of magnesium on the surface of particles.



* n=2, SD: Not more than (NMT) 5 %

Figure 18: Influence of blending speed on the distribution of magnesium at a blending time 5 min.

It is well known that the lubrication effect of magnesium stearate depends on its spreading ability on the surface of the particles. The spreading coefficient can be calculated via on the wetting contact angles. From these data, it is possible to calculate the total surface free energy, its polar and disperse parts, and the adhesion work. The data are presented on Table 18.

Table 18: Parameters of surface properties of particles

1st material	2nd material	S_E1 (mN/m)	Sd1 (mN/m)	Sp1 (mN/m)	SE2 (mN/m)	Sd2 (mN/m)	Sp2 (mN/m)	Wa (mJ/m2)	$S_{1,2}$ (mN/m)
Mgst (high spec. surface area)	**API 1**	22.68	22.68	0	84.87	49.05	35.82	62.04	16.68
	API 2	22.68	22.68	0	82.85	47.10	35.75	61.23	15.87
	Granule	22.68	22.68	0	82.10	48.28	33.82	61.72	16.36
Mgst (small spec. surface area)	**API 1**	32.18	27.93	4.25	84.87	49.05	35.82	86.38	22.02
	API 2	32.18	27.93	4.25	82.85	47.10	35.75	85.33	20.97
	Granule	32.18	27.93	4.25	82.10	48.28	33.82	85.88	21.52

Note: S_E=total surface free energy, S_d=disperse part of free energy, S_p=polar part of free energy, W_a=adhesion work, S_{12}=spreading coefficient

It can be seen from the data, that API 1 and API 2 have high surface free energies, and their characteristics strongly influence the surface properties of the granules. Both types of magnesium stearate have much lower surface free energies, but it is noteworthy that, for the magnesium stearate with the higher specific surface area, the polar part is zero, and the apolar nature therefore dominates. This affects the value of the spreading coefficient. Since the magnesium stearate with the higher specific surface area is totally apolar it has fewer binding points on the surface of the particles, whereas the magnesium stearate with the lower specific surface area can also bind to polar binding points. In this case, the use of magnesium stearate with the lower specific surface area is more advantageous.

Since the spreading coefficient value (S_{12}) is positive, magnesium stearate (material 1) spreads on the surface of the other components (material 2). The more positive S_{12}, the better is the spreading. It must be noted that the spreading of the magnesium stearate with the lower specific surface area is better and the adhesion work of these samples is higher than for the samples containing the other type of magnesium stearate.

This experiment explains the experiences with the granules mentioned above. Also calls attention to the fact that the solution is not always using high specific surface area magnesium stearate. In case similar problems it is needed to perform this kind of preformulation studies.

5 SECTION II - FORMULATION STUDY OF MEDICATED CHEWING GUM AND THE EFFECT OF MAGNESIUM STEARATE

5.1 Materials

During the experiments two types of commercial sourced "gum basic" was studied: the Pharmagum C, M, and S® named (gifts from SPI Pharma) and the Health-in-Gum® named (Cafosa Gum, S.A.U., Barcelona, Spain) products. Pharmagum C, M and S were used as gum bases. Pharmagum M has a 50% greater gum base than Pharmagum S, which consists primarily of gum base and sorbitol. Pharmagum M contains gum base, mannitol and isomalt. According to the manufacturer data, Pharmagum S is suitable for formulations with low drug loading and when incorporated into tablets gives them chewable character. Pharmagum M is suggested for medium drug loading (<50%); it improves the mouthfeel texture. Pharmagum C is suggested for high drug loading (>50%); it has a real chewing gum character. Based on the experience gained in preliminary experiments (inadequate flowability, uneven charging, excessive sticking - see below), mixtures were prepared using these products in different ratios to study the compactness and deformability (Table 19). Compactness means the permanent bindings which are formed during loading and deformability refers to the shape modification of the particles during loading.

In this formulation study ascorbic acid was used as model material (Ph. Eur.). Besides ascorbic acid as API, additional components of the mixtures were xylitol (frequently used in tablets as a sweetener), magnesium stearate (as a lubricant) and aroma (to give the tablets a better smell).

Table 19: Compositions of powder mixtures

	Pharmagum (%)			**Ascorbic acid (%)**	**Xylitol (%)**	**Aroma (%)**	**Mg.stear. (%)**
	C	**M**	**S**				
S 1	60	40	-	8.33	7.68	0.33	2.00
S 2	50	50	-				
S 3	40	60	-				
S 4	60	-	40				
S 5	50	-	50				
S 6	40	-	60				
S 7	-	60	40				
S 8	-	50	50				
S 9	-	40	60				

API concentration: 33 mg/tablet
Average tablet weight: 470 mg

In the next formulation study the other directly compressible gum composition was used as matrix former (Health in Gum) (Cafosa Gum, S.A.U., Barcelona, Spain) to get a broader picture of the properties of these new materials (Table 20).

Table 20: Composition of gum powders

Component	**Content**
Gum base	28-32
Sorbitol	Up to 100
Xylitol	8-12
Plasticizer	<1.5
Antitacking agent (E-551)	<2.0

Caffeine was used as API, stevioside as sweetener and in case the final investigation two types of magnesium stearate individually as lubricant, with different specific surface areas: 8-10 m^2/g (Peter Greven Nederland, Venlo, The Netherlands) and 2.5 m^2/g (Undesa, Union Derivan, S.A., Barcelona, Spain). The composition of the tablets can be seen in Table 21.

Table 21: Composition of tablets

Component	**Content (%)**
Caffeine	12.5
Stevioside	2.5
Magnesium stearate*	1.5
Gum base powder	83.0

API concentration: 50 mg/tablet
Average tablet weight: 400 mg

**Two type of magnesium stearate were used individually in the final experiments.*

All the materials used (apart from the gum base) in this product complied with their Ph. Eur. and USP monographs and all the components of the gum base complied with the USA Food and Drug Administration Code of Federal Regulations, title 21, sect. 172.615 and Food Chemicals Codex Specifications.

5.2 Methods

5.2.1 Preparation of mixtures

Pharmagum based chewing gum tablets: The mixtures of two of the Pharmagum materials in various ratios were prepared with a Turbula mixer (Willy A Bachofen, Switzerland) at 50 rpm for 8 min, after which the other components were added, and mixing was continued for a further 2 min (Table 19). The mass of each powder mixture was 200 g.

Cafosa based chewing gum tablets: After sieving, the components with the exception of magnesium stearate (Table 21) were mixed in a Turbula mixer at 50 rpm for 8 min, the magnesium stearate was then added, and mixing was continued for 2 minutes. The total mass of each powder mixture was 200 g.

5.2.2 Flow properties and moisture content

The flow properties of the gum powder were determined with a Pharma Test PTG-1 powder rheological tester (Pharma Test Appartebau, Germany). The compaction behaviour of the materials was tested with an Engelsmann stampfvolumeter (J. Engelsmann A-G, Ludwigshafen, Germany). The moisture content of the gum powder was determined with a moisture analyzer (HR73 Halogen Moisture Analyzer, Mettler-Toledo GmbH, Greifensee, Switzerland). The standard drying program was used, with a drying temperature of 105 °C. The sample was heated to 105 °C and then held constant at that temperature. The powder was dried to constant mass.

Three parallel experiments were performed.

5.2.3 Tableting

Two type of compression machines were used during these experiments.

The Pharmagum and the first Cafosa based tablets were prepared with a Korsch EK0 eccentric tableting machine. The compression tools were flat-faced bevel-edged punches 10 mm in diameter and equipped with strain gauges and a displacement transducer. The strain gauges allowed the pressure forces on the upper and lower punches to be followed with force-measuring equipment. The displacement transducer was fitted over the upper punch. The compression was carried out electrically at 36 rpm, at an air temperature of 24 °C and a relative air humidity of 45%. The Pharmagum tablets were compressed at compression forces of 5, 7.5, 10, 12.5 and 15 kN for each sample (when possible) and the Cafosa tablets were compressed at compression forces of approximately 5, 10, 12.5 and 15 ± 1 kN. Lots with relative standard deviations not exceeding 5% were accepted. The force–displacement curves were plotted, and the different energy/work relations were calculated from the curves with our own software [61].

Cafosa gum base containing caffeine were prepared with a Manesty eccentric tableting machine (BWI Manesty, Liverpool, England) and evaluated by a literature method [61]. The compression tools (punches) have the same geometrical parameters (diameter, shape) as in case Korsch EK0 compression machine. The displacement transducer was fitted over the upper and under the lower punch. The compression was carried out electrically at 45 rpm, at an air temperature of 24 °C and a relative air humidity of 45%. The average mass of the tablets was 0.40 ± 0.02 g. 150 tablets were compressed at ~ 5 and 10 ± 1 kN. Lots with relative standard deviations not exceeding 5% were accepted. The force–displacement curves were plotted, and the different energy/work relations were calculated from the curves by means of F3CCA software. The measurement was repeated 10 times.

All type of tablets was stored in airtight plastic containers at an air temperature of 24 ºC and a relative air humidity of 45%.

The E_1, E_2 and E_3 energies are calculated by the following equations:

$$E_1 = \frac{F_{max} C}{2} - (E_2 + E_3) \quad (3)$$

$$E_2 = \int_A^B F_{upper} ds - E_3 \quad (4)$$

$$E_3 = \int_B^D F_{upper} ds \quad (5)$$

where

F_{max} = maximum force during compressing; C = displacement; F_{upper} = maximum force measured on the upper punch; ds = elemental value of the displacement. The plasticity was calculated with the formula: Pl = E2/ E2 + E3.

In case when the lubricant in the formulations was not enough to avoid the sticking to the punches, teflon layer was used on the surface of the tools (Figure 19).

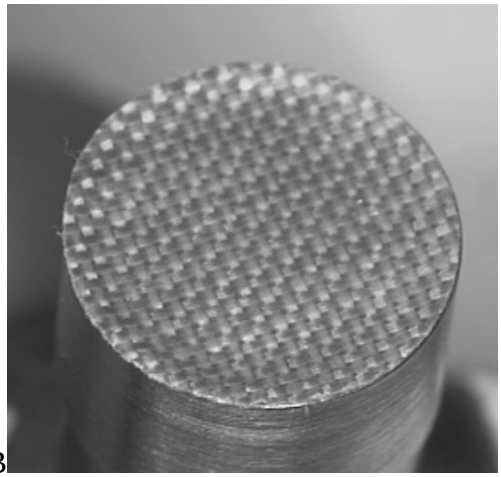
A  B 

Figure 19: Punch without Teflon layer (A) and with Teflon layer (B)

5.2.4 Friability test

The friability of the chewing gum tablets was tested with an Erweka TA 100 friabilator (Erweka GmbH, Heusenstamm, Germany).

5.2.5 Deformability test

The deformability was tested with a modified breaking hardness tester, which was connected to a computer, and special owndeveloped software was applied to record the force–time diagram.

The tester contained a specimen holder and a jowl, and was connected to a computer via an interface. The specimen was located horizontally on a special plate and the jowl moved vertically. Twenty parallel measurements were performed.

The measurement range was 0–200 N, the speed of the stamp was 20 mm/min and the output was 0–5 V. The sensor was a Unicell force-measuring instrument (MIKI), calibrated with the C9B 200 N cell.

5.2.6 Geometrical parameters measurement

The height and the diameter of the tablets were measured with a digital micrometer (Mitutoyo, Tokyo, Japan). The measured and the calculated average values were printed out. Twenty tablets were measured for each sample. The average tablet volume was determined according to the following equation:

$$V = t\left(\frac{d}{2}\right)^2 \pi \qquad (6)$$

where t is a thickness, d is a diameter.

The geometrical parameters were measured at the following sampling times: directly after compression, and after storage times of 1, 4, 8 and 24 h and 2, 3, 4, 5, 6 and 7 days following tablet pressing. (In view of the large number of data, only selected data on the fresh tablet and the data after 1 and 7 days of storage are presented in the tables.)

5.2.7 Surface free energy

The surface free energies of solid materials can be determined by means of contact angle measurements. The contact angles were measured on the same way as described in 4.2.2.4 point and the calculation of surface free energy is decribed in the 3.2 point.

5.2.8 Dissolution tests

Chewing gum tablets are intended not to be swallowed, but to be masticated in the mouth, where the amount of the dissolution medium (saliva) is small. The API must dissolve in the saliva, which is swallowed and reaches the stomach. Accordingly, the dissolution testers that are official in the Pharmacopoeias for conventional tablets or capsules are not applicable in this case. For dissolution tests there are recommendations in the Ph. Eur. [62]

Pharmagum based chewing gum tablets: For the dissolution tests, an Erweka chewing apparatus was used [52]. Each chewing gum sample was chewed with this apparatus

for 10, 20 or 30 min, in the presence of 20 of dissolution medium (purified water), after which the ascorbic acid content of the liquid was determined by spectrometry.

Cafosa based chewing gum tablets: However, a special apparatus for this purpose is described in the Ph.Eur. In the lack of this apparatus, we used a new method for the dissolution testing. “Chewing” was simulated in phosphate buffer (pH=7.0 ± 0.5) in a mortar grinder (type RM200, Retsch GmbH, Haan, Germany).

The chewing gum tablet was placed under the pestle and 50 ml phosphate buffer was poured into the mortar. The apparatus was switched on, and the pressure-induced movement of the pestle led to deformation of the tablet and dissolution of some of the API from the tablet. After various times (5, 10, 15, 20, 25 and 30 min), a 5-ml sample was taken and the dissolution medium was supplemented with 5 ml phosphate buffer up to 50 ml. The caffeine contents of the 5-ml samples were determined by spectrometrically Genesys 10S UV-Vis BIO, Thermo Fisher Scientific, Madison, Wi, USA, λ = 273 nm). The measurement was repeated 3 times.

5.2.9 Microscopic study

The microscopic measurements were performed on the same way as described in 4.2.2.3 point.

5.2.10 Porosity

The true density of the tablets was determined with a Quantachrome helium stereopycnometer (Quantachrome GmbH & Co., Odelzhausen, Germany). The measurement was repeated 5 times. The porosity was calculated according to the following equation:

$$\phi = 1 - \frac{\rho_{apparent}}{\rho_{true}} \qquad (7)$$

5.3 Experimental results of Pharmagum chewing gum tablets

5.3.1 Compressibility tests

The tests on the flow properties of the bulk gum samples showed that Pharmagum C and M could not flow out from either a teflon or a metal funnel, in spite of the agitation of the powder. Pharmagum S displayed good flowability from a teflon funnel on mixing at 25 rpm (Table 22). The API flowed from a teflon funnel on agitation at 25 rpm.

Table 22: Powder rheological test

	Material of the funnel	Flowing time (s)	Agitation speed (r/min)	Angle of slope (o)	Heap volume (ml)	Heap mass (g)
Ascorb. acid	T	12.3	25	33.1	85.6	77.8
Pharmagum C	T/M	-	-	-	-	-
Pharmagum M	T/M	-	-	-	-	-
Pharmagum S	T	7.5	25	26.2	64.4	56.6
S 1	M	12.3	10	29.3	73.4	58.8
S 2	M	10.3	10	29.4	73.9	59.7
S 3	M	10.0	10	29.8	75.0	58.8
S 4	M	7.6	5	26.6	65.6	66.9
S 5	M	7.3	10	27.5	68.2	67.8
S 6	M	7.4	10	28.3	70.6	65.5
S 7	M	8.3	10	29.1	73.0	66.4
S 8	M	8.4	10	28.4	70.9	68.6
S 9	M	8.1	10	28.1	71.5	69.3

T = teflon; M = metal; - = not measurable

The compaction tests on the bulk materials resulted in every case in high elastic recovery. As concerns tablettability, the flowability and compactness can be important properties. Solid bridges formed during compression phase can be broken in the elastic recovery phase. In the tablet compositions, therefore the bulk gum powders were mixed with the other components in different ratios (Table 19).

The data in Table 22 reveal that the powder mixtures could flow from a metal funnel on moderate stirring. Mixture S4, which contains Pharmagum S, exhibited the best flowability to which an agitation speed of only 5 rpm was applied. The flowability properties of the mixtures containing Pharmagum S were generally better. These data are in accordance with the other powder rheological parameters.

The Carr index, calculated from the bulk and tapped densities, indicates that the powder mixtures have excellent compressibility (Table 23). However the mixtures adhered to the punches during tableting, which is an unfavorable property. Fortunately, this could be eliminated through the use of a teflon film on the punch surface.

Table 23: Compressibility of the mixtures

	L.d. g/cm^3	T.d. g/cm^3	C.i. %	Tr.d. g/cm^3
S 1	0.59	0.64	8.72	7.15
S 2	0.58	0.64	10.00	6.93
S 3	0.59	0.64	7.95	6.85
S 4	0.68	0.74	8.46	6.80
S 5	0.71	0.76	5.38	6.74
S 6	0.70	0.74	4.88	6.85
S 7	0.70	0.73	4.61	6.69
S 8	0.70	0.75	5.90	6.75
S 9	0.72	0.77	6.41	6.51

L.d.=loose density; T.d.=tapped density; Hf=Hausner's factor;
C.i.=Carr's index; Tr.d.=true density

The different compression parameters for the mixtures were calculated at different compression forces (effective work = E_2, elastic recovery = E_3, plasticity = P_l). For gums, elasticity is the most important property. After the compression maximum, when the upper punch starts to move upwards, elastic materials display some recovery. This phenomena only comes from the gum base. The elastic properties of the API and other ingredients do not have such high effect which causes any changes of the elastic behavior of the gum bases [63].

The friability of the tablets was less than 0.1 % in all cases, and they met the requirements of Ph.Eur. but this is expected from a gum tablet.

5.3.2 Chewability test

In the case of a chewing tablets the chewability is an important requirement. The test is not unique [64]. We used for this an instrumented breaking tester (5.2.5.). The chewing tablets differ from the conventional tablets because after crushing the tablets did not break completely. The deformation curves during loading demonstrate elastic deformation with a rather high slope (Figure 20 and 21).

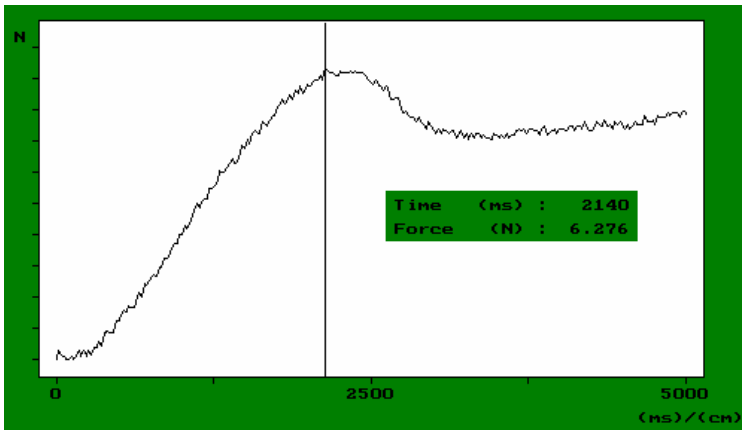


Figure 20: Deformation curve of a chewing tablet

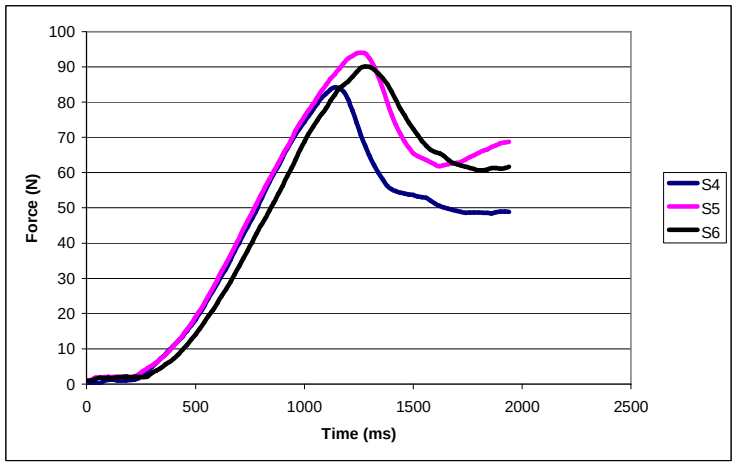
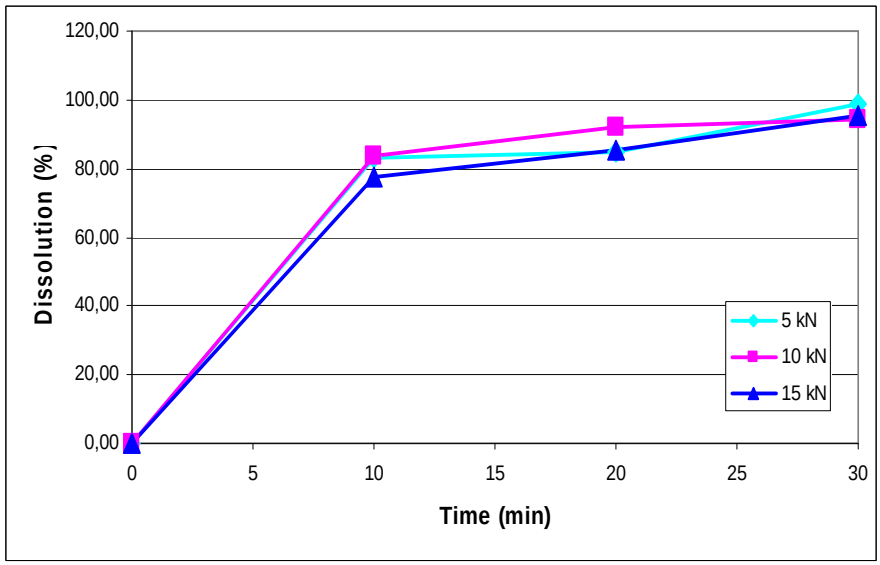


Figure 21: Deformation curves during loading (samples S4, S5 and S6)

After a maximum, the force decreased, but the tablet did not break into small pieces; only deformation was observed, with some cracks. Increase of the pressure did not cause any significant changes in the breaking process.

5.3.3 Dissolution test

During the dissolution investigation the 5, 10, and 15 kN, compressed samples were tested. The results show that the dissolution of ascorbic acid did not depend on the compression force (Figure 22). In all cases, 90% of the API dissolved in the first 10 min, and after chewing for 30 min the whole amount had dissolved.



n=6, SD: NMT ±5 %

Figure 22: Dissolution profile of sample S5

The dissolution results show that applying high compression force is not necessary during the manufacturing process.

5.4 Experimental results of Cafosa chewing gum tablets

5.4.1 Investigation of elastic recovery of tablets

The objective of this work was to study the elastic recovery of one of the gum base for direct compression at room temperature by a direct compression technique. The elastic recovery mentioned was examined by thickness, diameter and hardness measurement.

Because of the elastic recovery various phenomena can be observed after compression in the structure of tablets, which change the volume and the porosity. The driving force for the elastic recovery the bonding forces (i.e. Van der Waals forces, solid bridges, electrostatic forces, hydrogen bonds, etc.) and the elastic energy (stress) stored in the particles during densification. The stored stress can resolve and increase the tablet volume

and porosity. However the bonding forces which are working with the stress simultaneously decrease the tablet volume and porosity. The elastic recovery can be define as

$$ER = \frac{V_t - V_{\min}}{V_{\min}} \qquad (8)$$

where V_{min} is the minimum volume of the tablet under load and V_t the volume of the tablet at different times t after compressing. It gives information on the remaining elasticity of the materials [65]. The degree of the elastic recovery depends on the property of the materials. It starts immadiatelly after the compression phase and is finished dependent on the material after several days.

Generally accepts the definition of tablet hardness as being the force required to break a tablet in a diametrical compression test. To measure the force required to break a tablet we obtained the tensile strength of the tablet as the following form:

$$\sigma_x = \frac{2 \cdot F}{\pi \cdot d \cdot t} \qquad (9)$$

where F is a force necessary to cause fracture, d is the diameter and t is the thickness of the tablet [66].

