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Graduate School of Pharmaceutical Sciences

Department of Pharmaceutical Technology

Ph.D. Thesis

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

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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. 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 .

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.)

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 Section I - The effects of Magnesium Stearate

3.1 Manufacturing problems in pharmaceutical industry

3.2 Background

I work as pharmatechnologist and 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. Three different products were examined in this section.

3.3 Product I

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.

3.3.1 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 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 1), but only in few cases were out of specification result.

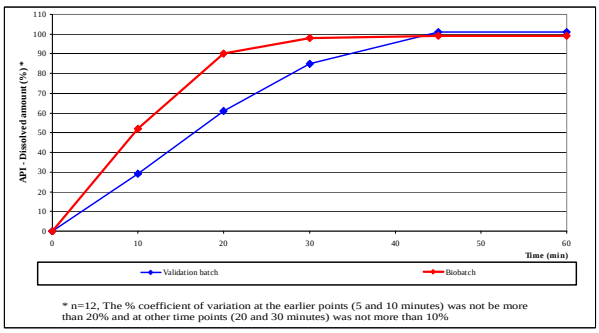


Figure 1: Dissolution profiles of the Biobatch and Validation batch

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 m² / g – Peter Greven) magnesium stearate to the lower specific surface area (1.5-3.5 m² / 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.

3.4 Product II

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

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.

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.

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 sieve analysis results show that the granule has “finer grain” than in case the previous batches. Based on the validation test results 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%.

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.

3.5 Product III

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).

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. The granule productions were in line with expectations. After granulation the granules has been charged in capsule, and the associated speed validation (low, high and target speed) was performed. The encapsulation of the two batches was planned. After low and high speed the target speed optimum selected were set up and the encapsulation continued. 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.

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 2 and 3 show clearly this progress.

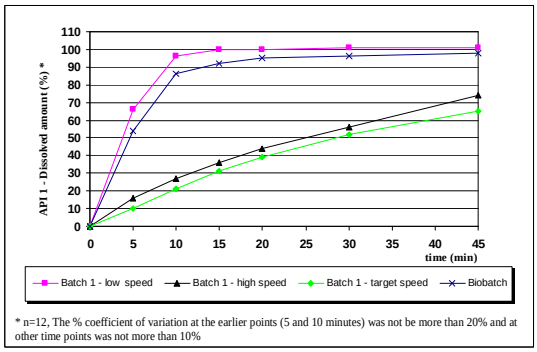


Figure 2: Dissolution profile of API 1

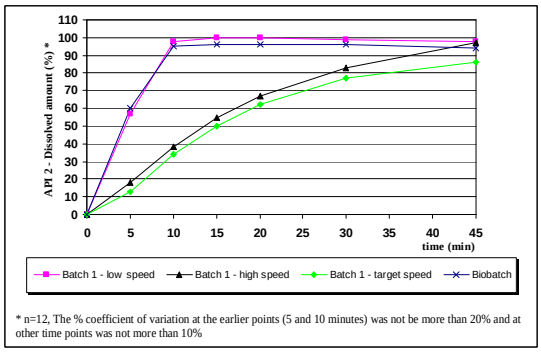


Figure 3: Dissolution profile of API 2

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.

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 4) 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.

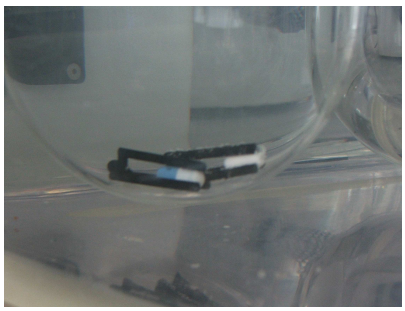


Figure 4: Whole capsule and not dissolved filled granule at the bottom of the dissolution vessel

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 5). In contrast, the non-filled granules and the filling of well dissolved capsules contact solution quickly, almost instantaneously. (Figure 6) 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 5: Non-wettable layer on the surface

Figure 6: The behaviour of he easily dissoluted granule

The addditional test was carried out. 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.

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.

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 1).

Table 1: 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 2), thus reducing the chances of particles coating by MgSt.