Moisture content determination is an important preformulation test before tableting. It influences the flow properties of granules or powders, which must flow freely into the die cavity during tableting. The Hausner factor and Carr's index are calculated from the poured and tapped densities of the powder. A Hausner factor of less than 1.25 (equivalent to a Carr's index of 20%) indicates good flow; when it is greater than 1.5 (a Carr's index of 33%), it indicates poor flow. The moisture content of the gum powder was rather low (0.3%), and the flowability was very good (flow time: 8.4 s). This means that the gum powder could flow freely in the die during the compression. The values of the Hausner factor (1.102) and Carr's (Carri = 9.23%) showed that the arrangement of the particles was also good [67].

It is clear from the tablet volume changes (Figure 23) that the application of higher compression forces imposes too much on the gum stress during storage. When the compression force is higher than a certain limit, the gum loses its elasticity. As noted above, the driving forces for the final stage of tablet formation are the bonding forces and the stress stored in the gum. The gum strives to release the stored stress by increasing the volume of the tablet, while the bonding forces decrease the volume. This phenomenon is very well observable at pressure force of 5, 10 and 12.5 kN (Figure 23). At 15 kN, the gum loses its elasticity and thus the main driving forces in the final formation stage are the bonding forces.

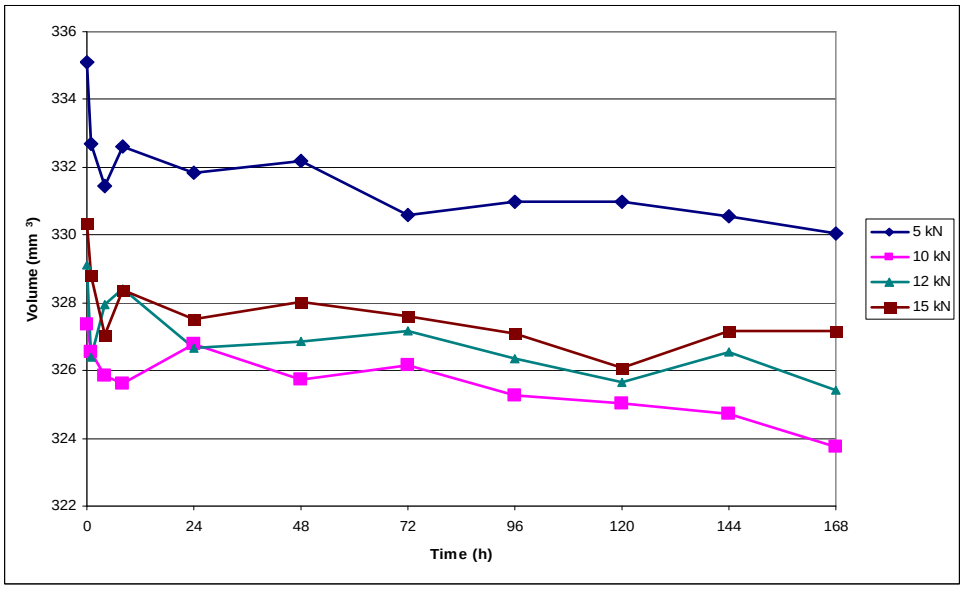


Figure 23: Volume changes of the comprimates

The geometrical parameters of the tablets can be seen in Table 24. The post-compressional geometrical changes in the tablets must be taken into consideration, especially in blister packaging. In this case, the geometrical parameters determine the depth and diameter of the blister cavity.

Table 24: Data of geometrical parameters of tablets

Compression force (kN)	Diameter* (mm)			Thickness* (mm)		
	Fresh	1 day	7 day	Fresh	1 day	7 day
5	10.030	10.010	9.997	4.242	4.217	4.206
10	10.041	10.021	10.005	4.136	4.142	4.120
12.5	10.044	10.027	10.013	4.155	4.139	4.135
15	10.044	10.025	10.021	4.172	4.151	4.150

*SD<±5%

It can be concluded from the data that both the diameter and the thickness of the tablets decreased continuously during 7 days of storage, but the degree of contraction differed. This is reflected in the volume changes.

The testing of the mechanical strength of the tablets is very important because they must remain intact during handling, i.e. packaging and transportation. The mechanical characterization of different materials and preparations is investigated in different scientific fields [68–70]. In our work the breaking strength of the preparation was studied. The data are summarized in Table 25. It can be seen that the greatest strengths were measured in every case at a compression force of 5 kN, and the breaking strength increased during storage. With increase of the compression force, the tablets exhibited lower strength and the increases in strength during storage were more moderate. It is noteworthy that the tablet strengths at 12.5 and 15 kN were almost the same in every situation.

Table 25: Tablet strength data

Compression force (kN)	Breaking strength* (N)			Tensile strength* (mPa)		
	Fresh	1 day	7 day	Fresh	1 day	7 day
5	60.36	69.80	85.29	0.9036	1.0532	1.2919
10	58.60	60.83	74.32	0.8986	0.9332	1.1484
12.5	55.19	61.14	75.84	0.8423	0.9382	1.1667
15	55.31	61.29	76.73	0.8408	0.9380	1.1752

*SD<±5%

Investigation of the breaking hardness of direct compressed chewing gum tablets is important not only for determination of their general parameters, but also from the aspect of the user's satisfaction. The preparations should provide adequate strength and ease of processability, and the consumer should find them pleasant and easy to use. It is not necessary to apply an extremely high compression force to prepare a good chewing gum tablets, because this will not cause any significant difference in quality wich shows great similarity with the previous results [63].

Determination of the breaking (deformation) force (Figure 20 and 21) is important because it is necessary to know what energy is needed to break the chewing gum tablet. If the compression force is too high, the gum will not acceptable by the patient, but if it is too low, the tablet will not be formed during compression.

The breaking process, which reflects the elastic/plastic behaviour of the tablet after compression, occurred in accordance with the volume changes. With increase of the compression force, the degree of elasticity decreased (Figures 24 – 26). The action of the compression force can be observed very well in the case of fresh tablets (Figure 24). The degree of elastic recovery was highest for tablets compressed at 5 kN, but the linear section of the deformation curve was not too long and soft-viscous (viscoelastic) deformation occurred.

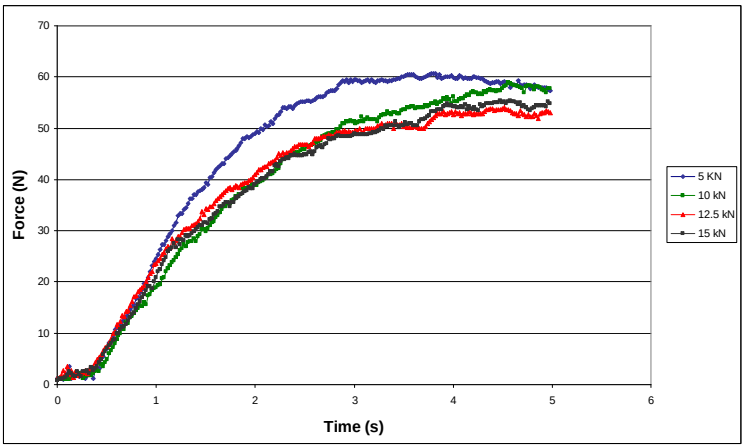


Figure 24: Breaking process of fresh tablets

After storage for 1 day, the tablet compressed at 5 kN exhibited a higher elastic nature because the macromolecules underwent rearrangement within 1 day (Figure 25).

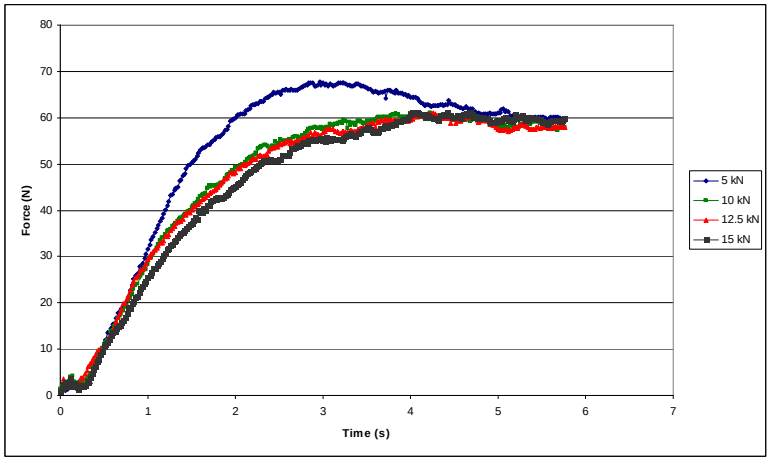


Figure 25: Breaking process of tablets after 1 day

The deformation profiles of the other tablets did not reveal a significant change. Practically no difference could be observed between the curves. Despite the increase in the deformation maximum of the tablet compressed at 5 kN, the shape of the deformation curves did not change during storage (Figure 26).

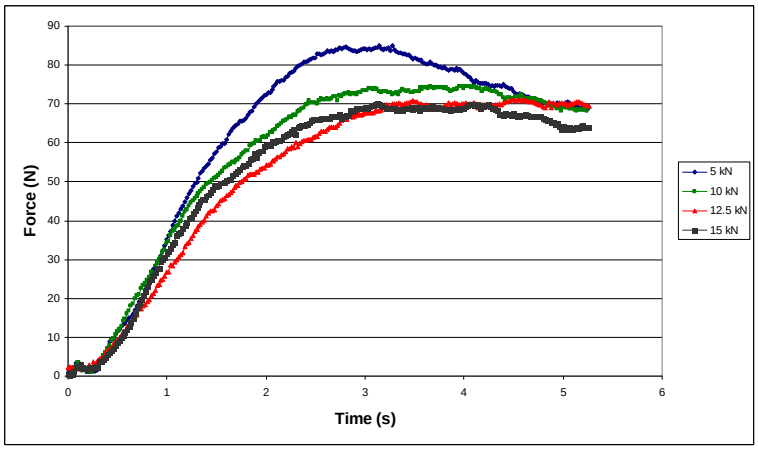


Figure 26: Breaking process of tablets after 7 days

5.4.2 Formulation study of Cafosa-based chewing gum and its applicability as an oral drug delivery system

5.4.2.1 Formulation tests

In the preformulation tests, the morphology of the gum base was revealed by the SEM photo (Figure 27) to involve irregular particles. With increasing magnification (Figuress 28-31), these were seen to be aggregated, formed from crystalline and noncrystalline smaller particles. The small crystals displayed a needle habit (Figure 30 and 31) and the larger ones were intimate column crystals (Figure 29 and 30).

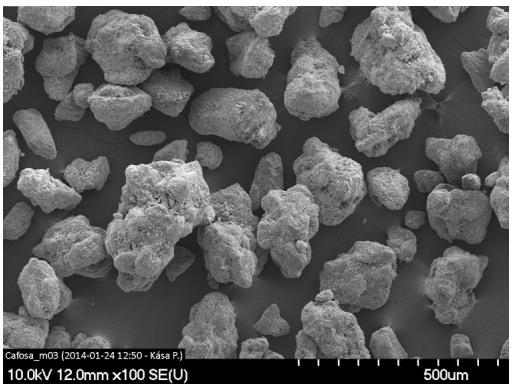


Figure 27: Particles of gum base (SEM) Magn. 100x

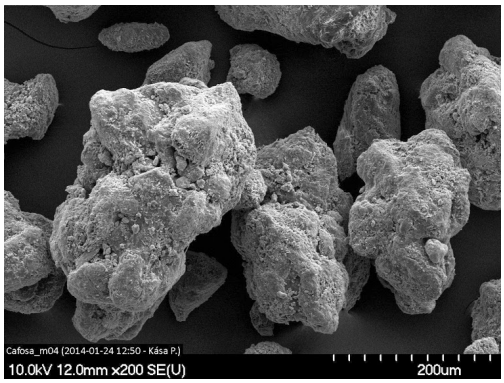


Figure 28: Particles of gum base (SEM) Magn. 200x

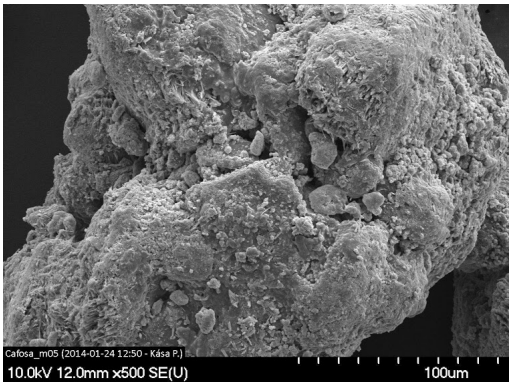


Figure *29: Particle of gum base (SEM) Magn. 500x*

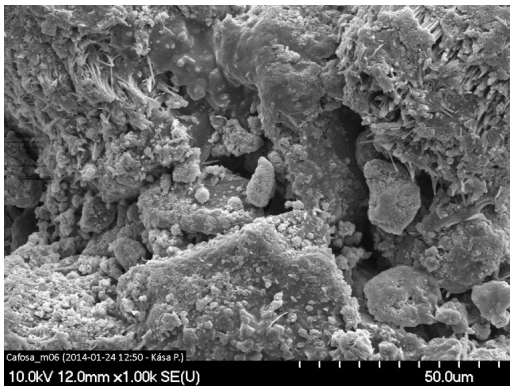


Figure 30: Particle of gum base (SEM) Magn. 1000x

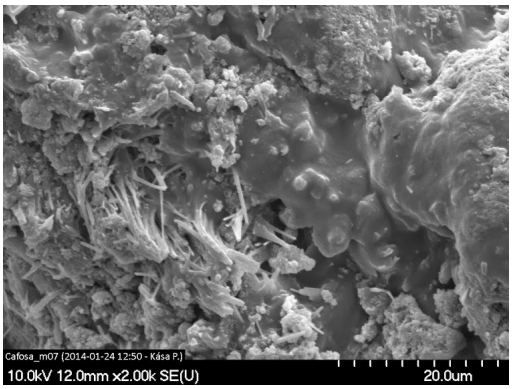


Figure 31: Particle of gum base (SEM) Magn. 2000x

Caffeine consisted of particles of different sizes and shapes (Figure 32). At higher magnification, small needle crystals were observed to be agglomerated in each larger particle (Figure 33-35).

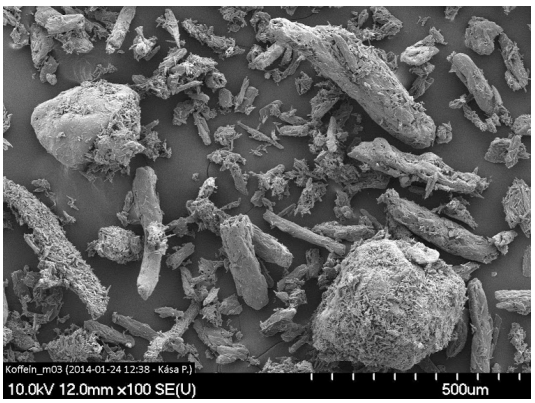


Figure 32: Particles of caffeine (SEM) Magn. 100x

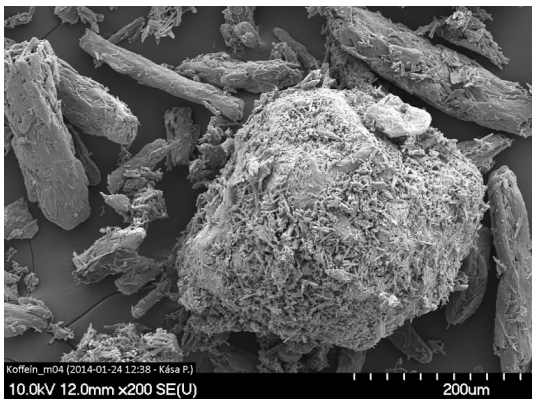


Figure 33: Particles of caffeine (SEM) Magn. 200x

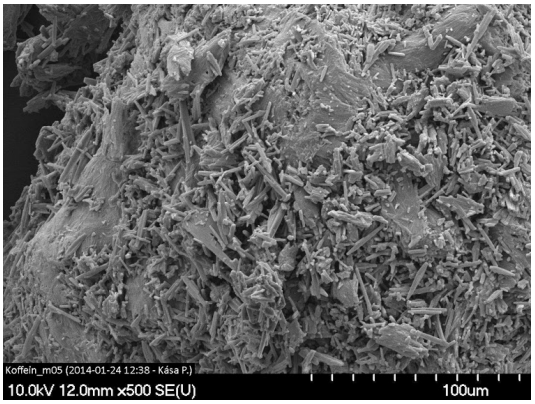


Figure 34: Needle crystals of caffeine (SEM) Magn. 500x

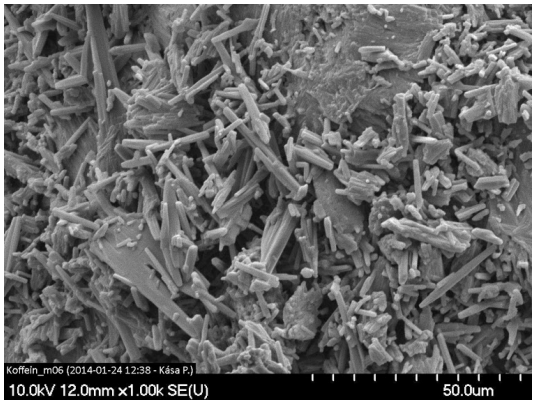


Figure 35: Needle crystals of caffeine (SEM) Magn. 1000x

The preformulation data relating to the surface free energy are displayed in the Table 26. The total free energy of caffeine was the highest, almost double that of the bulk Cafosa sample. The two types of magnesium stearate decreased these values a little, but there was basically no difference between the actions of the two magnesium stearates. The total free energy of the caffeine-Cafosa mixture (Cafcof) was lower than that of caffeine. It is interesting that the magnesium stearate with the smaller specific surface area (Cafcof-U) did not influence the free energy, which was similar to that for the Cafcof mixture, whereas the magnesium stearate with high specific surface area (Cafcof-PG) decreased the free energy to a higher degree.

Table 26: Surface free energy of samples

	Caffeine	**Cafosa* gum**	**Cafcof****	**Cafosa-U^{+}**	**Cafosa-PG'**	**Cafcof-U^{++}**	**Cafcof-PG''**
γ^{total} (mN/m)	78.15	39.00	45.59	35.50	34.25	43.94	35.01
γ^{D}(mN/m)	42.33	32.99	34.83	29.50	29.90	30.58	27.78
γ^{P}(mN/m)	35.82	6.02	10.75	5.61	4.34	13.35	7.23
Polarity (%)	45.83	15.43	23.58	15.80	12.44	30.38	20.65

***gum powder, ****gum powder with caffeine,*
$^{+}$gum powder with magnesium stearate Undesa, $^{++}$gum powder with caffeine and magnesium stearate Undesa,
'gum powder with magnesium stearate Peter Greven, '' gum powder with caffeine and magnesium stearate Peter Greven

During the preformulation compression the gum base product stuck strongly to the punches, and particularly the lower punch. A Teflon strip was therefore applied to the surface of the punches, and a lubricant (magnesium stearate) was necessary in the tablet composition. Two types of magnesium stearate were applied, one with a low, and one with a higher specific surface area. The compressional parameters of the tablets are listed in Table 27.

The data of the Table demonstrate that the elastic recovery ($E3_W$) increased on increase of the compression force from ~5 kN to ~ 10 kN, but not greatly so in the case of the magnesium stearate with the higher specific surface area (Cafcof-PG). On the application of the magnesium stearate with the smaller specific surface area, $E3_W$ was much higher (Cafcof-U). The actions of the two types of magnesium stearate are displayed in the other parameters of the tablets during compression.

Table 27: Compressional parameters of tablets

Cafcof-PG

tabl.	UF (kN)	LF	thicknessmm)	EjF (kN)	Uw (Nm)	Lw (Nm)	Ejw (Nm)	Frw (Nm)	E3w (Nm)
1	4.33	1.43	6.26	0.36	4.23	1.44	0.05	2.79	2.55
2	4.24	1.3	6.27	0.33	2.63	1.05	0.08	1.59	1.37
3	4.33	1.6	6.61	0.36	4.39	1.53	0.01	2.85	2.83
4	4.44	1.5	6.2	0.33	2.37	0.8	0.03	1.57	0.95
5	4.47	1.5	6.23	0.33	2.49	0.85	0.01	1.67	1.08
Avg	4.36	1.48	6.31	0.34	3.22	1.14	0.04	2.09	1.76
SD	0.094	0.142	0.17	0.018	1	0.33	0.03	0.67	0.87

Cafcof-PG

tabl.	UF (kN)	LF	Thickness(mm)	EjF (kN)	Uw (Nm)	Lw (Nm)	Ejw (Nm)	Frw (Nm)	E3w (Nm)
1	8.92	1.98	5.82	0.38	4.71	1.45	0.15	3.26	2.63
2	9.11	1.95	5.82	0.43	4.75	1.32	0.12	3.43	2.42
3	9.98	2.36	5.88	0.66	5.76	1.82	0.58	3.94	4.64
4	9.77	2.7	5.81	0.61	8.9	3.7	0.55	5.2	5.42
5	10	2.44	5.84	0.87	11.72	5.21	2.19	6.51	9.72
Avg	9.56	2.29	5.84	0.58	7.17	2.7	0.72	4.47	4.97
SD	0.51	0.32	0.03	1.96	3.07	1.7	0.85	1.37	2.95

Cafcof-U

tabl.	UF (kN)	LF	Thickness(mm)	EjF (kN)	Uw (Nm)	Lw (Nm)	Ejw (Nm)	Frw (Nm)	E3w (Nm)
1	4.89	1.95	6.47	1.03	24.19	13.47	4.12	10.73	21.33
2	4.7	1.74	6.52	0.9	22.28	11.32	2.98	10.95	18.4
3	4.78	1.74	6.23	0.9	14.01	6.17	2.61	7.84	12.68
4	4.63	1.56	6.28	0.8	19.12	9.12	2.73	10	10.94
5	5.28	1.8	6.49	0.92	24.62	12.85	2.62	11.76	18.74
Avg	4.86	1.76	6.4	0.91	20.84	10.59	3.01	10.26	16.42
SD	0.26	0.14	0.13	0.08	4.39	2.99	0.64	1.49	4.4

Cafcof-U

tabl.	UF (kN)	LF	Thickness(mm)	EjF (kN)	Uw (Nm)	Lw (Nm)	Ejw (Nm)	Frw (Nm)	E3w (Nm)
1	10.50	3.54	6.03	0.84	23.03	9.94	2.87	13.09	20.46
2	10.10	3.28	5.88	0.85	22.72	7.02	2.59	15.70	19.14
3	10.20	3.10	5.94	0.72	28.70	9.06	2.26	19.65	19.75
4	9.80	3.09	6.17	0.90	28.91	11.17	2.54	17.74	23.09
5	8.90	2.81	6.17	0.90	23.41	11.17	2.54	17.74	23.09
Avg	9.90	3.16	6.04	0.84	25.35	9.67	2.56	16.78	21.10
SD	0.61	0.27	0.13	0.07	3.16	1.72	0.21	2.49	1.87

UF=Upper force; LF=Lower force; EjF=Ejection force; Uw=Upper work; Lw=Lower work; Ejw=Ejection work;

The sticking (to the punches and to the die) mentioned on the previous page can be observed on the force-time and on the force-distance diagrams, reported by the software of Manesty compression machine. (Figure 36 and 37)

High difference can be seen between the the maximum pressure force of the upper and lower punch and the residual force is significant on the lower punch force-time diagram (Figure 36). Furthermore, the high degree of sticking can be observed on the force-distance curve of lower punch (Figure 37).