Table 2: 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

The change has successfully solved the previous solving/dissolution problems. (Fig 7,8)

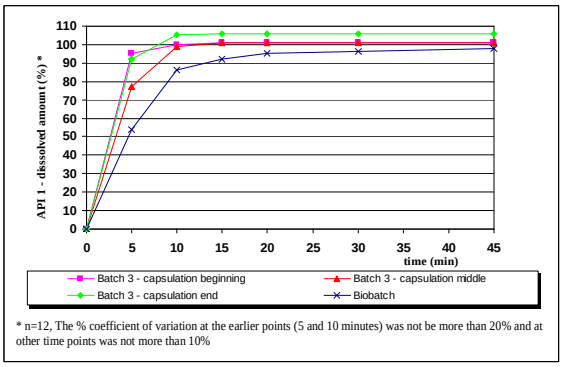


Figure 7: Dissolution profile of API 1

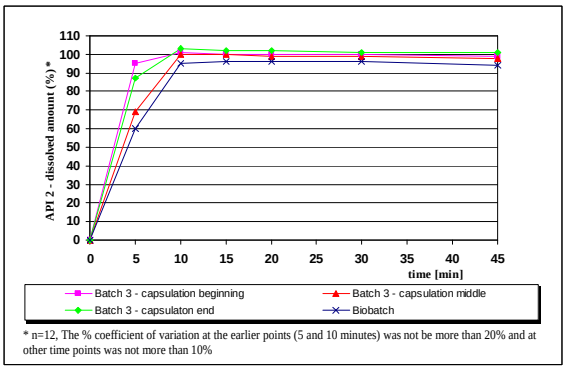


Figure 8: Dissolution profile of API 2

Temperature increasing was observed as during the encapsulation of previous batch but the product quality was not gone wrong.

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.

3.6 Investigation the effect of magnesium stearate

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

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.

Morphological study

The surfaces of the samples were tested with a scanning electron microscope (SEM) (Hitachi S4700, Hitachi Scientific Instruments Ltd., Tokyo, Japan).

The SEM pictures showed that the magnesium stearate with the higher specific surface area (Peter Greven) (Figure 9) was evenly distributed over the granule surface, while the magnesium stearate with the lower specific surface area (Undesa) (Figure 10) exhibited enrichment on the surface of the particles. The difference in grain size between the two types of magnesium stearate was clearly visible.

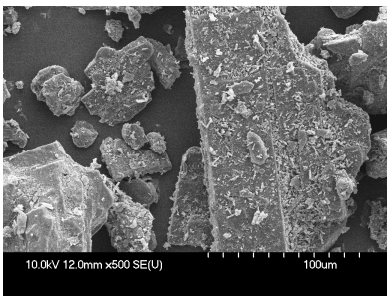


Fig. 9:Distribution of Mg-stearate with the higher specific surface area on the surface of the granules

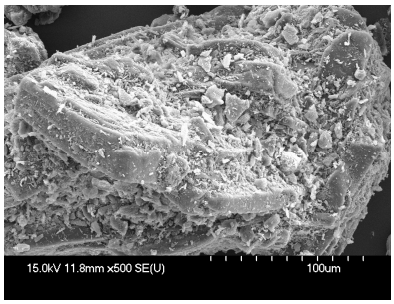


Fig. 10:Distribution of Mg-stearate with the lower specific surface area on the surface of the granules

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. 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 11). 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 9 and 10), 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 12), 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.

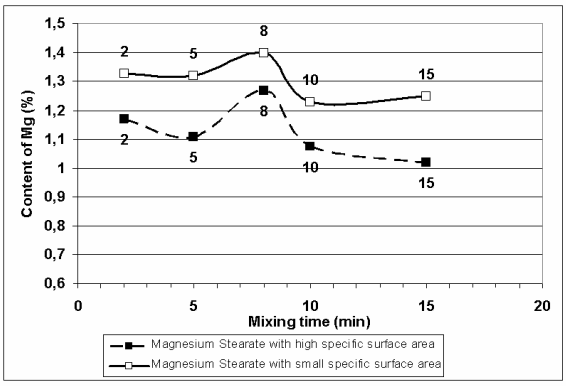


Figure 11: Influence of blending time at blending speed of 25 rpm on the distribution of magnesium on the surface of particles.

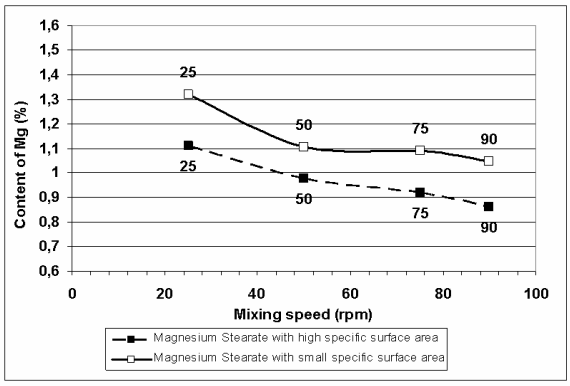


Figure 12: Influence of blending speed on the distribution of magnesium at a blending time 5 min.