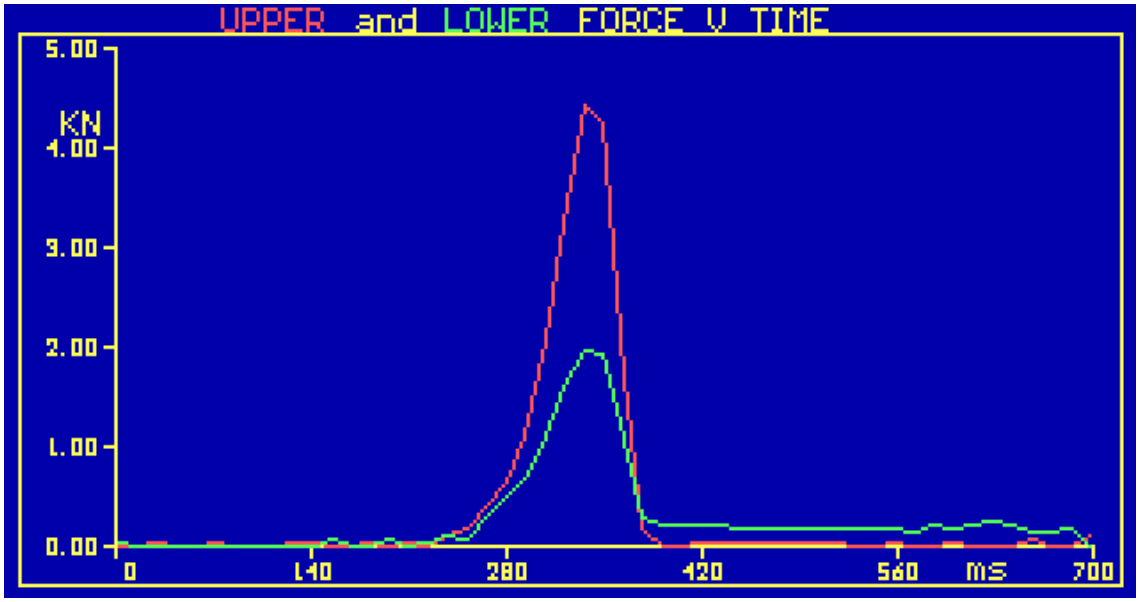


Figure 36: Force-time diagram

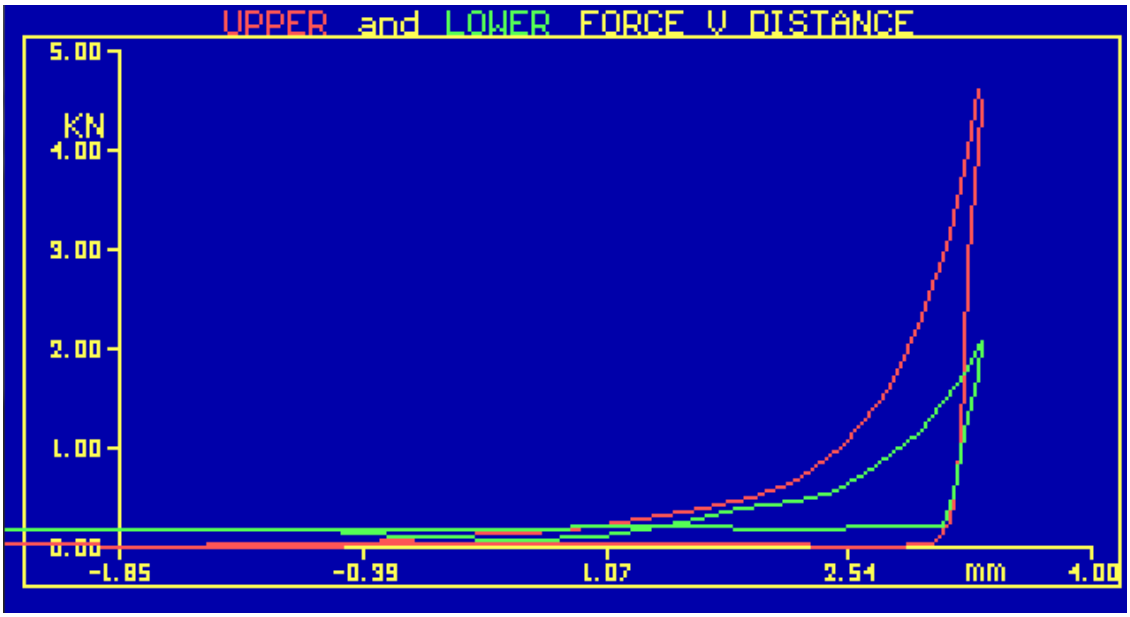


Figure 37: Force-distance/displacement diagram

5.4.2.2 Dissolution tests

Dissolution of the API from a medicated chewing gum tablet is very important. The results of our tests showed that the total amount of caffeine was dissolved in a short time (Table 28) and neither the type of the magnesium stearate nor the magnitude of the compression force caused any appreciable difference in the dissolution.

Table 28: Dissolution of caffeine from tablets

	Cafcof tablet							
	Undesa				**Peter Greven**			
	5 kN		**10 kN**		**5 kN**		**10 kN**	
Time (min)	**Mean (%)**	***RSD (%)***	**Mean (%)**	***RSD (%)***	**Mean (%)**	***RSD (%)***	**Mean (%)**	***RSD (%)***
5	71		70		68		67	
		1.3		*2.3*		*0.5*		*2.0*
10	78		77		75		75	
		1.2		*1.7*		*0.6*		*1.2*
15	86		86		82		82	
		1.6		*1.7*		*0.2*		*0.5*
20	94		94		89		89	
		0.4		*2.0*		*0.1*		*0.6*
25	100		101		96		97	
		1.4		*2.3*		*0.1*		*1.2*
30	100		102		96		97	
		1.2		*3.2*		*0.8*		*1.3*

This result was rather surprising because a considerable difference in elastic recovery was observed between the tablets prepared with the different forms of magnesium stearate. In this phase the binding can break more easily, which influences the porosity of the texture. Table 29 reveals that neither the apparent density nor the true density of the tablets differed significantly and each of the tablets had the same high porosity.

Table 29: Density and porosity of tablets

Type of magnesium stearate in tablet	**Apparent density (g/cm^3)**		**True density (g/cm^3)**		**Porosity**	
	5 kN	**10 kN**	**5 kN**	**10 kN**	**5 kN**	**10 kN**
Undesa	0.1372 (s=± 0.0004)	0.1369 (s=±0.0013)	0.9637 (s=±0.0045)	0.9591 (s=±0.0056)	0.86	0.86
Peter Greven	0.1365 (s=±0.0005)	0.1359 (s=±0.0005)	0.9728 (s=±0.0055)	0.9678 (s=±0.0047)	0.86	0.86

5.4.3 Evaluation of results

In the present work, we investigated the morphology, surface free energy and compactibility of Cafosa gum, a directly compressible gum composition, as a new vehicle for use as a drug delivery system.

The morphology study showed that the product consists of irregularly shaped, aggregated particles, formed from crystalline and noncrystalline smaller particles. The results of surface free energy determinations clearly indicated that Cafosa is a co-processed product with rather low polarity.

The API (caffeine) also consisted of irregular particles, SEM demonstrating small needle crystals agglomerated into larger particles. This morphology does not facilitate the flowability of the gum base, and the die was filled unevenly during compression. Magnesium stearate applied as an additive promoted the flowability somewhat, but not perfectly.

The surface free energy of caffeine and the polarity also proved to be rather high. A high polarity is generally very good as concerns the dissolution of an API from a tablet. However, the gum base and the lubricant yielded low values. There was seen to be a difference in the effects of the two types of magnesium stearate. In the event of higher surface area (Cafosa-PG) the polarity was lower.

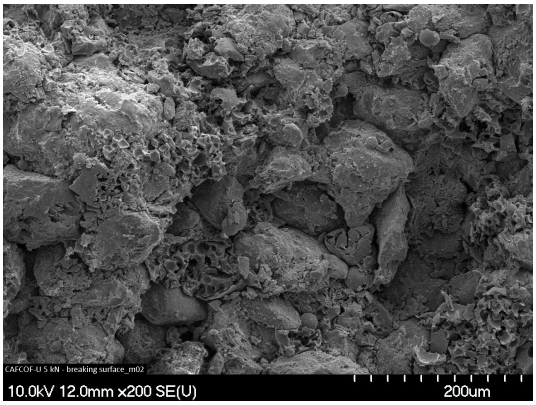
As regards the compressional parameters, it was concluded that an increase of force increased the values, thereby worsening the compressibility and compactibility of the tablet.

At the same compression force, the elastic recovery and friction work were much higher in the case of the magnesium stearate with lower specific surface area (Cafcof-U) than for Cafcof-PG. The reason lies in the polarity. The Cafcof-U powder mixture was much more hydrophilic than that of Cafcof-PG. Since the magnesium stearate in Cafosa-PG has higher specific surface area, the distribution of the smaller particles between the particles of the tablet composition was better, ensuring improved lubrication. The distribution of the magnesium stearate particles with lower specific surface area was not so good, and unevenness and more binding could form in the die during loading, and in the elastic recovery phase the friction work was high because of the considerable friction between the side of the tablet and the die wall. It is interesting, that in contrast, the comprssion force had practically no influence on the ejection work. This may be explained by the elasticity, which may be so high at higher compression force that the tablet almost “jumps” from the die.

These results suggested that will differences would be observed between the tablets in the dissolution and the release profile. Unexpectedly, however no difference was seen

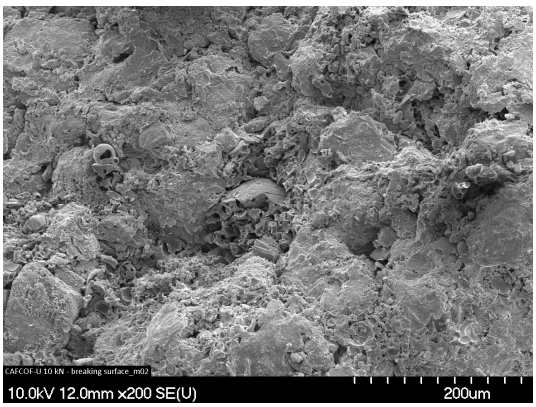
between the dissolution from the tablets, independently of the compression force or the type of magnesium stearate (Table 28).

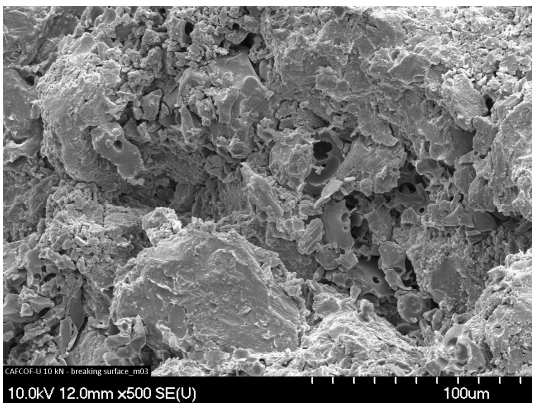
As mentioned above, the elastic recovery influences the formation of the texture of the tablet, the binding breaks and the porosity is rather high. This is in accord with the results of the texture investigation. Figures 38-41 demonstrate that there is practically no difference in the texture of the tablets independently of the compression force and the type of lubricant. A matrix system can be seen in every case, with numerous pores formed inside the particles of the gum base, and with many narrow crevices and shattered small particles among the different larger particles. The sponge-like matrix can be observed especially at higher magnification (500x). The porosity is concordant with these observations (Table 29), which explains why there was no difference in dissolution rate.



Magn. 200x *Magn. 500x*

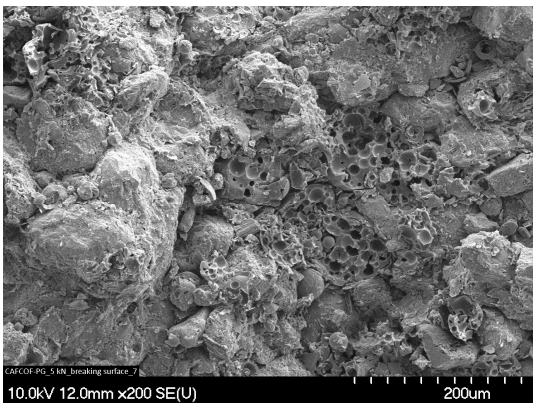
Figure 38: Breaking surface of Cafcof-U tablet
Compression force 5 kN

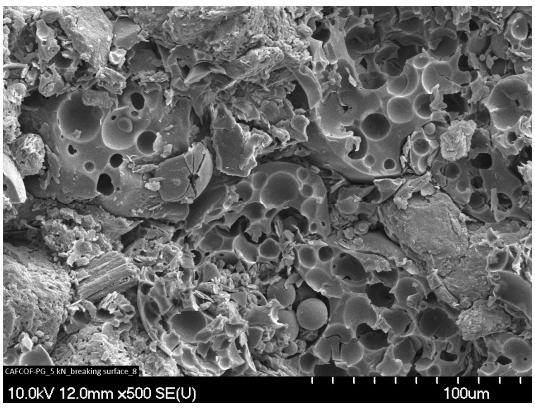




Magn. 200x *Magn. 500x*

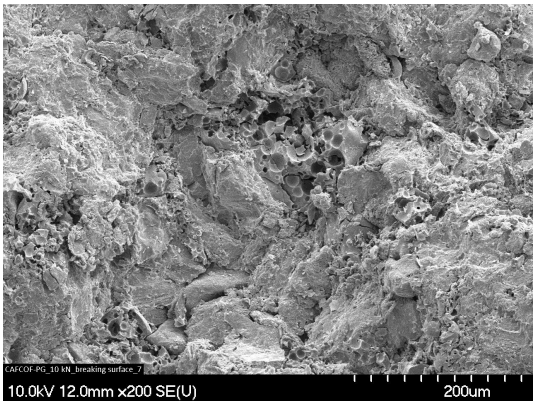
Figure 39: Breaking surface of Cafcof-U tablet
Compression force 10 kN

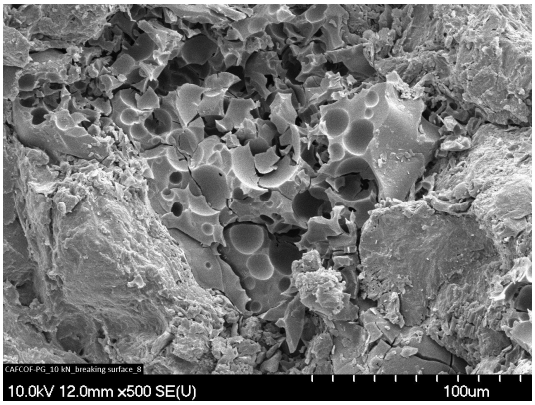




Magn. 200x *Magn. 500x*

Figure 40: Breaking surface of Cafcof-PG tablet
Compression force 5 kN





Magn. 200x ***Magn. 500x***

Figure 41: Breaking surface of Cafcof-PG tablet
Compression force 10 kN

As concerns the fitting of the dissolution profile, it has been reported that the Korsmeyer-Peppas model can be used to analyze data on drug release from polymer matrix [71]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (10)$$

where M_t/M_∞ is the fraction of drug released at time *t*, *k* is the rate constant and *n* is the release exponent. We found that the release of caffein obeyed the Korsmeyer-Peppas equation with a very high correlation coefficient. The results of fitting are presented in Table 30.

Table 30: Dissolution parameters according to the Korsmeyer-Peppas model

Sample	k	n	R^2
Cafcof-U 5 kN	71.4206	0.007	0.9998
Cafcof-U 10 kN	67.1431	0.032	0.9999
Cafcof-PG 5 kN	70.4679	0.007	1.0000
Cafcof-PG 10 kN	67.825	0.019	1.0000

6 CONCLUSIONS, PRACTICAL USEFULNESS

Based on the introduced manufacturing problems and the measurements results (Section I) it is suggested to investigate during the process development what kind of magnesium stearate (with lower or higher surface area) is preferable to avoid the difficulties arising from the lubricant during further production.

It can be stated that the manufacturing problems have been encountered when using the magnesium stearate with high specific surface area therefore it is suggested to start the composition development using the magnesium stearate with smaller specific surface area.

It can be stated that using the correct type of magnesium stearate might helps to increase the similarity between the dissolution profiles of the original and the generic products.

It can be concluded that the two types of magnesium stearate were distributed to different extents on the surface of the particles. The magnesium stearate with higher specific surface area was more polar with higher adhesion work, and it was able to create a very thin homogeneous layer on the surface of the particles. In the case of the magnesium stearate with lower specific surface area, enrichment was observed on the surface of the particles, decreasing the free energy. It is clear that the surface free energy and polarity of the materials influence the choice of the suitable magnesium stearate (low or high specific surface). It can be stated that the blending speed should not be too high because at longer mixing time the free energy of the other component will be dominant (see Figure 18). [72]

Energy-dispersive X-ray fluorescence analysis was successfully used for the in-process determination of the distribution of magnesium stearate on the surface of the particles. The measurement was rapid and did not require any special sample preparation.

The powder rheological parameters, and especially the flowability, conclude that Pharmagum C and M are not suitable for the preparation of direct-compressed chewing gum tablets. Pharmagum S increased the powder rheological properties and the compressibility, but all of the compositions resulted in suitable tablets at a compression force of 5 kN. The physical parameters and the dissolution rate from these tablets were very good, so that increase of the compression force was unnecessary. It can be stated that chewing gum is an alternative drug delivery system with several advantages especially for kids and geriatric patients who experience difficulties swallowing the traditional oral solid dosage forms, and it is possible to prepare by direct compression, which is economic preparation procedure. [63]

It can be concluded that the flowability of Cafosa gum powder is very good and its direct compression is possible. The post-compressional tests demonstrated that a compression force of 5 kN is sufficient for preparation. The elastic behaviour of these tablets

is the best from the aspect of the chewability. The advantage of these tablets is that the patient can chew such a tablet easily and the drug can be released in the mouth. The drug can then be swallowed and pass into the stomach or intestine or may be absorbed through the mucosa and a rapid drug effect will be obtained. [73]

Overall, we concluded that Cafosa gum base is a co-processed product that is compressible in spite of its elasticity, but during loading the tablets stick strongly to the punches and there is considerable friction with the die wall. The use of lubricants and suitable (e.g. Teflon-coated) punches therefore is necessary inon a production scale. The compressional parameters were better when magnesium stearate with higher specific surface area was used. The *in vitro* dissolution test employed showed that the release of caffeine in response to the mechanical action was rapid and quantitative and the profile obeyed the Korsmeyer-Peppas equation (which is valid in the case of matrix systems) very well. The type of magnesium stearate and the compression force applied did not influence the dissolution.

One aim of modern pharmaceutical technology is the development of different matrix tablets [74] with good bioavailability. The study confirmed that directly compressible gum may be used to prepare matrix tablets for oral transmucosal administration.

REFERENCES

[1] Kottke MK, Rudnic EM.: Tablet dosage forms. In: Banker GS, Rhodes ChT, editors. Modern pharmaceutics. New York (NY): Marcel Dekker Inc, 292–294, 2002

[2] Aulton ME.: Aulton's pharmaceutics, the desing and manufacture of medicines. 3rd ed. Edinburgh: Churchill Livingstone, Elsevier, 452–454, 2007

[3] Jinjiang Li , Yongmei Wu.: Lubricants in Pharmaceutical Solid Dosage Forms Lubricants, 2:21-43, 2014

[4] Peck G.E., Baley G.: Tablet formulation and design. In: Lieberman HA, Lachman L, editors. Pharmaceutical dosage forms: tablets. New York (NY): Marcel Dekker Inc, 61–98, 1980

[5] Imfeld T.: Chewing gum - facts and fiction: A review of gum-chewing and oral health. Crit. Rev. Oral. Biol. Med., [PubMed: 10759416], 10:405–419, 1999

[6] 5th ed. Strasbourg, France: European Directorate for the Quality of Medicines, Council of Europe; General Monograph on Dosage Forms: Chewing Gums, Medicated, European Pharmacopoeia, 601, 2005

[7] 5th ed. Suppl. 5.2. Strasbourg, France: European Directorate for the Quality of Medicines, Council of Europe; General Monograph 2.9.25: Dissolution Test for Medicated Chewing Gums, European Pharmacopoeia, 3116–3117, 2005

[8] Raymon C. R., Paul J. S., Marian E. Q.: Handbook of Pharmaceutical Excipients. Seventh Edition, 457-462, 2012

[9] Pintye-Hódi K., Tóth I., Kata M.: Investigation of the formation of magnesium stearate film by energy dispersive X-ray microanalysis. Pharmaceutica Acta Helvetiae, 56:320–324, 1981

[10] Szalay A., Pintye-Hódi K., Joó K., Erős I.: Study of distribution of magnesium stearate with an energy dispersive X-ray fluorescence analyser. Pharmaceutical Industries, 66:221–223, 2004

[11] Roblot-Treupel L., Puisieux F.: Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. International Journal of Pharmaceutics, 31:131–136, 1986

[12] Miller T.A., York P.: Pharmaceutical tablet lubrication. International Journal of Pharmaceutics, 41:1–19, 1988

[13] Buckton G., Darcy P.: The influence of additives on the recrystallisation of amorphous spray dried lactose. International Journal of Pharmaceutics, 121:81–87, 1995

[14] Podczeck F.: Particle–particle adhesion in pharmaceutical powder handling. London: Imperial College Press, 29–34, 1998

[15] Buckton G.: Characterisation of small changes in the physical properties of powders of significance for dry powder inhaler formulations. Advanced Drug Delivery Reviews, 26:17–27, 1997

[16] Planinšek O., Trojak A., Srčič S.: The dispersive component of the surface free energy of powders assessed using inverse gas chromatography and contact angle measurements. International Journal of Pharmaceutics, 221:211–217, 2001

[17] Bajdik J., Fehér M., Pintye-Hódi K.: Effect of plasticizer on surface of free films prepared from aqueous solutions of salts of cationic polymers with different plasticizers. Applied Surface Science, 253:7303–7308, 2007

[18] Wu S., Brzozowski K.J.: Surface free energy and polarity of organic pigments. Journal of Colloidand Interface Science, 37:686–690, 1971

[19] Rowe R.C.: Binder-substrate interactions in granulation: a theoretical approach based on surface freeenergy and polarity. International Journal of Pharmaceutics, 52:149–154, 1989

[20] Reimer L.: Scanning electron microscopy, physics of image formation and microanalysis. Heidelberg: Springer-Verlag, 394–395, 1985

[21] Brouwer P.: Theory of XRF. Almelo: PANalytical B.V., 14–19, 56–58, 2003

[22] Anonymous: A concise history of chewing gum. Dent Stud Magazine, 47(9):626–641, Jun. 1969

[23] Hendrickson R.: The great American chewing gum book. 1st ed. Radnor (PA): Clinton Book Company, 1976

[24] Cloys L.A., Christen A.G., Christen J.A.: The development and history of chewing gum. Bull. Hist. Dent., 40(2):57–65, Oct. 1992

[25] Growth through research: a history of Schering-Plough Corporation [brochure]. Kenilworth: Schering-Plough Corporation, 3, 1992

[26] Anonymous: History of chewing gum, Adams,Division of Pfizer, Morris Plains, NJ, U. S. A.(http://www.prodhelp.com/historyofgum.shtml), 2001

[27] Anonymous: How chewing gum began, Wm. Wrigley Jr. Company, Chicago, IL, U. S. A. (http://www.wrigley.com/wrigley/kids/gumstory.pdf), 2002

[28] Christrup L.L., Rasmussen S.N., Rassing M.R.: Chewing gum as a drug delivery system. Farm. Sci. Ed.: 16:44–47, 1988

[29] Rassing M.R.: Specialized oral mucosal drug delivery systems: chewing gum. In: Rathbone MJ, editor. Oral mucosal drug delivery. New York: Marcel Dekker Inc. ,319–358, Oct. 1992

[30] 5th ed. Strasbourg, France: European Directorate for the Quality of Medicines, Council of Europe; General Monograph on Dosage Forms: Chewing Gums, Medicated, European Pharmacopoeia, 601, 2005

[31] 5th ed. Suppl. 5.2. Strasbourg, France: European Directorate for the Quality of Medicines, Council of Europe; General Monograph 2.9.25: Dissolution Test for Medicated Chewing Gums, European Pharmacopoeia, 3116–3117, 2005

[32] 6th ed. Suppl. 5.2. Strasbourg, France: European Directorate for the Quality of Medicines, Council of Europe; General Monograph 2.9.25: Dissolution Test for Medicated Chewing Gums, European Pharmacopoeia, 304–306, 2008

[33] Jacobsen J., Christrup L.L., Jensen N.H.: Medicated chewing gum: Pros and cons. Am. J. Drug. Deliv., 2:75–88, 2004

[34] Treanor J.J.: Influenza virus. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 5th ed. New York: Churchill Livingstone, 1823–1849, 2000

[35] Rassing M.R.: Chewing gum as a drug delivery system. Adv. Drug. Deliv. Rev., 13:89–121, 1994

[36] Drug Information collected from www.drugs.com/cetirizine-hcl.html .

[37] Stoltenberg I., Winzenburg G., Breitkreutz J.: Solid oral dosage forms for children – formulations excipients and acceptance issues. European Industrial Pharmacy, 8:4-7, 2011

[38] Farhad M., Piyush T.: Formulation and texture characterization of medicated chewing gum delivery of Dimenhydrinate Hydrochloride. Der Pharmacia Lettre, 3(6):179-192, 2011

[39] Prashant K. P., Chandrakant S. S., Varsha M. J., Vilasrao K. Medicated Chewing Gum: A Novel Drug Delivery System, Journal of Applied Pharmaceutical Science, 02(06):40-54, 2012

[40] Rider J.N., Brunson E.L., Chambliss W.G., Cleary R.W, Hikal A.H, Rider P.H. et al.: Development and evaluation of a novel dissolution apparatus for medicated chewing gum products. Pharm Res, 9:255–259, 1992

[41] Kása P. jr, Jójárt I., Hódi K.: Régi-új gyógyszerforma, avagy a gyógyszeres rágógumi főnix-effektusa Gyógyszerészet, 53:527-535, 2009

[42] Barabolak R., Hoerman K., Kroll B., Record D.: Gum chewing profiles in the U.S. population. Community Dent. Oral Epidemiol, 19:125–126, 1991

[43] Eisenstadt B., Cash P.A., Bakal A.I.: US Patent, 5:846, 557, 1998

[44] Pedersen M, Rassing M.R.: Chewing gum as a drug delivery system for nystatin influence of solubilising agents upon the release of water insoluble drugs. Drug Dev Ind Pharm, 16:2015–2030, 1990

[45] Rowe R.C.: By gum–a buccal delivery system. Drug Discov. Today, 8:617–618, 2003

[46] Rassing M.R., Jacobsen J. Medicated chewing gum. In: Rathbone M.J., Hadgraft J., Roberts M.S., editors. Modified release drug delivery technology. New York: Marcel Dekker Inc., 419–430, 2003

[47] Zyck D.J., Greenberg M.J., Barkalow D.G., Marske S.W., Schnell P.G., Mazzone P., Witkewits D.L.: US Patent, 6:541,048, 1999

[48] Testa E.S.: US Patent, 5:866,179, 1999

[49] Naik H., Gupta S.: Medicated chewing gums – Updated review, Int J of Pharm Res and Dev. 66-76, 2010

[50] http://www.cafosa.com/EN_Health_in_Gum

[51] L.L. Christrup, N. Moeller, Arch. Pharm. Chem. Sci. Ed. 14, 30–36, 1986

[52] Kvist C., Andersson S.B., Fors S., Wennergren B., Berglund J.: Apparatus for studying in vitro drug release from medicated chewing gums. Int J Pharm., 189:57–65, 1999

[53] Azarmi S., Roa W., Löbenberg R.: Current perspectives in dissolution testing of conventional and novel dosage forms. Int J Pharm., 328:12–21, 2007

[54] Guidance for Industry, Process Validation: General Principles and Practices, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, 2011

[55] Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP /CVMP/QWP/BWP/70278/2012-Rev1 Committee for Medicinal Products for Human Use (CHMP), 2014

[56] EU Guide to GMP Volume 4 – Chapter1; Annex 1; Annex 15 sections 20-35; Annex 18 sections 12.4-12.5, January 2013

[57] ICH Q8, Pharmaceutical Development, November 2008

[58] ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients Draft EU Guidance on Process Validation, March 2012

[59] Health Canada: Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029), / December 1, 2009

[60] Ström G.: Krüss users manual, contact angle and adsorption measuring system. Hamburg: Krüss GmbH, 50–77, 1996

[61] Kása P. jr., Bajdik J., Zsigmond Zs., Pintye-Hódi K.: Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. Chem Eng Proc, 48:859–863, 2009

[62] European Pharmacopoeia, Dissolution test for medicated chewing gums, 2.9.25:325-329, 2000

[63] Kása P. Jr., Jójárt I., Kelemen A., Pintye-Hódi K.: Formulation study of directly compressible chewable polymers containing ascorbic acid. Pharmaceutical Development and Technology, 1–6, 2012

[64] Lanz M., Baldischweiler J., Kriwet B., Schill J., Stafford J., Imanidis G.: Chewability testing in the development of a chewable tablet for hyperphosphatemia, Drug Dev Ind Pharm, [PubMed - 24010939], 2013

[65] Malamataris S., Bin Baie S., Pilpel N.: Plasto-elasticity and tableting of paracetamol, Avicel and other powders. J Pharm Pharmacol, 36:616–617,1984 [in van Veen B. Compaction of Powder Blends, doctoral dissertation, 2003].

[66] Fell J.T, Newton M.: Determination of tablet strength by the diametralcompression test. J Pharm Sci, 59:688–691, 1970

[67] Wells I.J.: Powder flow properties. In Pharmaceutical preformulation. The physicochemical properties of drug substances. Chichester: Ellis Horwood Limited Publishers – Chichester, 209–211, 1988

[68] Pérez E., Famá L., Pardo S.G., Abad M.J., Bernal C.: Tensile and fracture behaviour of PP/wood flour composites. Composites: Part B, 43:2795–2800, 2012

[69] Ramli M., Tabassi A.A.: Mechanical behaviour of polymer-modified ferrocement under different exposure conditions: an experimental study. Composites: Part B, 43:447–56. 2012

[70] Oprea S.: Effects of guar gum content on structure and properties of multicrosslinked polyurethane composite films. Composites: Part B, 44:76–83, 2012

[71] Peppas N.A.: Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv, 60:110–111, 1985

[72] Jójárt I., Sovány T., Pintye-Hódi K., Kása P. jr.: Study of the behaviour of magnesium stearate with different specific surface areas on the surface of particles during mixing. Journal of Adhesion Science and Technology, 26:2737-2744, 2012

[73] Jójárt I., Kelemen A., Pintye-Hódi K., Kása P. jr.: Tracking of the post-compressional behaviour of chewing gum tablets. Composites: Part B, 49:1–5, 2013

[74] Zhihong Z., Bo P., Xinggang Y., Chao W., Guangmei S., Weisan P.: Design and Evaluatiom of a Novel Floating osmotic Pump System, J Pharm Pharm. Sci, 12: 129-137, 2009

ACKNOWLEDGEMENTS

I am very grateful to my supervisor

Professor Dr. Habil. Klára Pintye-Hódi Ph.D., D.Sc.

for her support. I greatly appreciate her continuous help during the preparation of my thesis and providing the excellent facilities for my Ph. D. studies.

I would like to thank

Professor Dr. Habil. Piroska Szabó-Révész Ph.D, D.Sc.

Head of the Ph. D. programme Pharmaceutical Technology and present Head of the Department of Pharmaceutical Technology for providing me with the possibility to complete my work under her guidance.

I would like to thank

Dr. Péter Kása junior

for his good advice and his continuous support and for the excellent technical assistance.

My warmest thank to

Magdolna Dr. Györgyné Dr. Vágó

for her maximal support during my studies.

I express my kindest thanks all my co-authors for their collaboration in this work. Help from all members in the Department of Pharmaceutical Technology, and some other departments will be greatly appreciated.

I owe my thanks to my family, my friends, and especially my fiancée for their support, encouragement and understanding attitude during these years.

This work was supported by the **TEVA Pharmaceutical Industries Ltd.**

APPENDIX

PUBLICATIONS RELATED TO THE THESIS

I.

TOVÁBBKÉPZŐ KÖZLEMÉNYEK

Gyógyszerészet 53. 527-535. 2009.

Régi-új gyógyszerforma, avagy a gyógyszeres rágógumi főnix-effektusa

ifj. Kása Péter[1], Jójárt Imre[2], Hódi Klára[1]

A szerzők ismertetik a rágógumi-használat történetét, majd részletesen foglalkoznak a gyógyszeres rágógumik kialakulásával, előnyeivel és hátrányaival. Ismertetik azokat a terápiás területeket, ahol a gyógyszeres rágógumik használata az eddigiekhez képest jobb és/vagy biztonságosabb gyógyszerelés lehetőségét hordozza. Bemutatják a gyógyszeres rágógumi előállításának a lehetőségeit és sorra veszik azokat az eljárásokat, amelyek a gyógyszeres rágógumi mint gyógyszerforma vizsgálatára a rendelkezésünkre állnak.

Bevezetés

Az ember már régóta ismeri a rágógumi élvezetét. A mayák már 2000 évvel ezelőtt használták a sapodilla fa gyantáját (chicle) fogtisztításra és a lehelet javítására. Ezek után a fehér gyarmatosítók terjesztették el ezt a szokást. Az első rágógumi 1848-ban jelent meg a piacon, az első szabadalmat pedig 1869-ben adták ki. A II. Világháború után jelentek meg az első szintetikus rágógumik.

Az első hatóanyagot tartalmazó rágógumi Aspergum® néven 1928-ban jelent meg és még ma is kapható. Acetilszalicilsavat tartalmaz, melyet fájdalomcsillapításra használnak. Létezik még dimenhidrinát tartalmú rágógumi is, melyet utazási betegség kezelésére, megelőzésére alkalmaznak. A rágógumit gyógyszerformaként valójában 1978 óta ismerik el. Ekkor jelent meg az első nikotin tartalmú rágógumi, melyet dohányzásról való leszokás segítésére alkalmaznak.

Manapság a rágógumi egyre inkább elfogadott gyógyszerforma. A dohányzásról leszoktatás mellett fontos segítséget nyújt a fogak egészségének megőrzésében és nem hanyagolható el a szisztémás hatása sem [1].

A rágógumi története

A kutatások során kiderült, hogy a gumi rágásának szokása nem kizárólagosan az amerikaiaktól származik, annak ellenére, hogy az Egyesült Államok a világ legnagyobb rágógumi fogyasztója. Például az ősi görögök is kedvelték a mastiche nevű gumiszerű anyagot, melyet balzsammézga fa gyantájából nyertek. *Dioscorides* görög filozófus és gyógynövényszakértő az 1. században írásaiban gyógyerőt tulajdonított ennek az anyagnak.

1. ábra: Rágógumik

Mastic

A mastic (*Pistacia lentiscus L.*) egy 4 méter magasra megnövő örökzöld cserje (***2. ábra***), melyet Görögország Chios nevű szigetén az aromás gyantája miatt termesztik. Az egész mediterrán térségben, így Marokkóban, az Ibériai-félszigeten, Dél-Franciaországban, Törökországban, Szíriában és Dél-Palesztinában, sőt még a Kanári-szigeteken is őshonos növénynek számít. A neve is görög eredetű, fogcsikorgatást vagy rágást jelent [2]. A mastic-rágás szokása nem csak az ősi görögök körében volt jellemző: a görögök és más közép-keleti népek ma is használják ezt az anyagot, méhviasszal keverve.

2. ábra: Pistacia lentiscus L.

3. ábra: Manilkara zapota

5. ábra: Csapolás

A rágógumi fejlesztésében nem sokkal jártak a görögök mögött a mayák. Kutatások bizonyítják, hogy ez a közép-amerikai indián törzs a 2. században a sapodilla nevű fából nyert nedvből készített rágót.

Sapodilla

A sapodilla (*Manilkara zapota*) hosszú életű, örökzöld fa, mely közép- és dél-amerikai esőerdőkben őshonos (***3. ábra***). Akár 30-40 méter magasra is megnő és nagyon gyorsan növekszik. Jól ellenáll a viharoknak. A törzse nagy mennyiségben tartalmaz fehér gumiszerű anyagot, melyet „chicle"-nek neveznek. A sapodilla fák évente kétszer hoznak termést és egész évben virágoznak (***4. ábra***). A gyümölcs is nagy mennyiségű latexet tartalmaz.

Körülbelül 20-25 éves koruk után lehet ezeket a fákat „megcsapolni". A fa kérgén halcsontváz alakú bemetszéseket ejtenek. Körülbelül 5 kg gumi csorog ki 6 óra alatt. Egy fát 3-4 évente lehet megcsapolni (***5. ábra***) [3].

4. ábra: Sapodilla fa gyümölcse

A 800-as évek környékén a maya civilizáció rejtélyes módon kihalt. Csak az elhagyatott templomok és városok maradtak fenn, valamint a rágógumi, amit a térségben élők tovább alkalmaztak egészen a 19. századig.

Időközben az amerikai telepesek újfajta rágógumit állítottak elő lucfenyő gyantájából. Ennek használata a 19. század elejéig egyre inkább elterjedt, majd ezután jelentek meg az első kereskedelmi forgalomba szánt rágógumik. A lucfenyőből készült gumit fokozatosan felváltotta a paraffinviasz-gumi. Ahhoz viszont, hogy a paraffin gumi rágható legyen, megfelelő hőmérséklet és nedvességtartalom szükséges. Emiatt később más gumialapot kezdtek használni, azonban még ma is alkalmaznak édesített és ízesített paraffin viaszokat az újabb termékekben, valamint finomított paraffin viaszt rágógumi adalékként.

A modern rágógumi 1869-ben jelent meg. Egy mexikói vezérőrnagy, *Antonio Lopez de Santa Anna* fejlesztette ki, aki remélte, hogy a chicle nevű anyag megfelel a célra. *Thomas Adams* feltalálót alkalmazta, hogy kísérletezzen az anyaggal, de ő a chicle-t nem találta megfelelő gumialapnak. Azután egy napon *Adams* látott az utcán egy lányt, aki paraffin alapú rágógumit rágott. Eszébe jutott a Santa Anna kérésére vizsgált anyag. Újra megvizsgálta a chicle-t és úgy gondolta, hogy mégis ez a legmegfelelőbb rágógumi alapanyag. Egy helyi gyógyszerész közreműködését kérve lényegében újra felfedezték azt, amit a mayák már ezer évvel azelőtt használtak. Ezzel forradalmasították a rágógumi gyártást [4].

I. táblázat

A rágógumi modernkori történetének fontosabb eseményei

1848.: *John B. Curtis* kereskedelmi forgalomba hozza az első elkészített rágógumit „State of Maine Pure Spruce Gum”.
1850.: *Curtis* elkészíti az első ízesített paraffin gumit.
1869. december 28.: *William Finley Semple* elsőként szabadalmaztatta a rágógumit (U.S patent: 98,304).
1869.: *Antonio Lopez de Santa Anna* megismertette *Thomas Adams*-al a chicle-t.
1871.: *Thomas Adams* szabadalmaztatta a rágógumi-készítő gépet.
1880.: *John Colgan* kitalálta, hogyan lehet a rágógumi ízét „meghosszabítani”.
1888.: *Thomas Adams* a „Tutti-Frutti” rágógumiját elkezdte automatából árusítani a New York-i metróállomásokon.
1899.: *Franklin V. Canning* New York-i gyógyszerész elkészítette az első Dentyne tartalmú rágógumit.
1906.: *Frank Fleer* feltalálta az első buborékot képző rágót, melyet „Blibber-Blubber gum”-nak nevezett el.
1914.: *William Wrigley, Jr.* és *Henry Fleer* bejegyezték a „Wrigley Doublemint” márkát.
1928.: *Walter Diemer* a Frank H. Fleer társaság alkalmazottja elkészítette az első színes (rózsaszín) rágógumit a „Double Bubble”-t [5].

Manapság a rágógumikat igen sok helyen árusítják különböző automatákból (***6. ábra***). Sajnos a legtöbb országban a rágás során ízét vesztett rágógumit egyszerűen csak kiköpik vagy eldobják, ami igencsak gusztustalan, ráadásul ráragad a cipőtalpra. Ennek kiküszöbölésére az utcai parkolóórákhoz hasonló „használt rágógumi gyűjtők” felállításával próbálkoztak (***7. ábra***).

A gyógyszeres rágógumik kialakulása, definíciója

A modern gyógyszeres terápiában fontos, hogy a betegek a leghatékonyabb formában jussanak a megfelelő gyógyszerhez. Mivel a kezelt betegek jó része a fiatalkorúak, illetve a gyerekek köréből kerül ki, igen fontos, hogy olyan gyógyszerformát biztosítsunk, melyet szívesen alkalmaznak. Erre a célra igen megfelelő a gyógyszeres rágógumi. Ennek, mint gyógyszerformának – bár a gyógyszerkönyvek csak viszonylag későn vették fel a palettájukra – igen jelentős múltja van:

– 1928.: Megjelent az Aspergum®, amely az első hatóanyag tartalmú rágógumi. Még ma is kapható (***8. ábra***). Acetilszalicilsavat tartalmaz, melyet fájdalomcsillapításra használnak. Ezt követően még dimenhidrinát tartalmú rágót is gyártottak, melyet utazási betegség kezelésére, megelőzésére alkalmaztak/alkalmaznak, valamint koffein tartalmú készítmények is készültek.

6. ábra: Rágógumi adagoló készülék

– 1978.: Megjelent az első nikotinos rágógumi, melyet dohányzásról leszoktatásra fejlesztettek ki (***9. ábra***). Annak ellenére, hogy még nem igazán elterjedt gyógyszerforma, ettől kezdve fogadják el a rágógumit, mint gyógyszerhordozó rendszert.

– 1991.: Az Európai Tanács Bizottsága a rágógumit önálló gyógyszerformaként ismerte el [6].

A gyógyszeres rágógumi (*Masticabilia gummis medicata*) olyan szilárd, egyadagos, főként gumi vivőanyagot tartalmazó készítmény, amelyet rágásra és nem lenyelésre szánnak [Ph. Hg. VIII]. A gyógyszeres rágógumik egy vagy több hatóanyagot tartalmaznak, melye(ke)t a rágás folyamán adnak le. A nyálban feloldott vagy diszpergálódott hatóanyag(ok) révén a rágógumik szájbetegségek helyi kezelésére, vagy – amikor a hatóanyagok a száj nyálkahártyáján, illetve a tápcsatornán keresztül felszívódnak – szisztémás kezelésre is alkalmazhatók [7].

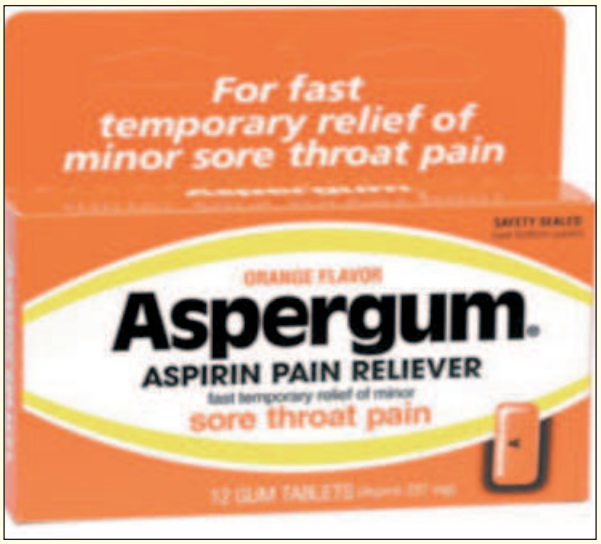
A gyógyszeres rágógumi előnyei

Hatáskifejtés

Helyi hatás

A rágógumi megfelelő gyógyszerforma a szájüreg és a torok gyógyszeres kezelésére. Így folyamatos hatás érhető el. Általában a rágógumi rágása több ideig tart, mint egy rágótablettáé, így a hatástartam is hosszabb. A hagyományos rágótablettával összevetve a rágógumi hatóanyag-kioldódási sebessége sokkal kontrolláltabb, annak ellenére, hogy a rágás erőssége és sebessége nagyban befolyásolhatja azt. Sok esetben

7. ábra: Utcai, használt rágógumi gyűjtő



8. ábra: Narancs ízű acetilszalicilsav tartalmú rágógumi

9. ábra: Nikotin tartalmú rágógumi

problémát jelent, hogy a rágótablettát rendszertelenül alkalmazzák.

Gyors szisztémás hatás
A hatóanyagok a szájnyálkahártyán keresztül, vagy a nyállal keveredve, abban feloldódva, a nyálat lenyelve a gasztrointesztinális rendszeren keresztül szívódhatnak fel. Mindkét esetben a vérbe kerülve szisztémás hatás érhető el.

Kevesebb mellékhatás
A szájnyálkahártyán felszívódó hatóanyagok a májat elkerülve jutnak a szisztémás keringésbe. Így nincs *„first pass effect”*, tehát nagyobb a hatóanyag biológiai hasznosíthatósága. Ebből következik, hogy kisebb mennyiségű hatóanyagra van szükség a megfelelő hatás kifejtésére. Az alacsonyabb dózis pedig kevesebb mellékhatást okoz, ennek megfelelően csökken az adott hatóanyag alkalmazásának kockázata.

A túladagolás kisebb veszélye
Rágás szükséges ahhoz, hogy a hatóanyag kioldódjon a rágógumiból. Ha a rágógumi véletlenül lenyelésre kerül, a hatóanyag csak hosszú idő után oldódik ki. Ez nem hordozza magában a túladagolás veszélyét.

Egyéb előnyök
Normális esetben a gumi nem jut le a gyomorba, így a gasztrointesztinális traktusba nem kerül segédanyag. A gyomor nem érintkezik közvetlenül nagy koncentrációjú hatóanyaggal (nyálkahártya védelem). A hatóanyag hatása hosszabb ideig tart. Az acetilszalicilsav, a dimenhidrinát és a koffein gyorsabb felszívódást mutat, mint tablettákból.

Komfortosság

Elfogadottság a gyerekek körében
Sok gyereknek nehézséget jelent a tabletta lenyelése. Emiatt a folyékony gyógyszerformák fejlesztését szorgalmazzák, annak ellenére, hogy köztudottan ezeknek a gyógyszerformáknak az adagolása nem kellő pontosságú. Rágógumi formában gyakran egyszerűbb a hatóanyag keserű és rossz ízét elfedni. Ez a gyerekek szempontjából előnyös, viszont fontos, hogy a gyerekek az előírt ideig rágják a rágót.

Elfogadottság a nyelési problémákkal szenvedők körében
A nyelési problémákkal küzdők kezelésében a rágógumi előnyös gyógyszerforma. Emellett hányinger esetén is jobban tolerálható, mint a tabletta.

Felhasználóbarát
A bevételéhez nincs szükség vízre, ezért akut kezelésre megfelel. A gyógykezelés nincs helyhez és időhöz kötve, alkalmazása „komfortos” [8].

A rágógumik hátrányai

A szorbit tartalmú rágógumik hasmenést, illetve gázfejlődést okozhatnak, abból adódóan, hogy megemelkedik az ozmotikus nyomás a gasztrointesztinális traktusban. Az ízesítéshez alkalmazott segédanyagok fekélyt (pl. fahéj) vagy magas vérnyomást (pl. édesgyökér) okozhatnak. A klórhexidin tartalmú rágógumi kellemetlen ízű, rövid ideig használható. Különböző mértékben odaragadhat a fogakhoz, fogtömésekhez. Hosszú idejű rágás fájdalmat okozhat az arcizmokban és a rágóizmok görcsét okozhatja [6].

Alkalmazási lehetőségek

Fogszuvasodás kezelése

A fogszuvasodás kezelésére és megelőzésére kézenfekvő a rágógumi, mint gyógyszerforma. A cukormentes rágó-

gumik rágása köztudottan előnyös a fogak egészségének megőrzése érdekében. Ismert, hogy a húsételek fogyasztása után a cukormentes rágógumi rágása újra megemeli a száj pH-értékét. Az alacsony pH nagy szerepet játszik a fogszuvasodás kialakulásában. Ennek megfelelően az étkezések után a cukormentes rágógumi alkalmazása kiegészítő kezelése lehet a fogszuvasodás megelőzésének a fogmosás mellett.

A klórhexidin tartalmú rágógumi alkalmazása csökkenti a gingivitis, periodontitis és egyéb szájüregi fertőzések kialakulását, valamint csökkenti azok tüneteit. Bizonyított, hogy a klórhexidin gátolja a lepedékképződést, emellett gátolja a fogak elszíneződését, rágógumiként pedig kényelmesebben alkalmazható, mint szájvíz formájában. Rágás során egyenletesen szabadul fel a hatóanyag és egyenletesen eloszlik a szájüregben, ezáltal megnyúlik a hatástartam. A fluorid tartalmú rágógumit gyerekeknél olyan területeken alkalmazzák, ahol az ivóvíz nem tartalmaz elegendő fluoridot, felnőtteknél pedig, ha fokozott a fogszuvasodás kialakulásának veszélye. Xerostomiás betegek kezelésére is alkalmaznak fluorid tartalmú rágógumit. A gombaellenes mikonazolt candidiasis kezelésére alkalmazzák. Rágógumi formájában sokkal hatásosabb, mint orális gélben eloszlatva. Emellett a betegek jobban kedvelik a kevesebb mellékhatás miatt.

10. ábra: A gyógyszeres rágógumi a képregényekben

Dohányzásról leszoktatás

Klinikai vizsgálatok alapján a nikotin, lobelin és ezüst-acetát tartalmú rágógumik segíthetnek leszokni a dohányzásról. A nikotin alkalmazása segít a dohányosoknak abban, hogy a cigarettázás abbahagyása után könnyebben „átvészeljék" az elvonási tüneteket. Egy farmakokinetikai tanulmány rámutatott, hogy a rágógumiból felszabadult nikotin 80%-a a szájnyálkahártyán keresztül szívódik fel.

Elhízás

Számos rágógumi-összetétel tartalmaz koffeint, guaranát vagy krómot. A koffein és a guarana fokozza a lipolízist, fokozza a teljesítőképességet és csökkenti az éhségérzetet. A króm javítja a vércukorszintet. Ez alapján ilyen hatóanyag tartalmú rágógumi alkalmazásával csökkenthető a testtömeg.

Fájdalomcsillapítás

A már korábban említett Aspergum® volt az első hatóanyag tartalmú rágógumi, melyet fájdalomcsillapításra alkalmaztak. A fájdalomcsillapítás mellett lázcsillapító hatással is rendelkezik, valamint gátolja a trombocita-aggregációt és így lassítja a véralvadást. Vizsgálták az acetilszalicilsav biológiai hasznosíthatóságát tabletta és rágógumi formájában is. A felszívódás sebessége a rágógumiból gyorsabbnak bizonyult, mint tablettából. Ennek megfelelően az acetilszalicilsav tartalmú rágógumi gyorsabban fejti ki a hatását, mint a tabletta, így gyorsabban csökkenthető a fájdalom. A rágógumi emiatt sokkal alkalmasabb akut, erős fájdalom kezelésére.

Metadon hatóanyag esetén a tabletta és rágógumi között a felszívódásban nem volt szignifikáns különbség. Azonban a hozzászokás/visszaélés/túlzott bevitel esélye jelentősen csökkenthető, ha a hatóanyagot rágógumi formában alkalmazzuk, mert a hatóanyag csak rágás hatására szabadul fel.

Utazási betegség

A rágógumi, mint gyógyszerhordozó rendszer ideális az utazási betegség és a hányinger kezelésére, megelőzésére. A dimenhidrinát tartalmú rágógumi már forgalomban van, de egyéb hasonló indikációjú hatóanyagok (pl. szkopolamin, metoklopramid, ondanszetron és dolaszetron) ilyen formájú alkalmazása még „várat magára" [6].

Allergia kezelése

Az iparosodott országokban a gyerekek kb. 20%-a szenved valamilyen allergiás megbetegedésben. A legjellemzőbb tünetek az eldugult orr vagy orrfolyás, a tüsszögés, a szemviszketés, esetleg szájviszketés. A gyermekek a tünetek miatt gyakran nyugtalanul alszanak, csökkent koncentrálóképességűek, nehezen hallanak, csökkent étvágyúak és lassabban fejlődnek. Az allergiás rhinitis kezelésére használt hatóanyagok, melyeket rágógumi formájában is alkalmaznak: antihisztaminok, dekongesztánsok, antileukotriének.

ADHD kezelése

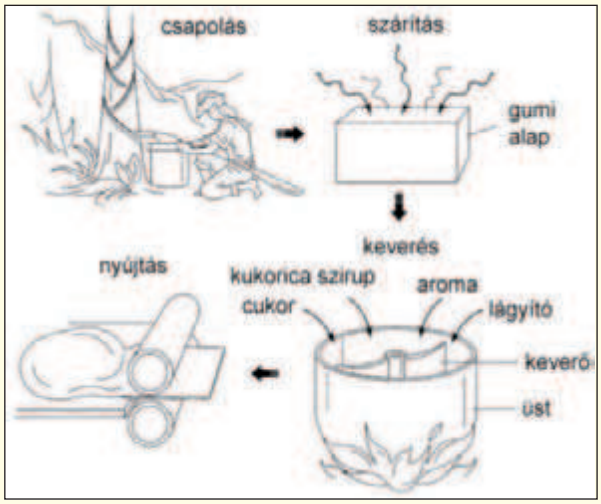
Az ADHD (Attention Deficit Hyperactivity Disorder) figyelemhiánnyal vagy hiperaktivitással járó kórforma. Egy USA-ban végzett felmérés alapján az iskolaévek alatt a gyermekek 5-10%-a szenved ebben a betegségben. Jellemző tünetek: tanulási nehézségek, zavart viselkedés, barátkozási nehézségek, rongálási hajlam. Az ezekben az esetekben használt gyógyszerekben a következő hatóanyagokat alkalmazták: metilfenidát, amfetamin, dextroamfetamin, pemolin, atomoxetin. Irodalmi adatok vannak arra vonatkozóan is, hogy a hatóanyag tartalmú rágógumi alkalmazása ennél a betegségcsoportnál is hatásos lehet [9].

Előállítási lehetőségek

A rágógumi előállítása során a hagyományos (olvasztásos) módszert, az extrudálást és a közvetlen tablettázást lehet használni.

Hagyományos előállítás

A rágógumi-gyártásnál használnak gumialapot és adalékokat (pl. kukoricaszirup, glukóz, porcukor, lágyító és ízesítőanyagok). Ezen anyagoknak szigorú minőségi követelményeknek kell megfelelniük. A legtöbb rágógumit hasonló gyártásmenet szerint készítik. Habár rendelkezésre állnak a rágógumi-gyártáshoz a természetes anyagok, a növekvő igények miatt szükség van mesterséges anyagok alkalmazására is. A gumialapot egy nagy, kb. 150 °C hőmérsékletű gőzfürdős üstben olvasztják meg [10] (***11. ábra***). Így szirupszerű anyagot nyernek. Ezután ezt a szirupot többféle lyuknagyságú szűrőn szűrik át. Ez alatt az olvadék végig forró marad. Ezután az anyag keverő medencékbe kerül, amelyekben lassan forgó lapátok vannak felszerelve. A kukoricaszirupot és a cukrot a gyártási folyamatnak ebben a szakaszában adják hozzá. Az adalékok – például a porcukor – meghatározzák a gumi tördelhetőségét, rugalmasságát. Az adalékanyagok megtartják a nedvességet és segítik a cukor elegyedését a gumialappal. Ezután adják hozzá a különböző lágyító és ízesítő anyagokat.



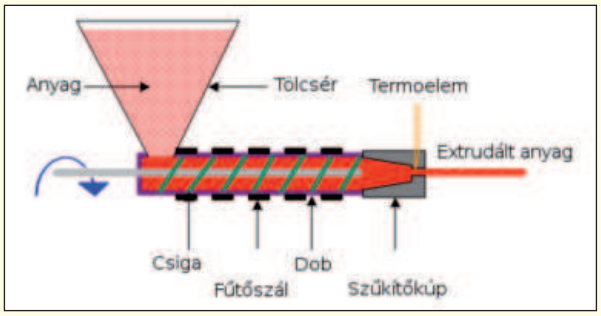
11. ábra: A rágógumi- gyártás menete

A kikevert gumi hűtőszalagokra kerül és hideg levegővel hűtik. Ezután préselik, hogy megfelelően lágy és sima állományú legyen. Ezt követően ellapítják az anyagot erre szolgáló gépekkel. Itt nyeri el a rágógumi a végleges vastagságát (***12. ábra***). A különböző vastagságúakból különböző rágótípusok gyárthatók: a legvékonyabból a lapkarágó, vastagabból a bevonatos rágó, a legvastagabból a „bubble gum" készül. Ezeket különböző gépekkel formázzák. A rágógumikat a formázási műveletek elvégzése után, ha kell, különféle bevonatokkal látják el [4].

Extrudálás

Extrudálás esetén a feldolgozni kívánt anyagot egy arra alkalmas berendezés segítségével többé-kevésbé vékony szállá vagy rúddá formálják (***13. ábra***), amit egy megfelelő daraboló berendezéssel egyforma darabokra vágnak, majd kialakítják a végleges formát. Ez az esetek nagy többségében gömb alak, amit speciális hengerekkel vagy hengerekben érnek el. A kapott terméket később különböző színű és ízű bevonattal is elláthatják. A művelet során fontos a megfelelő hőmér-

12. ábra: Rágógumi gyártása manufakturális módon

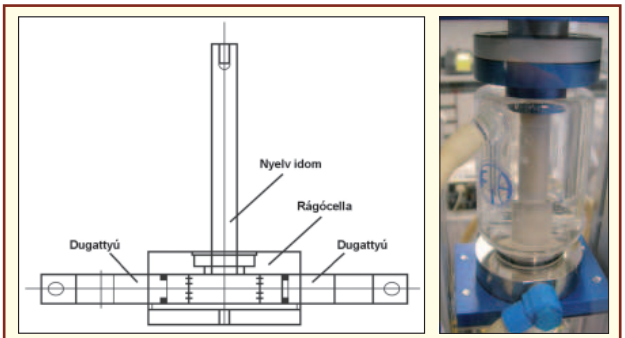


13. ábra: Extrudáló sematikus ábrája

séklet megválasztása, amivel az anyagot olyan állapotba hozhatják, hogy az „szállá” alakítható. A szálak kialakítása a berendezés dobja körül lévő fűtőszálak segítségével folyik. A dob körül kialakított fűtő-, illetve adott esetben hűtőköpeny segítségével a termék számára legkedvezőbb hőmérséklettartomány állítható be.

Közvetlen tablettázás

A rohamos fejlődés miatt, valamint az egyre nagyobb igények kielégítése és egyúttal a költségek csökkentése érdekében a közvetlen tablettázás is előtérbe került a rágógumik előállítása során. Ma már rendelkezésre állnak olyan gumialapok, amelyek szilárd formában (por) hozzáférhetők, s megfelelő arányban kombinálva, a különböző segéd- és hatóanyagot/hatóanyagokat hozzáadva és homogenizálva direkt préseléssel is kialakítható a végleges alak. Tartalmazhatnak pl. töltőanyagokat, lágyítókat, édesítőszereket, ízjavítókat, stabilizátorokat, képlékenységet növelő anyagokat, továbbá engedélyezett színezékeket. Ebben az esetben inkább rágógumi tablettáról kell beszéljünk, hiszen a kialakított forma inkább tablettához hasonlít! A tablettázógéppel történő kialakítás során az extrudálással szemben nem fűtést, hanem hűtést kell alkalmazni az anyag megfelelő reológiai tulajdonságainak megtartása érdekében. Ügyelni kell arra, hogy a préselni kívánt anyag az összepréselés után lehetőleg ne ragadjon a présszerszámokhoz. A ragadás a présszerszámok felületén kialakított speciális bevonattal nagymértékben lecsökkenthető. Problémát okozhat, ha az így előállított termék túlságosan szilárd, hiszen össze kell rágni!



14. ábra: A Gyógyszerkönyvben hivatalos (A) és az Erweka cég által kifejlesztett (B) rágógumi vizsgáló készülék

A gyógyszeres rágógumik vizsgálata

Kioldódás vizsgálat

A gyógyszerkönyv a gyógyszeres rágógumikra különböző vizsgálatokat ír elő. Ezek közé tartozik a hatóanyag kioldódásának vizsgálata [7]. Ehhez egy speciális rágócellát ír elő, amelyben a vizsgálni kívánt terméket, különböző rágóidomok segítségével adott ideig „rágatja”, majd az idő függvényében kioldódott hatóanyagot megfelelő analitikai módszerekkel határoztatja meg (***14. ábra***).

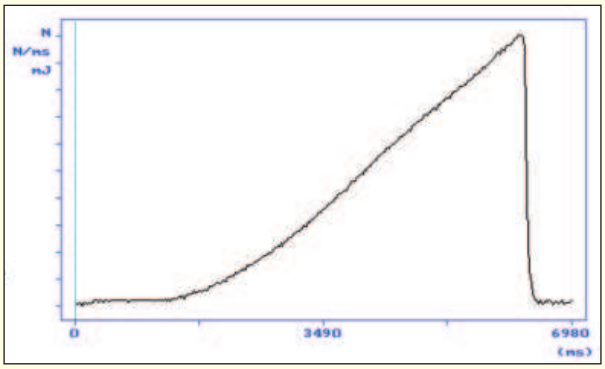
A gyógyszerkönyvi rágást szimuláló készülék ***(14. ábra A.)*** egy kb. 40 ml-es „rágókamrából” áll, amelyben a rágógumit két, vízszintes irányba mozgó dugatyú mesterségesen rágja. A dugattyúk állandó sebességgel, összehangoltan működnek, képesek a saját tengelyük körül, egymással ellentétes irányban forogni és ily módon erős rágást szimulálni. Egy harmadik (függőleges) dugattyú (a „nyelv”) a két vízszintes dugattyúval váltakozva működik és biztosítja, hogy a rágógumi a két vízszintes dugattyú között, a megfelelő helyen maradjon. A dugattyúkat sűrített levegő mozgatja, egymáshoz viszonyított mozgásuk szabályozott. A készülék minden eleme rozsdamentes acélból készül.

Beállítható a vizsgáló közeg hőmérséklete (37 ± 0,5 °C) és a dugattyúk sebessége. Általában 20 ml, pH 6 körüli tompítóoldatban történik a vizsgálat. A vizsgálatot üres berendezéssel kezdik, ellenőrizendő, hogy nem maradt-e az előző vizsgálatból bármiféle maradék a rendszerben, majd pontosan mért rágógumit helyeznek a cellába. Megadott időközönként mintát vesznek és meghatározzák a kioldódott hatóanyag mennyiséget. A szokásos rágófrekvencia percenként 60 rágóciklus.

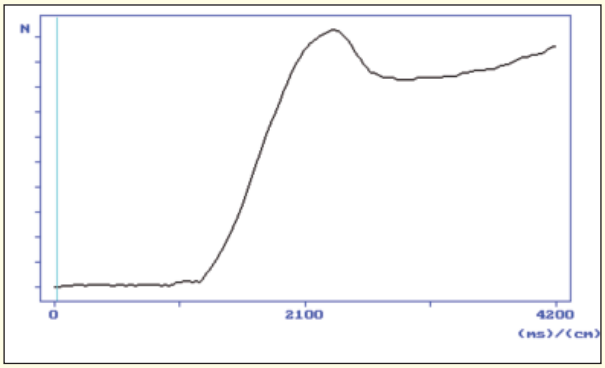
Az Erweka által kifejlesztett rágócella (***14. ábra B.***) némileg eltér a gyógyszerkönyvben szereplőtől. Ebben a cellában egy mozgó dugattyú található, amely vertikális irányban és a saját tengelye körül is mozog. A tengely körüli elfordulás mértéke, valamint a függőleges irányú elmozdulás – ami a rágás erősségét imitálja – szabályozható. A dugattyút ebben a készülékben is sűrített levegővel mozgatják. A készülék kb. 20-30 ml vizsgálóközeget tartalmaz egy temperálható tartályban. A mintát a rágóidom részben összenyomja, részben pedig meg is csavarja, mintegy imitálva a természetes rágási folyamatot. A pontosan mért mintát a kettős falú cellába helyezik. Adott időközönként itt is mintát vesznek a kioldóközegből, s a kioldódott hatóanyagot határozzák meg.

Rághatósági vizsgálat

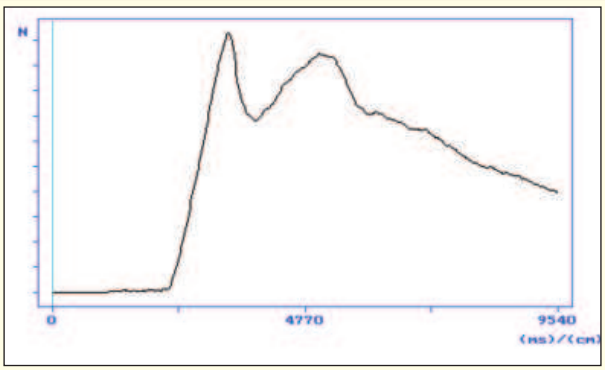
Az előállítási eljárástól függően egyéb vizsgálatokat (pl. szilárdságvizsgálatot) is kell végezni. Erre a célra a tabletták vizsgálatához előírt szilárdságvizsgáló berende-



15. ábra: Hagyományos tabletta törési folyamata



16. ábra: Gyógyszeres rágógumi törési folyamata



17. ábra: Tárolt (3 hónap) gyógyszeres rágógumi törési folyamata

zést használják. Szükséges ugyanis, hogy az elkészített termékek rághatóak legyenek, azaz ne kelljen túl nagy erő a szétrágásukhoz.

Elaszticitás vizsgálat

A rágógumik tulajdonságuknál fogva több-kevesebb rugalmassággal is rendelkeznek, amelyet az összetételben szereplő anyagok aránya is nagymértékben befolyásol. Ennek vizsgálata speciális interface és program segítségével, valamint számítógéppel összekötött készülékkel történhet. A ***15. ábrán*** egy hagyományos tabletta törési folyamata, a ***16.*** és ***17. ábrán*** a frissen készített, valamint a 3 hónapig tárolt gyógyszeres rágógumi törési folyamata látható. Az ábrákon igen szembetűnők a különbségek. A ***15. ábrán*** a hagyományos tabletta esetében a maximális törési erő elérése után az erő értéke gyakorlatilag azonnal nullára esik, ami azt mutatja, hogy a tabletta teljesen eltört. A ***16.*** és ***17. ábrán*** a maximális törési erő elérése után az erő értéke nem esik nullára, ami azt mutatja, hogy a készülékbe helyezett minta nem került ki a nyomóidom alól, csak „megroggyan", nem esik két részre, hanem az összetételben szereplő anyagok összetartják a darabokat, amelyek a nyomás hatására távolodnak egymástól. A ***17. ábrán*** a tárolás következtében fellépő utókeményedés is megfigyelhető.

Csomagolás

A gyógyszeres rágógumik gyártása, csomagolása, tárolása és forgalmazása folyamán megfelelő intézkedésekkel biztosítani kell a mikrobiológiai tisztaságot [7]. Ezen készítményeket a tablettákhoz hasonlóan bliszterezhetik, műanyag dobozba tehetik vagy egyenként csomagolhatják. Minden esetben fontos annak biztosítása, hogy a termék a levegőtől, a nedvességtől megfelelően elzárva legyen.

Összefoglalás

A szilárd gyógyszerformák, valamint az ezekben alkalmazott segédanyagok fejlődése lehetővé tette, hogy egy régi-új forma, a gyógyszeres rágógumi ismét előtérbe kerülhessen. Az ebben a gyógyszerformában használatos alapanyagok feldolgozhatósága nagymértékben egyszerűsödött, s a korábbiakkal szemben biztosítják az egyenletes hatóanyag-eloszlást és a megfelelő hatóanyag-felszabadulást. Újabb lehetőség a gyógyszeres rágógumik tablettázógéppel történő előállítása, mely jelentős költség- és időcsökkentő tényező, hiszen az anyagok homogenizálása után azonnal tablettázható. Természetesen ezen termékek esetében is megfelelő vizsgálatokkal kell meggyőződni az előállított „rágógumi-tabletták" minőségéről. Mivel a hatóanyagmentes rágógumi világszerte igen nagy mennyiségben eladott termék, feltételezhető, hogy a betegek kedvezően fogadják, hiszen bizonyos tekintetben (nem kell lenyelni, nem kell víz hozzá) sokkal egyszerűbb és kényelmesebb az alkalmazása, mint a klasszikus tablettának. Világszerte egyre többféle hatóanyagot próbálnak ebben a gyógyszerformában feldolgozni, ezzel is szélesítve a gyógyszerforma palettát. Ily módon ez a sokáig elfeledett gyógyszerforma ismét bekerülve a gyógyszerkönyvekbe, mint a főnixmadár, újra éledve kerülhet elő.

IRODALOM

1. *Rassing, M.R., Jacobsen, J., Morck Nielsen, H.:* Chewing gum as a drug delivery system, Ellermann Carecom International, Copenhagen. 2. kiad. p. 2. 2003. – 2. http://www.fertin.com/fileadmin/pdf/Chewing_gum_

as_a_DDS.pdf – 3. http://en.wikipedia.org/wiki/Mastic – 3. http://en.wikipedia.org/wiki/Sapodilla – 4. http://www.fordgum.com/story.html – 5. *Bellis, M.*: The History of Chewing Gum and Bubble Gum http://inventors.about.com/od/gstartinventions/a/gum.htm – 6. *Patel, S.S., Patel, N.M.*: Chewing Gum is No Longer a Sure-Fire Way to Get Kicked Out of Class. http://www.pharmaquality.com/mag/09012006/pfq_09012006_FO2.htm – 7. VIII. Magyar Gyógyszerkönyv, Medicina könyvkiadó, 2003., 1. köt. p. 69, p. 246, p. 248-249, p. 276, p. 278-279, p. 696-697. – 8. *Ratlam, N.Z.*: Chewing Gum As Drug Delivery System, http://www.pharmainfo.net/pharma-student-magazine/chewing-gum-drug-delivery-system – 9. http://www.fertin.com/fileadmin/pdf/Brochure_Children.pdf – 10. http://www.madehow.com/Volume-1/Chewing-Gum.html – 11. http://www.spipharma.com/default.asp?contentID=618 – 12. http://www.spipharma.com/default.asp?contentID=619 – 13. http://www.spipharma.com/default.asp?contentID=620 – 14. *Bajdik, J.*: Anyagismeret a gyógyszerkészítéshez, JATE Press könyvkiadó, 2005. p. 10, p. 74. – 15. http://www.e-szam.hu/mutat/318 – 16. *Kása, P. jun.*: Szilárd gyógyszerformák előállítása és vizsgálata, JATE Press könyvkiadó, 2005. p. 21, p. 32. – 17. *Rácz, I, Selmeczi, B.*: Gyógyszertechnológia, Medicina könyvkiadó, 2001., 3. köt.. p. 464-465, p. 470, p. 473.

Az irodalmi hivatkozásban felhasznált internetes címek a gyűjtés idején elérhetőek voltak.

K á s a, P. j u n.[1], J ó j á r t, I.[2], H ó d i, K.[1]: ***An old-new dosage form or the Phoenix effect of the medicated chewing gum***

The evolution of the solid dosage forms and the applied auxiliary materials made it possible for an old-new dosage form, the medicated chewing gum, to come to the forefront again. The processing of the base materials in this form has been greatly simplified and this guarantees the uniform distribution of the effective agent and its appropriate dissolution. A modern possibility is to prepare medicated chewing gums with tabletting machines by direct compression, which is a significant cost and time decreasing factor because the powder mixture can be tabletted immediately after homogenization. Needless to say, it is also necessary to check the properties of medicated chewing gums with different investigations described in the Pharmacopoeia. As the effective agent-free (conventional) chewing gums are widely used preparations, it is assumed that the patients will accept the medicated ones because in some respects their use is much simpler and more comfortable than that of the conventional tablets (it is not necessary to swallow, no need for water). Nowadays more and more effective materials processable in this form come into the focus worldwide, thereby extending the range of dosage forms. Thus, this long time forgotten dosage form could be included in the Pharmacopoeia, like the mythical firebird phoenix, reborn anew to live again.

[1]Szegedi Tudományegyetem, Gyógyszertechnológiai Intézet, Szeged, Eötvös u. 6. – 6720
[2]Teva Gyógyszergyár Zrt., Debrecen, Pallagi út 13. – 4042

A dolgozathoz tartozó tesztkérdések az utolsó oldalon találhatók

II.

Journal of Adhesion Science and Technology
2012, 1–8, iFirst article

Study of the behaviour of magnesium stearate with different specific surface areas on the surface of particles during mixing

I. Jójárt[a], T. Sovány[b], K. Pintye-Hódi[b] and P. Kása[b]*

[a]*TEVA Pharmaceutical Works Private Limited Company, Pallagi u. 13., H-4042 Debrecen, Hungary;*
[b]*Department of Pharmaceutical, Technology University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary*

(*Received 27 October 2011; final version received 29 February 2012; accepted 7 June 2012*)

The behaviour of two types of magnesium stearate with different specific surface areas on granule particles was examined. The magnesium stearate concentration was measured with an energy-dispersive X-ray fluorescence analyser. Different measurement procedures were used to investigate the properties of the two types of magnesium stearate when using different blending times and rotation speeds. Correlations were found between the specific surface area of the magnesium stearate, the blending time, the rotation speed and the specific surface free energy of the excipients. If magnesium stearate has a high specific surface area it shows higher adhesion work and is able to create a very thin homogeneous layer on the surface of the particles. Magnesium concentration was detected with the energy-dispersive X-ray fluorescence analyser. Based on the X-ray investigation the optimum blending time and rotation speed can be determined.

Keywords: magnesium stearate; specific surface; spreading; X-ray analysis; surface energy

1. Introduction

Solid dosage forms such as tablets and capsules are the most popular drug delivery systems. Tablet and capsule dosage forms mainly contain active pharmaceutical ingredients and excipients [1]. The excipients may be diluents, binders, disintegrants, glidants and lubricants; lubricants are usually added in the final stages of mixing of the formulation components, prior to compression or encapsulation. Both tablets and capsules require lubricants in their formulations in order to reduce the friction between the powder and metal surfaces. The main function of the lubricants is to prevent the adhesion of compacts to the surface of the punches, dyes or encapsulating tools used in pharmaceutical manufacture [2,3].

Magnesium stearate is the lubricant most widely used during tablet compaction and capsule filling operations in the pharmaceutical industry. It is preferred because of its low cost, its high lubrication potential, its high melting point and its chemical stability. It is well known that magnesium stearate acts as a lubricant by forming a semi-continuous film on larger excipient particles due to its very small particle size [4–6]. As with other salts of fatty acids, its activity is believed to derive from the adhesion of the polar metal portion of the molecule to the powder/granule particle surface. As a consequence, the non-polar hydrocarbon moiety of the molecule is oriented away from the surface [7] towards the adjacent powder/granules particles and structures such as the press or encapsulate tooling. The advantages and

*Corresponding author. Email: p.kasa@pharm.u-szeged.hu

ISSN 0169-4243 print/ISSN 1568-5616 online

http://dx.doi.org/10.1080/01694243.2012.701481
http://www.tandfonline.com

disadvantages of the use of magnesium stearate in tablets or capsules arise from the behaviour of this non-polar layer. For example, its hydrophobic nature often retards liquid penetration into the capsule ingredients, so that a capsule-shaped plug often remains after the shell has dissolved in the gastrointestinal fluids, especially when the contents have been machine-filled as a consolidated plug [2].

The lubrication effect is influenced by the mixing time and speed, the specific surface area and the spreading coefficient of the magnesium stearate. The spreading coefficient can be calculated via the free surface energy [8,9], which is widely assessed indirectly from wettability measurements [10–12]. In the method of Wu and Brzozowski, the surface free energy is taken as the sum of the dispersive and the polar components. The surface free energies of solid materials can be determined by means of contact angle measurements, using two liquids with known polarities, which involve the solution of an equation with two unknowns (Equation (1)) [13]:

$$(1+\cos\Theta)\gamma_l = \frac{4(\gamma_s^d\gamma_l^d)}{\gamma_s^d+\gamma_l^d} + \frac{4(\gamma_s^p\gamma_l^p)}{\gamma_s^p+\gamma_l^p} \tag{1}$$

where Θ is the contact angle, γ_s is the solid surface free energy, and γ_l is the liquid surface tension. If the surface free energies of the solid materials are known, the spreading coefficient (S) can be computed and the interactions between the two materials can be predicted. S is calculated as the difference between the adhesion work and the cohesion work. The two materials that interact can be two powders, a powder and a liquid (e.g. a core and a layering fluid), or any material and an equipment.

The spreading coefficient (S_{12}) of one material (1) over the surface of another material (2) can be determined according to the following equation (Equation (2)) [14]:

$$S_{12} = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d} + \frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p} - \frac{\gamma_1}{2}\right] \tag{2}$$

The spreading coefficient shows how one of the substances extends over the other one. If this is a positive number, then the examined substance spreading is preferred. The higher the number, the greater the spreading. If this number is small or negative it means that the material cannot stretch out on the granules of the other substance. So, if the spreading of the layering material on the surface of the core is insufficient, the efficiency of layering and the properties of the layer formed may be restricted.

The aim of the present study was to test the effects of various parameters on the distribution of magnesium stearate on the surface of particles in the mixtures.

A compact table-top energy-dispersive X-ray fluorimeter was used for the elemental analysis of magnesium. This technique is suitable for the direct measurement in drugs of the elements ranging from sodium to uranium [5,15].

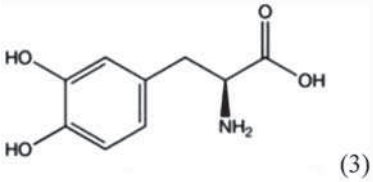
When a material is irradiated by the beam from an X-ray tube, its constituent atoms are excited. This causes them to emit X-ray fluorescence. Each element in the sample emits its own uniquely characteristic fluorescent radiation, with an intensity directly related to the concentration of that element in the material. This phenomenon is the basis of X-ray fluorescence spectrometry. The fluorescence comprises discrete X-ray photons emitted at various (characteristic) energy levels. Photons of all energies are received simultaneously by the detector of the spectrometer and converted into a series of electrical signals, which are electronically amplified, processed and transformed into digital values. The digital values are stored in a multichannel analyser, which separates them according to the energy levels of the photon. The result is the spectrum for the sample, which is further processed by the software to deliver a result calculated directly in terms of element concentrations [16].

2. Materials and methods

2.1. Materials

Two types of magnesium stearate were used as lubricants, with different specific surface areas: 8–10 m^2/g (Peter Greven Nederland, Venlo, the Netherlands) and 2.5 m^2/g (Undesa, Union Derivan, S.A., Barcelona, Spain)

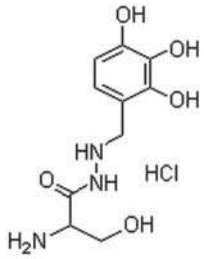
The other materials applied were levodopa (TEVA PFC S.R.L., Italy) (3) and benserazide hydrochloride (CHEMI S. p. A., Italy) (4) (Ph.Eur.) and granule containing both the active ingredients.



(3)

Levodopa

(S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid



(4)

Benserazide hydrochloride

2'-(2,3,4-Trihydroxybenzyl)-DL-serinohydrazide monohydrochloride

2.2. Methods

2.2.1. Blending

The granules were mixed separately with 1 w/w% of the two types of magnesium stearate in a Turbula mixer (W.A. Bachofen Maschinenfabrik, Switzerland). The two mixtures were blended in two ways to prepare samples for examinations:

(a) at a fixed blending speed of 25 rpm for various times (2, 5, 8, 10 and 15 min), and
(b) at various blending speeds (25, 50, 75 and 90 rpm) for a fixed time of 5 min.

2.2.2. X-ray fluorescence analysis

Measurements on the samples were made with a Philips MiniPal PW 4025 (MiniPal, Philips Analytical, Almelo, the Netherlands) energy dispersive X-ray fluorescence analyser. During the measurements, the conditions applied were 4 kV, 1000 A and 1 bar He purge. The samples were measured for 600 s, and the measurements were repeated in triplicate for each sample. The concentration of magnesium was calculated by means of linear calibration ($r^2 = 0.9980$) from the intensities of the *K* lines of the detected radiation. The *K* value of magnesium occurs at 1.253 keV (Figure 1).

2.2.3. Morphological study

The surfaces of the samples were tested with a scanning electron microscope (SEM) (Hitachi S4700, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A sputter coating unit (Polaron E5100, VG Microtech, UK) with gold cathode was used to charge the surfaces for the SEM measurements. The air pressure during the analyses was 1.3–13 mPa.

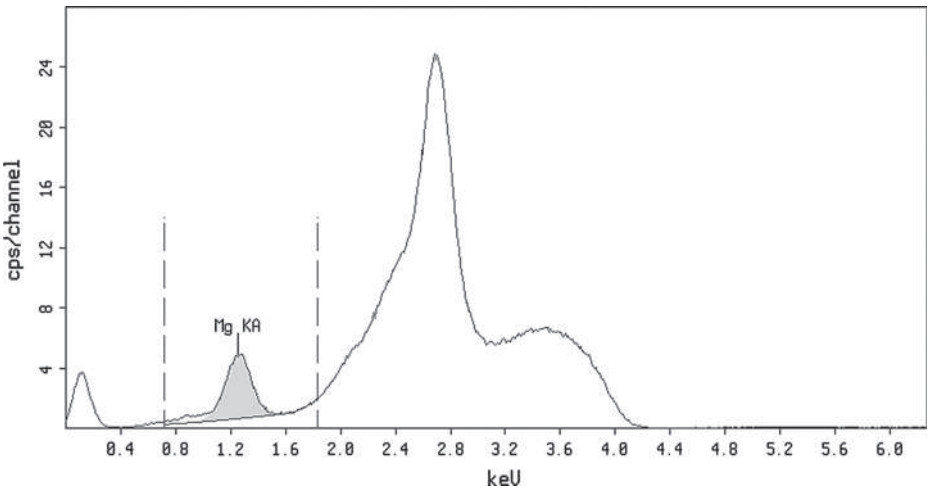


Figure 1. Energy dispersive spectrum of Mg.

2.2.4. *Measurement of contact angle*

Contact angles were measured on flat comprimates 12 mm in diameter and 4 mm in height, compressed with a hydraulic press (Röltgen GmbH & Company KG, Sollingen, Germany) at 1 MPa from the bulk materials (levodopa, benserazide hydrochloride, granules and magnesium stearate).

An automatic syringe was used for the dropping, and circle fitting was applied to determine the contact angles formed on comprimates prepared from different samples. The test fluids were distilled water and diiodomethane (Merck KGaA, Darmstadt, Germany). In the case of water, the drop volume was 10 µl (hydrophilic liquid), while in the case of diiodomethane (hydrophobic liquid), it was 3 µl. The advancing contact angles were measured. In the case of water the drop age was 5 s, and in the case of diiodomethane, it was 2 s. According to Ström [17], the dispersion component of the surface tension is 21.8 mN/m for water and 50.8 mN/m for diiodomethane, while the polar component of the surface tension is 51.0 mN/m for water and 0.0 mN/m for diiodomethane.

3. Results and discussion

The SEM micrographs showed that the magnesium stearate with higher specific surface area (Figure 2) was evenly distributed over the granule surface, while the magnesium stearate with lower specific surface area (Figure 3) exhibited enrichment on the surface of the particles. The difference in grain size between the two types of magnesium stearate was clearly visible.

The samples were examined by X-ray fluorimeter. At constant blending speed, with variation of the duration of blending, magnesium concentration was the highest at the duration of 8 min (Figure 4) for both types pf magnesium stearate. This phenomenon demonstrates that the covering of the particles by magnesium stearate is the highest at this time. After a longer mixing time, an overmixing can be observed.

Additionally, it was seen that the magnesium stearate with lower specific surface area resulted in higher magnesium concentrations. This is in accordance with the visual observations (Figures 2 and 3) that the particles containing magnesium stearate with higher specific surface area formed a thinner, but uniform layer.

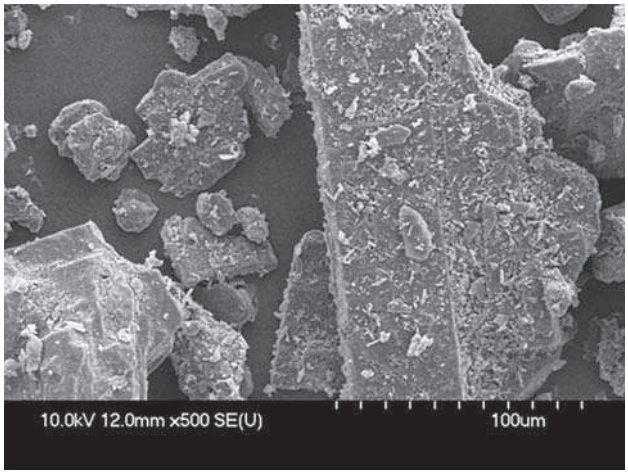


Figure 2. Distribution of magnesium stearate with the higher specific surface area (Peter Greven) on the surface of the granules.

When the blending was performed for a fixed period of time at different blending speeds, it was found that the highest magnesium content was measured at 25 rpm for both forms of magnesium stearate (Figure 5), with higher speeds again leading to overmixing. The magnesium stearate layer was thinner, but further increase in the speed did not cause any change in the homogeneity for the 5-min blending.

The lubrication effect of magnesium stearate depends on its spreading ability on the surface of the particles. The spreading coefficient can be calculated from the wetting contact angles. From these data, it is possible to calculate the total surface free energy, its polar and dispersive parts, and the adhesion work. The data are presented in Table 1.

It can be seen from the data that levodopa and benserazide have high surface free energies and their characteristics strongly influence the surface properties of the granules (Table 1,

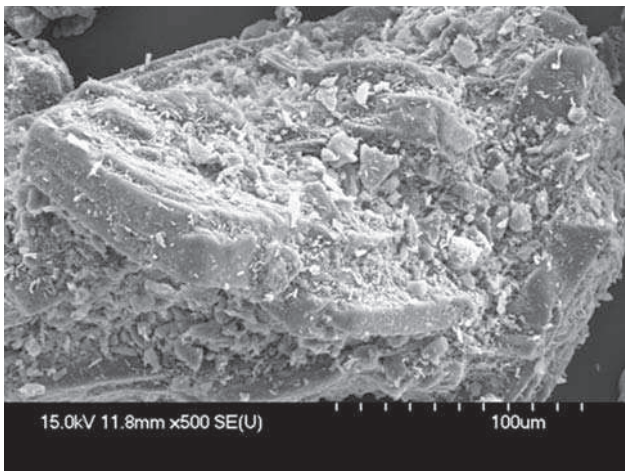


Figure 3. Distribution of magnesium stearate with the lower specific surface area (Undesa) on the surface of the granules.

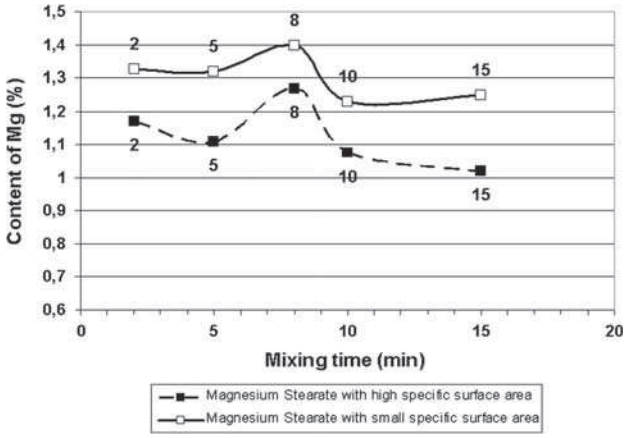


Figure 4. Influence of blending time at blending speed of 25 rpm on the distribution of magnesium on the surface of particles.

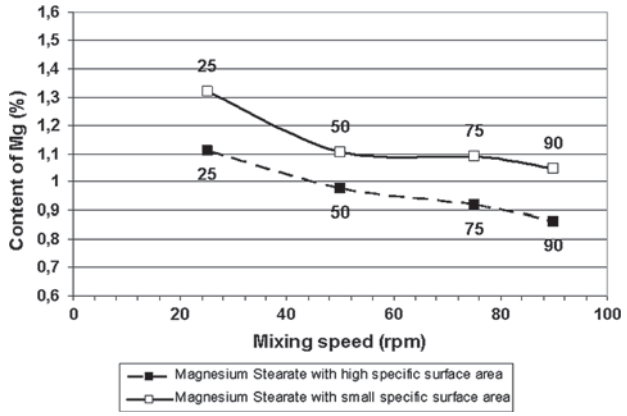


Figure 5. Influence of blending speed on the distribution of magnesium at a blending time 5 min.

Table 1. Parameters of surface properties of particles.

First material	Second material	S_E1 (mN/m)	S_d1 (mN/m)	S_p1 (mN/m)	S_E2 (mN/m)	S_d2 (mN/m)	S_p2 (mN/m)	W_a (mJ/m^2)	$S_{1,2}$ (mN/m)
Mgst (high spec. surface area)	Levodopa	22.68	22.68	0	84.87	49.05	35.82	62.04	16.68
	Benserazide	22.68	22.68	0	82.85	47.10	35.75	61.23	15.87
	Granule	22.68	22.68	0	82.10	48.28	33.82	61.72	16.36
Mgst (small spec. surface area)	Levodopa	32.18	27.93	4.25	84.87	49.05	35.82	86.38	22.02
	Benserazid	32.18	27.93	4.25	82.85	47.10	35.75	85.33	20.97
	Granule	32.18	27.93	4.25	82.10	48.28	33.82	85.88	21.52

Note: S_E = total surface free energy, S_d = disperse part of free energy, S_p = polar part of free energy, W_a = adhesion work, S_{12} = spreading coefficient.

S_E2). Both types of magnesium stearate have much lower surface free energies, but it is noteworthy that for the magnesium stearate with higher specific surface area, the polar part is zero, and the apolar nature therefore dominates. This affects the value of the spreading

coefficient. Since the magnesium stearate with higher specific surface area is totally apolar it has fewer binding points on the surface of the particles, whereas the magnesium stearate with lower specific surface area can bind only to polar binding points. In this case, the use of magnesium stearate with lower specific surface area is more advantageous.

Since the spreading coefficient value (S_{12}) is positive, magnesium stearate (material 1) spreads on the surface of the other components (material 2). The more positive the S_{12}, the better the spreading. It must be noted that the spreading of the magnesium stearate with lower specific surface area is better and the adhesion work of these samples is higher than for the samples containing magnesium stearate with higher specific surface area.

4. Conclusions

It can be concluded that the two types of magnesium stearate were distributed to different extents on the surface of the particles. The magnesium stearate with higher specific surface area was more polar with higher adhesion work, and it was able to create a very thin homogeneous layer on the surface of the particles. In the case of the magnesium stearate with lower specific surface area, enrichment was observed on the surface of the particles, decreasing the free energy.

It is clear that the surface free energy and polarity of the materials influence the choice of the suitable magnesium stearate (low or high specific surface). It can be stated that the blending speed should not be too high because at longer mixing time the free energy of the other component will be dominant (see Figure 4).

Energy-dispersive X-ray fluorescence analysis was successfully used for the in-process determination of the distribution of magnesium stearate on the surface of the particles. The measurement was rapid and did not require any special sample preparation.

Acknowledgement

The project named "TÁMOP-4.2.1/B-09/1/KONV-2010-0005 – Creating the Center of Excellence at the University of Szeged" is supported by the European Union and co-financed by the European Social Fund.

References

[1] Kottke MK, Rudnic EM. Tablet dosage forms. In: Banker GS, Rhodes ChT, editors. Modern pharmaceutics. New York (NY): Marcel Dekker Inc.; 2002. p. 292–294.

[2] Aulton ME. Aulton's pharmaceutics, the desing and manufacture of medicines. 3rd ed. Edinburgh: Churchill Livingstone, Elsevier; 2007. p. 452–4.

[3] Peck GE, Baley G. Tablet formulation and design. In: Lieberman HA, Lachman L, editors. Pharmaceutical dosage forms: tablets. New York (NY): Marcel Dekker Inc.; 1980. p. 61–98.

[4] Pintye-Hódi K, Tóth I, Kata M. Investigation of the formation of magnesium stearate film by energy dispersive X-ray microanalysis. Pharmaceutica Acta Helvetiae. 1981;56:320–4.

[5] Szalay A, Pintye-Hódi K, Joó K, Erős I. Study of distribution of magnesium stearate with an energy dispersive X-ray fluorescence analyser. Pharmaceutical Industries. 2004;66:221–3.

[6] Roblot-Treupel L, Puisieux F. Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. International Journal of Pharmaceutics. 1986;31:131–6.

[7] Miller TA, York P. Pharmaceutical tablet lubrication. International Journal of Pharmaceutics. 1988;41:1–19.

[8] Buckton G, Darcy P. The influence of additives on the recrystallisation of amorphous spray dried lactose. International Journal of Pharmaceutics. 1995;121:81–7.
[9] Podczeck F. Particle–particle adhesion in pharmaceutical powder handling. London: Imperial College Press; 1998. p. 29–34.
[10] Buckton G. Characterisation of small changes in the physical properties of powders of significance for dry powder inhaler formulations. Advanced Drug Delivery Reviews. 1997;26:17–27.
[11] Planinšek O, Trojak A, Srčič S. The dispersive component of the surface free energy of powders assessed using inverse gas chromatography and contact angle measurements. International Journal of Pharmaceutics. 2001;221:211–7.
[12] Bajdik J, Fehér M, Pintye-Hódi K. Effect of plasticizer on surface of free films prepared from aqueous solutions of salts of cationic polymers with different plasticizers. Applied Surface Science. 2007;253:7303–8.
[13] Wu S, Brzozowski KJ. Surface free energy and polarity of organic pigments. Journal of Colloid and Interface Science. 1971;37:686–90.
[14] Rowe RC. Binder-substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. International Journal of Pharmaceutics. 1989;52:149–54.
[15] Reimer L. Scanning electron microscopy, physics of image formation and microanalysis. Heidelberg: Springer-Verlag; 1985. p. 394–5.
[16] Brouwer P. Theory of XRF. Almelo: PANalytical B.V.; 2003. p. 14–19, 56–58.
[17] Ström G. Krüss users manual, contact angle and adsorption measuring system. Hamburg: Krüss GmbH; 1996. p. 50–77.

III.

Pharmaceutical Development and Technology, 2012; 1–6, Early Online

ISSN 1083-7450 print/ISSN 1097-9867 online
DOI: 10.3109/10837450.2011.646426

informa
healthcare

RESEARCH ARTICLE

Formulation study of directly compressible chewable polymers containing ascorbic acid

P. Kása[1], I. Jójárt[1], A. Kelemen[2], and K. Pintye-Hódi[1]

[1]*Department of Pharmaceutical Technology and* [2]*Department of Applied Informatics, University of Szeged, Szeged, Hungary*

Abstract

The topic of this article is the compression physics of different gum bases which can be used to prepare chewing gum tablets by direct compression. Three different gum bases, Pharmagum® C, M and S, were tested alone and in different combinations. The preparations were compressed with a Korsch EK0 eccentric tableting machine at compression forces of 5, 7.5, 10, 12.5 and 15 kN. The compression and breaking processes and the physical parameters of the tablets were investigated. The results revealed that increase of the compression force did not significantly change the studied parameters of the tablets.

Keywords: Chewing gum, direct compression, deformation, dissolution, Pharmagum, ascorbic acid

Introduction

Chewing gum has been used world-wide since ancient times when man experienced the pleasure of chewing a variety of gum-like substances, such as tree resins, leaves, waxes and animal skins.

The dosage form or delivery system is critical for the success of a pharmaceutical or a food product. Today, chewing gum is undergoing new consideration as a drug delivery system; it provides patient benefit and compliance, and has new competitive advantages from the technological and marketing aspects. Medicated chewing gums are solid, single-dose preparations that have to be chewed but not swallowed. Chewing gums contain one or more active pharmaceutical ingredients (APIs) that are released by chewing (Ph.Eur.).[1] A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded.[2, 3] During the chewing process, the drug contained in the gum product is released from the mass into the saliva and can be absorbed through the oral mucosa or swallowed, reaching the stomach for gastrointestinal absorption.

Chewing gum consists basically of a neutral and tasteless masticatory gumbase and several non-masticatory ingredients, such as fillers, softeners, sweeteners, favoring and texture regulating agents.[1, 4] The gum bases currently used are mostly of synthetic origin and comprised of elastomers, resins, waxes, fats and emulsifiers. The elastomers are styrene–butadiene copolymers mixed with polyisobutene. The addition of rosin esters and polyvinyl acetate improves the texture, allows longer-lasting flavor and reduces the tendency of the gum to stick to the teeth. Other agents, such as glycerol monostearate and lecithin, act as emulsifiers and promote the uptake of saliva during chewing.[5]

Powdered sugar and corn syrup were originally used as bulk sweeteners; nowadays, a mixture of sorbitol, xylitol, mannitol and aspartame is more commonly used in sugar-free, non-cariogenic gums and medicinal products.[6]

Unfortunately, the thermal instability of many active ingredients (vitamins, vegetable extracts, etc.) precludes traditional chewing gum production methods because the temperature profiles associated with this type of production may reach 90°C.[7]

Recently, chewing gums produced by direct compression have been proposed.[8] With this conventional tablet compression technology, these chewing gums can include higher levels of active ingredients than in traditional extruded gums; the lower temperature protects sensitive

Address for Correspondence: Prof. Klára Pintye-Hódi, Department of Pharmaceutical Technology, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary. Tel: +36/62545576. Fax: +36/62545571. E-mail: klara.hodi@pharm.u-szeged.hu

(Received 21 October 2011; revised 29 November 2011; accepted 29 November 2011)

bioactive and phytochemical components and the lower moisture content improves the shelf-life of active molecules. However, the most common drawback in direct compression of the gum base is that it sticks to the punches of the tableting equipment. This is due to the adhesive nature of the gum, the main component of the formulation; for this reason, the procedure is difficult and needs a lower production speed and cooling operations in order to prevent tableting machine damage. The tableting tools are kept at temperatures below 18°C; however, it should be noted that the temperature should not be so low as to interfere with the handling of the medicated gums and the tableting process. Thus, the temperature should be above 10–12°C.

For investigation of the dissolution of active pharmaceutical ingredients (API's) from medicated chewing gum tablets, different apparatuses have been developed. The chewing equipment applied was developed by Erweka GmbH, and described by Kvist et al.[9] Further descriptions of dissolution and chewing gum tablet investigations have been reported by Azarmi et al.[10]

The objective of this work was to study the compression and breaking processes of different gum bases at room temperature by a direct compression technique with conventional pharmaceutical equipment efficiently providing the product, and to investigate the dissolution of an API.

Materials and methods

Materials

Ascorbic acid was used as model material (Ph. Eur.). Pharmagum C, M and S (gifts from SPI Pharma) were used as gum bases. Pharmagum M has a 50% greater gum base than Pharmagum S, which consists primarily of gum base and sorbitol. Pharmagum M contains gum base, mannitol and isomalt.

According to the manufacturer data, Pharmagum S is suitable for formulations with low drug loading and when incorporated into tablets gives them chewable character. Pharmagum M is suggested for medium drug loading (<50%); it improves the mouthfeel texture. Pharmagum C is suggested for high drug loading (>50%); it has a real chewing gum character.

Pharmagum mixtures were prepared in different ratios to study the compactness and deformability (Table 1). Compactness means the permanent bindings which are formed during loading and deformability refers to the shape modification of the particles during loading. Besides ascorbic acid as API, additional components of the mixtures were xylitol (frequently used in tablets as a sweetener), magnesium stearate (as a lubricant) and aroma (to give the tablets a better smell).

Methods

Tableting

The tablets were prepared with a Korsch EK0 eccentric tableting machine, E. Korsch Maschinenfabrik, Germany. The compression tools were flat-faced, bevel-edged punches 10 mm in diameter and equipped with strain gauges and a displacement transducer. The strain gauges allowed the pressure forces on the upper and lower punches to be followed with force-measuring equipment, which was calibrated with a Wazau HM-HN-30kN-D cell (Kaliber Ltd., Budapest, Hungary). The displacement transducer (Micropulse, BTL5-A11-M0050-P-532, Balluff, Neuhausen/Filder, Germany) was fitted over the upper punch. The transducer distance accuracy was checked by using five measuring pieces of different accurately known thicknesses (2.0, 5.0, 7.5, 10.0 and 15.0 mm) under zero load (Mitutoyo, Tokyo, Japan). The compression was carried out electrically at 36 rpm, at an air temperature of 24°C and at a relative air humidity of 45%. The average mass of the tablets was 0.47 ± 0.01 g. Ten tablets were compressed at compression forces of 5, 7.5, 10, 12.5 and 15 kN for each sample (when possible). Lots with relative standard deviations not exceeding 5% were accepted.

The force–displacement curves were plotted, and the compression parameters – effective work (E_2), elastic recovery (E_3) and plasticity (P_l) – were calculated from the curves with our own software Kása et al.[11]

The E_1, E_2 and E_3 energies are calculated by the following equations:

$$E_1 = \frac{F_{max} C}{2} - (E_2 + E_3) \quad (1)$$

$$E_2 = \int_A^B F_{\text{upper}}\, ds - E_3 \quad (2)$$

$$E_3 = \int_B^D F_{\text{upper}}\, ds \quad (3)$$

where

F_{max} = maximum force during compressing; C = displacement; F_{upper} = maximum force measured on the upper punch; ds = elemental value of the displacement.

The plasticity was calculated with the formula: Pl = E2 / E2 + E3.

Table 1. Compositions of powder mixtures.

	Pharmagum (%)		
	C	M	S
S 1	60	40	
S 2	50	50	
S 3	40	60	
S 4	60		40
S 5	50		50
S 6	40		60
S 7		60	40
S 8		50	50
S 9		40	60
The amounts of the following materials were the same in all cases (%)			
Ascorbic acid	8.33		
Xylitol	7.68		
Aroma	0.33		
Magnesium stearate	2		

API concentration: 33 mg/tablet.
Average tablet weight: 0.47 g.

The real force–displacement diagram can be seen in Figure 1. (S1 sample) where $E_1 = 44.58\%$, $E_2 = 46.22\%$ and $E_3 = 9.21\%$.

Friability test

The friability of the chewing gum tablets was tested with an Erweka TA 100 friabilator (Erweka GmbH, Heusenstamm, Germany).

Breaking strength

The breaking strength was tested with a self-developed tablet hardness tester, which is connected to a computer and a special software is applied to edit the force–time diagram.

Technical parameters of the hardness tester:

- Range of measurement: 0–200 N
- Rate of pressing jaw: 20 mm/min
- Registration output: 0–500 mV
- Force sensor: Unicell load cell (MIKI) 200 N

Preparation of mixtures

The mixtures of two of the Pharmagum materials in various ratios were prepared with a Turbula mixer (Willy A Bachofen, Switzerland) at 50 rpm for 8 min, after which the other components were added, and mixing was continued for a further 2 min (Table 2). The mass of each powder mixture was 200 g.

Dissolution test

Conventional tablet or capsule dissolution testers are not applicable for the investigation of chewing gum tablets because of the nature of the preparation. Solid oral dosage forms are generally swallowed and the API subsequently dissolves in various parts of the gastrointestinal tract. Chewing gum tablets are usually not swallowed but masticated, and the API dissolves in a very small amount of dissolution medium. The effective material does not come into direct contact with the stomach, but must dissolve in the saliva. After dissolution, the saliva is swallowed and only a diluted quantity of the API reaches the gastric juice.

For the dissolution tests, an Erweka chewing apparatus was used.[9] Each chewing gum sample was chewed with this apparatus for 10, 20 or 30 min, in the presence of 20 of dissolution medium (purified water), after which the ascorbic acid content of the liquid was determined by spectrometry.

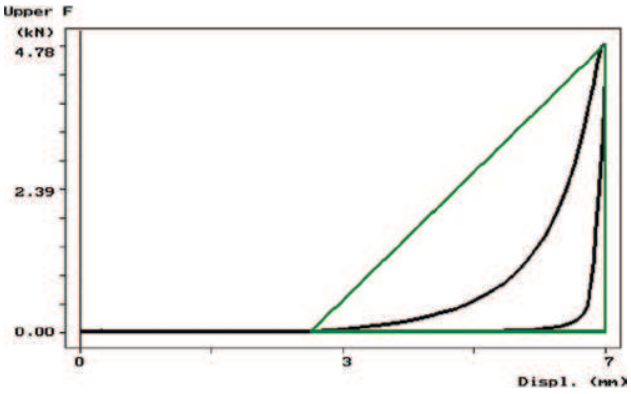


Figure 1. Recorded force–displacement diagram of S1 sample.

Table 3. Compressionability of the mixtures.

	B.d. g/cm^3	T.d. g/cm^3	C.i. %	Tr.d. g/cm^3
S 1	0.59	0.64	8.72	1.31
S 2	0.58	0.64	10.00	1.31
S 3	0.59	0.64	7.95	1.32
S 4	0.68	0.74	8.46	1.33
S 5	0.71	0.76	5.38	1.33
S 6	0.70	0.74	4.88	1.33
S 7	0.70	0.73	4.61	1.32
S 8	0.70	0.75	5.90	1.33
S 9	0.72	0.77	6.41	1.33

B.d., bulk density; C.i., Carr's index; T.d., tapped density; Tr.d., true density.

Table 2. Powder rheological test.

	Material of the funnel	Flowing time (s)	Agitation speed (r/min)	Angle of slope (°)	Heap volume (ml)	Heap mass (g)
Ascorb. acid	T	12.3	25	33.1	85.6	77.8
Phg C	T/M	–	–	–	–	–
Phg M	T/M	–	–	–	–	–
Phg S	T	7.5	25	26.2	64.4	56.6
S 1	M	12.3	10	29.3	73.4	58.8
S 2	M	10.3	10	29.4	73.9	59.7
S 3	M	10.0	10	29.8	75.0	58.8
S 4	M	7.6	5	26.6	65.6	66.9
S 5	M	7.3	10	27.5	68.2	67.8
S 6	M	7.4	10	28.3	70.6	65.5
S 7	M	8.3	10	29.1	73.0	66.4
S 8	M	8.4	10	28.4	70.9	68.6
S 9	M	8.1	10	28.1	71.5	69.3

M, metal; T, teflon.
– = not measurable.

Results and discussion

The tests on the flow properties of the bulk gum samples showed that Pharmagum C and M could not flow out from either a teflon or a metal funnel, in spite of the agitation of the powder. Pharmagum S displayed good flowability from a teflon funnel on mixing at 25 rpm (Table 3). The API flowed from a teflon funnel on agitation at 25 rpm.

Table 4. Effect of compression force on elasticity and friction for bulk gum bases.

Sample	F_{upper} (kN)	FW (J)	E_3 (J)
Gum C	5	0.022	0.43
	10	0.037	1.35
	15	0.047	3.61
Gum M	5	0.003	0.25
	10	0.013	1.24
	15	0.066	2.90
Gum S	5	0.100	0.49
	10	0.138	1.12
	15	0.162	3.91

FW shows the work which arises during the tablet ejection.
E_3 shows the elastic recovery.

The compaction tests on the bulk materials resulted in every case in high elastic recovery (Table 4). As concerns tablettability, the flowability and compactness can be important properties. Solid bridges formed during compression phase can be broken in the elastic recovery phase. In the tablet compositions, therefore the bulk gum powders were mixed with the other components in different ratios (Table 1).

Table 5. Relationship between compositions and E_3 areas.

	Compositions (Gum base)			E_3 (J) Compression forces (kN)				
Sample	C	M	S	5	7.5	10	12.5	15
S 1	60	40	–	0.48	1.07	1.69	2.51	3.36
S 2	50	50	–	0.42	1.10	1.76	2.16	2.59
S 3	40	60	–	0.36	0.98	1.56	2.04	2.60
S 4	60	–	40	0.70	1.30	1.84	2.30	2.72
S 5	50	–	50	0.62	1.07	1.52	2.26	2.89
S 6	40	–	60	0.67	1.05	1.49	2.19	3.05
S 7	–	60	40	0.56	1.03	1.55	2.36	3.01
S 8	–	50	50	0.61	1.05	1.55	2.27	3.02
S 9	–	40	60	0.58	1.06	1.56	2.29	3.02

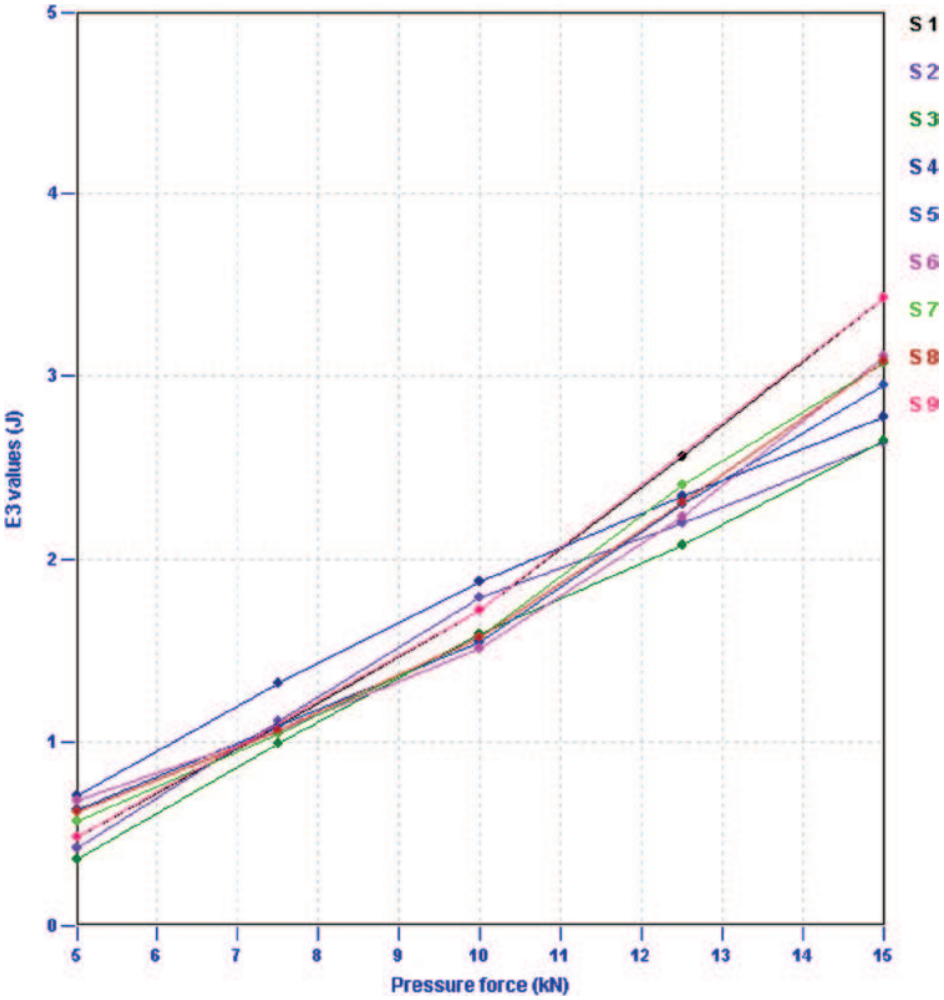


Figure 2. Relationship between the Pressure force and Elastic recovery. (See colour version of this figure online at www.informahealthcare.com/phd)

The data in Table 3 reveal that the powder mixtures could flow from a metal funnel on moderate stirring. Mixture S4, which contains Pharmagum S, exhibited the best flowability to which an agitation speed of only 5 rpm was applied. The flowability properties of the mixtures containing Pharmagum S were generally better. These data are in accordance with the other powder rheological parameters.

The Carr index, calculated from the bulk and tapped densities, indicates that the powder mixtures have excellent compressibility (Table 3). However the mixtures adhered to the punches during tableting, which is an unfavorable property. Fortunately, this could be eliminated through the use of a teflon film on the punch surface.

The different compression parameters for the mixtures were calculated at different compression forces (effective work = E_2, elastic recovery = E_3, plasticity = P_1).

For gums, elasticity is the most important property. After the compression maximum, when the upper punch starts to move upwards, elastic materials display some recovery. The degree of elastic recovery varied linearly with the compression force ($y = ax + b$, where $y = E_3$, a = slope, x = compression force, and b = intercept), with a very good correlation ($R^2 = 0.984–0.999$) (Figure 2). Further, the degree of elastic recovery increased in all mixtures after compression (Table 5). Pharmagum M influenced the elastic recovery to the highest degree. S1, S2 and S3 tablets had the smallest E_3 values at a compression force of 5 kN and these values decreased linearly with increasing Pharmagum M content. (from the aspect of tableting, the smallest E_3 value is advantageous.) For S2 and S3 tablets, the decreases in E_3 were smaller, and at 10 and 15 kN the Pharmagum M and C ratios of 50:50 and 40:60 had practically no effect on the E_3 values. For the other mixtures, the ratio usually had very little effect on the degree of elastic recovery at different compression forces, except for the S6 mixture compressed at 15 kN. The elastic properties of the API and other ingredients do not have such high effect which causes any changes of the elastic behavior of the gum bases.

The friability of the tablets was less than 0.1% in all cases, and they met the requirements of Ph.Eur., but this is expected from a gum tablet. Another postcompression test involves the breaking strength; this differs from the case of conventional tablets because after crushing the tablets did not break completely. The deformation curves during loading demonstrate elastic deformation with a rather high slope (Figure 3). After a maximum, the force decreased, but the tablet did not break into small pieces; only deformation was observed, with some cracks. Increase of the pressure did not cause any significant changes in the breaking process. If the E_3 value is low the deformation force is high, which means that the appropriate chewability needs a higher force.

During the dissolution investigation the 5, 10, and 15 kN, compressed samples were tested. The results show that the dissolution of ascorbic acid did not depend on the compression force (Figure 4). In all cases, 90% of the

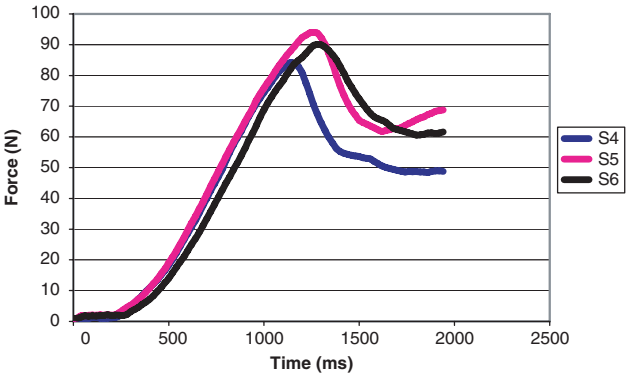


Figure 3. Deformation curves during loading (samples S4, S5 and S6, pressure force 5 kN). (See colour version of this figure online at www.informahealthcare.com/phd)

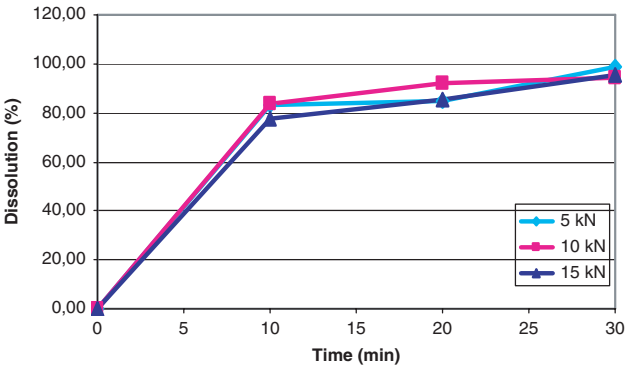


Figure 4. Dissolution profile of sample S5.

API dissolved in the first 10 min, and after chewing for 30 min the whole amount had dissolved.

Conclusions

The powder rheological parameters, and especially the flowability, conclude that Pharmagum C and M are not suitable for the preparation of direct-compressed chewing gum tablets. Pharmagum S increased the powder rheological properties and the compressibility, but all of the compositions resulted in suitable tablets at a compression force of 5 kN. The physical parameters and the dissolution rate from these tablets were very good, so that increase of the compression force was unnecessary.

Finally, it can be stated that chewing gum is an alternative drug delivery system with several advantages especially for kids and geriatric patients who experience difficulties swallowing the traditional oral solid dosage forms, and it is possible to prepare by direct compression, which is economic preparation procedure.

Acknowledgments

The authors' thanks go to Erweka GmbH, Heusenstamm, for help with the dissolution investigations.

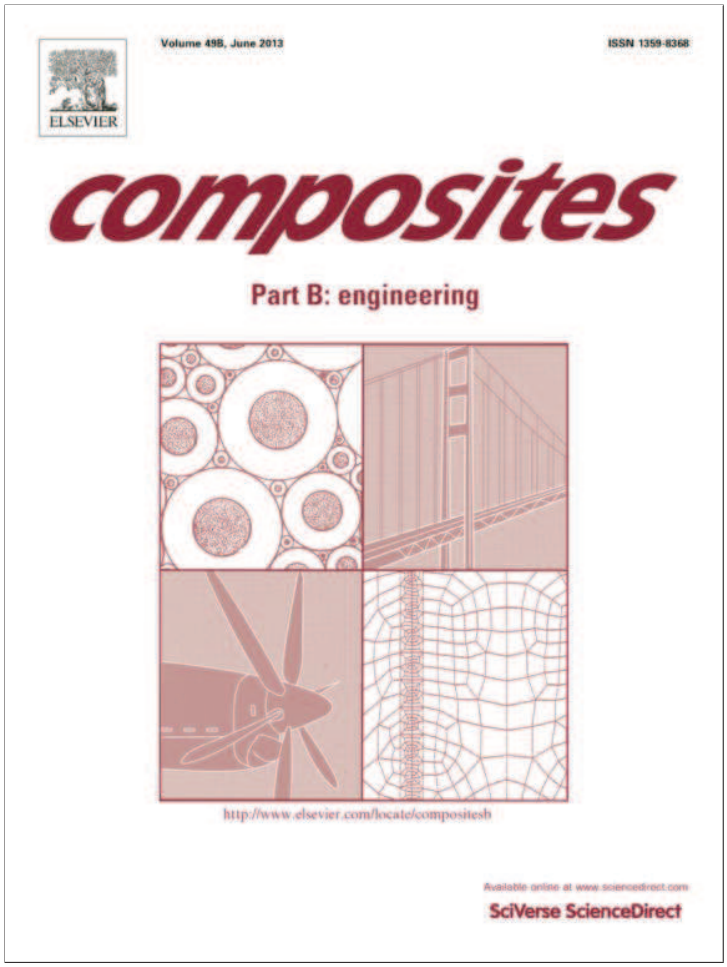
Declaration of interest

The project named TÁMOP-4.2.1/B-09/1/Konv-2010-0005– Creating the Center of Excellence at the University of Szeged" is supported by the European Union and co-financed by the European Regional Fund.

References

1. Barabolak R, Hoerman K, Kroll B, Record D. Gum chewing profiles in the U.S. population. Community Dent Oral Epidemiol 1991;19:125–126.
2. Rider JN, Brunson EL, Chambliss WG, Cleary RW, Hikal AH, Rider PH et al. Development and evaluation of a novel dissolution apparatus for medicated chewing gum products. Pharm Res 1992;9:255–259.
3. Rassing MR. Chewing gum as a drug delivery system. Adv Drug Del Rev 1994;13:89–121.
4. Eisenstadt B, Cash PA, Bakal AI. US Patent 1998;5:846,557.
5. Pedersen M, Rassing MR. Chewing gum as a drug delivery system for nystatin influence of solubilising agents upon the release of water insoluble drugs. Drug Dev Ind Pharm 1990;16: 2015–2030.
6. Rowe RC. By gum–a buccal delivery system. Drug Discov Today 2003;8:617–618.
7. Zyck DJ, Greenberg MJ, Barkalow DG, Marske SW, Schnell PG, Mazzone P, Witkewits DL. US Patent 1999;6:541,048.
8. Testa ES. US Patent 1999;5:866,179.
9. Kvist C, Andersson SB, Fors S, Wennergren B, Berglund J. Apparatus for studying *in vitro* drug release from medicated chewing gums. Int J Pharm 1999;189:57–65.
10. Azarmi S, Roa W, Löbenberg R. Current perspectives in dissolution testing of conventional and novel dosage forms. Int J Pharm 2007;328:12–21.
11. Kása P, Bajdik J, Zsigmond ZS, Pintye-Hódi K. Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. Chem Eng Process 2009;48:859–863.

IV.



Composites: Part B 49 (2013) 1–5

Contents lists available at SciVerse ScienceDirect

Composites: Part B

journal homepage: www.elsevier.com/locate/compositesb

Tracking of the post-compressional behaviour of chewing gum tablets

Imre Jójárt [a], András Kelemen [b], Péter Kása Jr. [a], Klára Pintye-Hódi [a,*]

[a] Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary
[b] Department of Applied Informatics, University of Szeged, Boldogasszony sgt. 6, H-6725 Szeged, Hungary

ARTICLE INFO

Article history:
Received 29 August 2012
Received in revised form 22 November 2012
Accepted 13 January 2013
Available online 22 January 2013

Keywords:
B. Elasticity
B. Plastic deformation
B. Stress relaxation
E. Powder processing

ABSTRACT

The elasticity and elastic recovery of chewing gum powder were tested in this work. Powder rheological tests (flowability and compressibility) showed that direct compression is a suitable method for the preparation of chewing gum tablets. The advantages of this method relative to preparation by extrusion are economic: a reduced processing time, fewer manufacturing steps, less equipment, less process validation and reduced labour costs.

A very important property of a chewing gum tablet is the chewability, which depends on the elasticity of the product. This was tested by breaking strength measurements and study of the deformation process. For a good chewable tablet, the authors suggest application of a compression force of 5 kN.

1. Introduction

Chewing gum is currently receiving increasing consideration as a drug delivery system. Medicated chewing gums are solid, single-dose preparations that have to be chewed and not swallowed; chewing gums contain one or more active ingredients that are released by chewing. Medicated chewing gums are made with a tasteless masticatory gum base that consists of natural or synthetic elastomers. They may contain other excipients, such as fillers, softeners, sweetening agents, flavouring substances, stabilizers, plasticizers and authorized colouring matter (European Pharmacopoea (Ph. Eur.)).

Chewing gums produced by direct compression have recently been proposed [1]. With conventional tablet compression technology, these chewing gums can include higher levels of active ingredients than those in traditional extruded gums, the lower temperature protects sensitive bioactive and phytochemical components, and the lower moisture content improves the shelf-life of active molecules. However, the most common drawback of the direct compression of the gum base is that it sticks to the punches of the tableting equipment. This is due to the adhesive nature of the gum, the main component of the formulation; for this reason, the procedure is rather difficult and demands a lower production speed and cooling operations in order to prevent tableting machine damage. From a formulation aspect, it is very important to know the properties of compressed tablets.

The objective of the present work was to study the elastic recovery of a gum base prepared at room temperature by a direct compression technique, by means of thickness, diameter and hardness measurements.

2. Background

As a result of the elastic recovery, the structure of tablets after compression exhibits various phenomena, which change the volume and the porosity. The driving forces for elastic recovery are the bonding forces (i.e. van der Waals forces, solid bridges, electrostatic forces, hydrogen-bonds, etc.) and the elastic energy (stress) stored in the particles during densification. The stored stress can be released, and increase the tablet volume and porosity. However, the bonding forces which are associated with the stress simultaneously decrease the tablet volume and porosity. The elastic recovery (ER) can be defined as the following equation:

$$\mathrm{ER} = \frac{V_t - V_{\min}}{V_{\min}} \tag{1}$$

The elastic recovery provides information on the residual elasticity of the given material [2]. The degree of elastic recovery depends on the properties of the materials. Elastic recovery starts immediately after the compression phase and is completed after several days, the duration depending on the material.

The definition of tablet hardness is generally accepted as the force required to break a tablet in a diametrical compression test. To measure the force required to break a tablet, we determined the tensile strength of the tablet via the following expression [3]:

$$\sigma_x = \frac{2 \cdot F}{\pi \cdot d \cdot t} \tag{2}$$

* Corresponding author. Tel.: +36 62 545576; fax: +36 62 545571.
E-mail address: klara.hodi@pharm.u-szeged.hu (K. Pintye-Hódi).

1359-8368/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.compositesb.2013.01.003

Table 1
Composition of the gum powder.

Material	Amount (%)
Gum base	28–32
Sorbitol	Up to 100
Xylitol	8–12
Plasticizer	<1.5
Antitacking agent (E-551)	<2.0

3. Materials and methods

3.1. Materials

A directly compressible gum composition was used as model material (Health in Gum) (CAFOSA GUM, S.A.U., Barcelona, Spain) (Table 1).

All the materials used (excluding the gum base) in this product comply with their Ph. Eur. and USP monographs. All the materials used in the gum base comply with the USA Food and Drug Administration, Code of Federal Regulations, title 21, sect. 172.615 and Food Chemicals Codex Specifications.

3.2. Methods

3.2.1. Flow properties and moisture content

The *flow properties* of the gum powder were determined with a Pharma Test PTG-1 powder rheological tester (Pharma Test Apparatebau, Germany).

The compaction behaviour of the materials was tested with an Engelsmann stampfvolumeter (J. Engelsmann A-G, Ludwigshafen, Germany).

The *moisture content* of the gum powder was determined with a moisture analyzer (HR73 Halogen Moisture Analyzer, Mettler-Toledo GmbH, Greifensee, Switzerland). The standard drying program was used, with a drying temperature of 105 °C. The sample was heated to 105 °C and then held constant at that temperature. The powder was dried to constant mass.

Three parallel experiments were performed.

3.2.2. Tableting

The tablets were prepared with a Korsch EK0 eccentric tableting machine. The compression tools were flat-faced bevel-edged punches 10 mm in diameter and equipped with strain gauges and a displacement transducer. The strain gauges allowed the pressure forces on the upper and lower punches to be followed with force-measuring equipment, which was calibrated with a Wazau HM-HN-30kN-D cell (Kaliber Ltd., Budapest, Hungary). The displacement transducer (Micropulse, BTL5-A11-M0050-P-532, Balluff, Neuhausen/Filder, Germany) was fitted over the upper punch. The transducer distance accuracy was checked by using five measuring pieces of different accurately known thicknesses (2.0, 5.0, 7.5, 10.0 and 15.0 mm) under zero load (Mitutoyo, Tokyo, Japan). The compression was carried out electrically at 36 rpm, at an air temperature of 24 °C and a relative air humidity of 45%. The average mass of the tablets was 0.40 ± 0.02 g. 150 tablets were compressed at compression forces of approximately 5, 10, 12.5 and 15 ± 1 kN. Lots with relative standard deviations not exceeding 5% were accepted. The force–displacement curves were plotted, and the different energy/work relations were calculated from the curves with our own software [4].

The tablets were stored in airtight plastic containers, at an air temperature of 24 °C and a relative air humidity of 45%.

3.2.3. Breaking strength

The breaking process was tested with a modified breaking hardness tester, which was connected to a computer, and special own-developed software was applied to record the force–time diagram.

The tester contained a specimen holder and a jowl, and was connected to a computer via an interface. The specimen was lo-

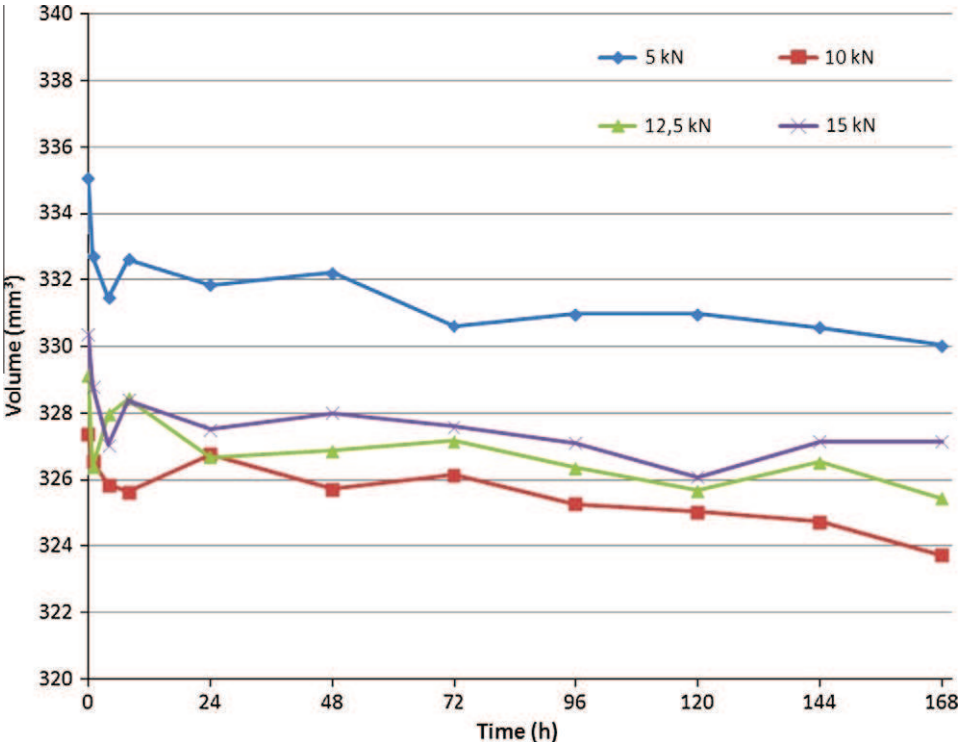


Fig. 1. Volume changes of the comprimates.

Table 2
Geometrical parameters of tablets.

Compression force (kN)	Diameter[a] (mm)			Thickness (mm)[a]		
	Fresh	1 day	7 days	Fresh	1 day	7 days
5	10.030	10.010	9.997	4.242	4.217	4.206
10	10.041	10.021	10.005	4.136	4.142	4.120
12.5	10.044	10.027	10.013	4.155	4.139	4.135
15	10.044	10.025	10.021	4.172	4.151	4.150

[a] *SD* < ±5%.

Table 3
Tablet strength data.

Compression force (kN)	Breaking strength[a] (N)			Tensile strength[a] (MPa)		
	Fresh	1 day	7 days	Fresh	1 day	7 days
5	60	70	85	0.90	1.05	1.29
10	59	61	74	0.90	0.93	1.15
12.5	55	61	76	0.84	0.94	1.17
15	55	61	77	0.84	0.94	1.18

[a] *SD* < ±5%.

cated horizontally on a special plate and the jowl moved vertically. Twenty parallel measurements were performed.

The measurement range was 0–200 N, the speed of the stamp was 20 mm/min and the output was 0–5 V. The sensor was a Unicell force-measuring instrument (MIKI), calibrated with the C9B 20 kN cell.

3.2.4. Geometrical parameter measurements

The height and the diameter of the tablets were measured with a digital micrometer (Mitutoyo, Tokyo, Japan). The measured and the calculated average values were printed out. Twenty tablets were measured for each sample. The average tablet volume was determined according to the following equation:

$$V = t\left(\frac{d}{2}\right)^2 \pi \tag{3}$$

where t is the thickness, and d is the diameter.

The geometrical parameters were measured at the following sampling times: directly after compression, and after storage times of 1, 4, 8 and 24 h and 2, 3, 4, 5, 6 and 7 days following tablet pressing. (In view of the large number of data, only selected data on the fresh tablet and the data after 1 and 7 days of storage are presented in the tables.)

4. Results and discussion

Moisture content determination is an important preformulation test before tableting. It influences the flow properties of granules or powders, which must flow freely into the die cavity during tableting. The Hausner factor and Carr's index are calculated from the poured and tapped densities of the powder. A Hausner factor of less than 1.25 (equivalent to a Carr's index of 20%) indicates good flow; when it is greater than 1.5 (a Carr's index of 33%), it indicates poor flow. The moisture content of the gum powder was rather low (0.3%), and the flowability was very good (flow time: 8.4 s). This means that the gum powder could flow freely in the die during the compression. The values of the Hausner factor (1.102) and Carr's ($Carr_i$ = 9.23%) showed that the arrangement of the particles was also good [5].

It is clear from the tablet volume changes (Fig. 1) that the application of higher compression forces imposes too much on the gum stress during storage. When the compression force is higher than a certain limit, the gum loses its elasticity. As noted above, the driving forces for the final stage of tablet formation are the bonding forces and the stress stored in the gum. The gum strives to release the stored stress by increasing the volume of the tablet, while the bonding forces decrease the volume. This phenomenon is very well observable at pressure force of 5, 10 and 12.5 kN (Fig. 1). At 15 kN, the gum loses its elasticity and thus the main driving forces in the final formation stage are the bonding forces.

The geometrical parameters of the tablets can be seen in Table 2. The post-compressional geometrical changes in the tablets must be taken into consideration, especially in blister packaging. In this case, the geometrical parameters determine the depth and diameter of the blister cavity.

It can be concluded from the data that both the diameter and the thickness of the tablets decreased continuously during 7 days

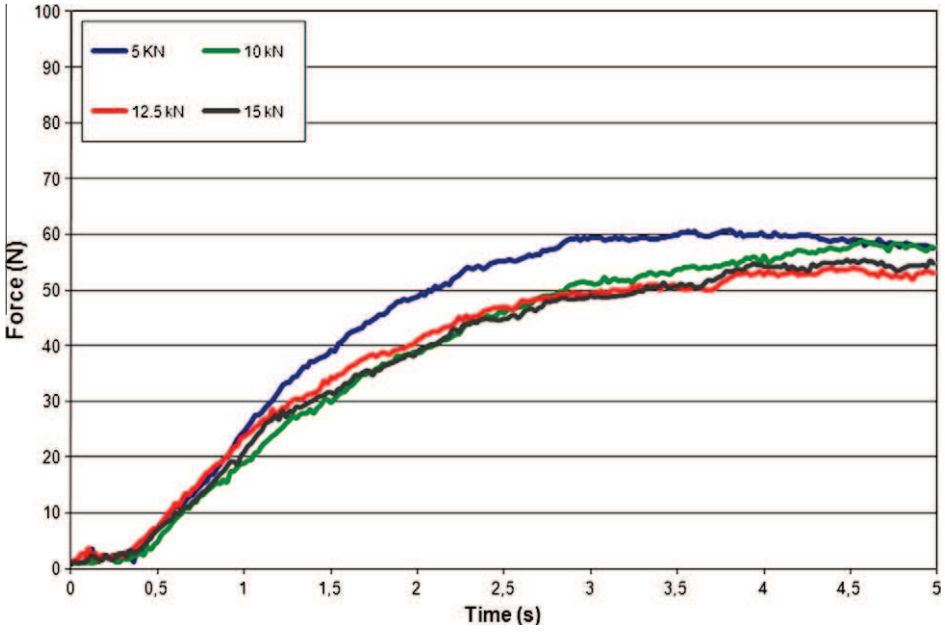


Fig. 2. Breaking process for fresh tablets.

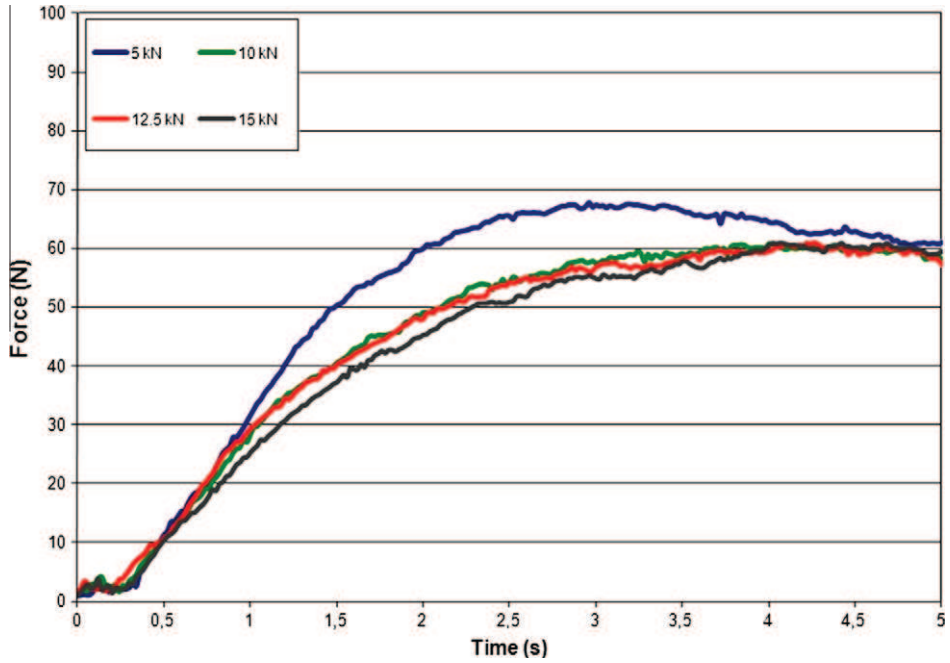


Fig. 3. Tablet breaking process after storage for 1 day.

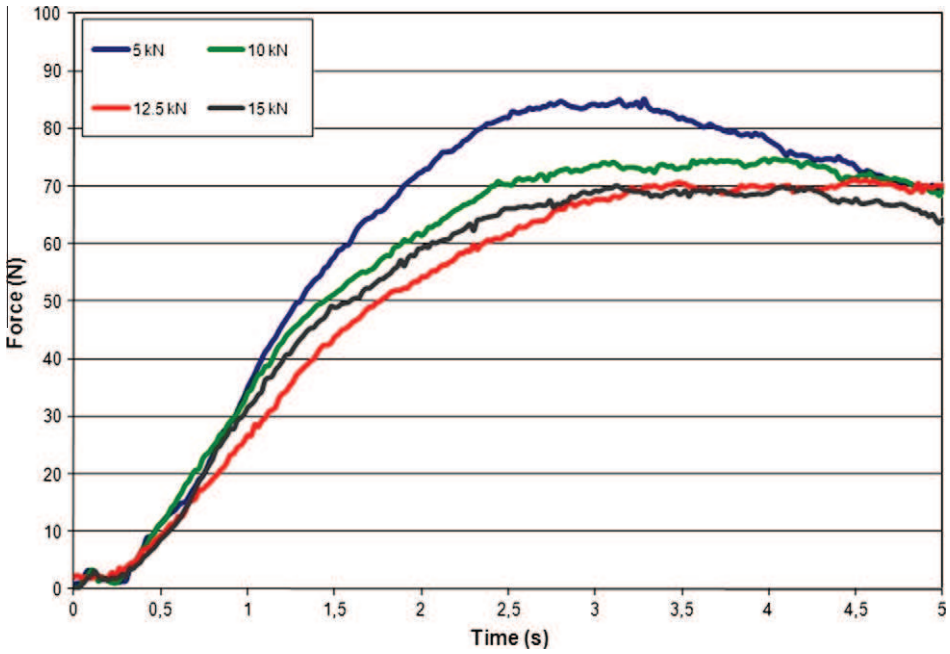


Fig. 4. Tablet breaking process after storage for 7 days.

of storage, but the degree of contraction differed. This is reflected in the volume changes.

The testing of the mechanical strength of the tablets is very important because they must remain intact during handling, i.e. packaging and transportation. The mechanical characterization of different materials and preparations is investigated in different scientific fields [6–8]. In our work the breaking strength of the preparation was studied. The data are summarized in Table 3. It can be seen that the greatest strengths were measured in every case at a compression force of 5 kN, and the breaking strength increased during storage. With increase of the compression force, the tablets exhibited lower strength and the increases in strength during storage were more moderate. It is noteworthy that the tablet strengths at 12.5 and 15 kN were almost the same in every situation.

Investigation of the breaking hardness of direct compressed chewing gum tablets is important not only for determination of their general parameters, but also from the aspect of the user's satisfaction. The preparations should provide adequate strength and ease of processability, and the consumer should find them pleasant and easy to use. It is not necessary to apply an extremely high compression force to prepare a good chewing gum tablets, because this will not cause any significant difference in quality.

Determination of the breaking (deformation) force is important because it is necessary to know what energy is needed to break the chewing gum tablet. If the compression force is too high, the gum will not acceptable by the patient, but if it is too low, the tablet will not be formed during compression.

The breaking process, which reflects the elastic/plastic behaviour of the tablet after compression, occurred in accordance with the volume changes. With increase of the compression force, the degree of elasticity decreased (Figs. 2–4). The action of the compression force can be observed very well in the case of fresh tablets (Fig. 2). The degree of elastic recovery was highest for tablets compressed at 5 kN, but the linear section of the deformation curve was not too long and soft-viscous (viscoelastic) deformation occurred.

After storage for 1 day, the tablet compressed at 5 kN exhibited a higher elastic nature because the macromolecules underwent rearrangement within 1 day (Fig. 3). The deformation profiles of the other tablets did not reveal a significant change. Practically no difference could be observed between the curves. Despite the increase in the deformation maximum of the tablet compressed at 5 kN, the shape of the deformation curves did not change during storage (Fig. 4).

5. Conclusions

Overall, it can be concluded that the flowability of Cafosa gum powder is very good and its direct compression is possible. The post-compressional tests demonstrated that a compression force of 5 kN is sufficient for preparation. The elastic behaviour of these tablets is the best from the aspect of the chewability. The advantage of these tablets is that the patient can chew such a tablet easily and the drug can be released in the mouth. The drug can then be swallowed and pass into the stomach or intestine or may be absorbed through the mucosa and a rapid drug effect will be obtained.

References

[1] Testa ES. Medicated chewing gum and a process for preparation thereof. US. 5:866.179; 1999.
[2] Malamataris S, Bin Baie S, Pilpel N. Plasto-elasticity and tableting of paracetamol, Avicel and other powders. J Pharm Pharmacol 1984;36:616–7 [in van Veen B. Compaction of Powder Blends, doctoral dissertation, 2003].
[3] Fell JT, Newton M. Determination of tablet strength by the diametral-compression test. J Pharm Sci 1970;59:688–91.
[4] Kása P, Bajdik J, Zsigmond Zs, Pintye-Hódi K. Study of the compaction behaviour and compressibility of binary mixtures of some pharmaceutical excipients during direct compression. Chem Eng Proc 2009;48:859–63.
[5] Wells IJ. Powder flow properties. In Pharmaceutical preformulation. The physicochemical properties of drug substances. Chichester: Ellis Horwood Limited Publishers – Chichester; 1988. p. 209–211.
[6] Pérez E, Famá L, Pardo SG, Abad MJ, Bernal C. Tensile and fracture behaviour of PP/wood flour composites. Composites: Part B 2012;43:2795–800.
[7] Ramli M, Tabassi AA. Mechanical behaviour of polymer-modified ferrocement under different exposure conditions: an experimental study. Composites: Part B 2012;43:447–56.
[8] Oprea S. Effects of guar gum content on structure and properties of multi-crosslinked polyurethane composite films. Composites: Part B 2012;44: 76–83.