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 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 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.

Discussion

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.

4. SECTION II - Formulation study of medicated chewing gum and the effect of magnesium stearate

4.1 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.

In case Pharmagum C, M and S gum bases mixtures were prepared using these products in different ratios to study the compactness and deformability. 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).

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.

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).

4.2 Methods

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. The mass of each powder mixture was 200 g.

Cafosa based chewing gum tablets: After sieving, the components with the exception of magnesium stearate 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.

Tableting

Two type of eccentric tableting machines (Korsch EK0 and Manesty) were used during these experiments. These machines were capable for force measuring.

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.

4.3 Experimental results of Pharmagum chewing gum tablets

Compressibility tests

The tests on the flow properties of the bulk gum samples showed that Pharmagum C and M had bad flow properties. The Pharmagum S and the API (ascorbic acid) displayed good flowability .

The compaction tests on the bulk materials resulted in every case in high elastic recovery. In the tablet compositions, therefore the bulk gum powders were mixed with the other components in different ratios.

The flowability tests of the powder mixtures showed that the flowability properties of the mixtures containing Pharmagum S were the best.

Based on the Carr index values, excellent compressibility was expected However the mixtures adhered to the punches during tableting. 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, elastic recovery, plasticity). Elastic materials display some recovery. This phenomena only comes from the gum base. The API and other ingredients do not have such high effects of this phenomena.

The friability of the tablets was less than 0.1 % in all cases.

Chewability test

In the case of a chewing tablets the chewability is an important requirement. The test is not unique. We used for this an instrumented breaking tester. The chewing tablets differ from the conventional tablets because after crushing the tablets did not break completely. 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. (Figure 13).

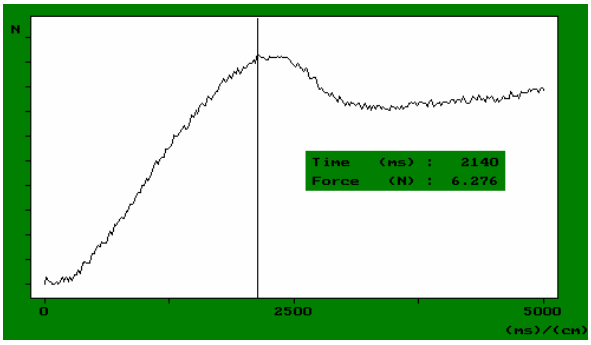


Figure 13: Deformation curve of a chewing tablet

Dissolution test

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

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. In all cases, 90% of the API dissolved in the first 10 min, and after chewing for 30 min the whole amount had dissolved. The dissolution results show that applying high compression force is not necessary during the manufacturing process.

4.4 Experimental results of Cafosa chewing gum tablets

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 degree of the elastic recovery depends on the property of the materials. It starts immediately after the compression phase and is finished dependent on the material after several days.

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 14). At 15 kN, the gum loses its elasticity and thus the main driving forces in the final formation stage are the bonding forces.

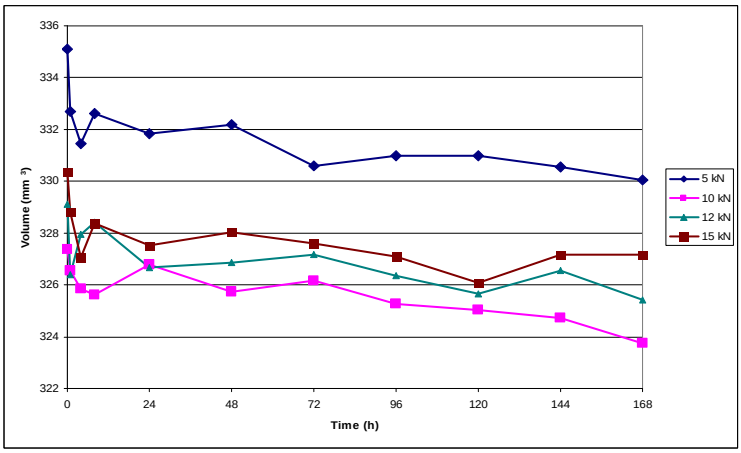


Figure 14: Volume changes of the comprimates

It can be concluded from the data that the volume of the tablets decreased continuously during 7 days of storage, but the degree of contraction differed.

The breaking strength of the preparation was studied. 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.

The breaking process results occurred in accordance with the volume changes. With increase of the compression force, the degree of elasticity decreased. The degree of elastic recovery was highest for tablets compressed at 5 kN. After storage for 1 day, the tablet compressed at 5 kN exhibited a higher elastic nature because the macromolecules underwent rearrangement within 1 day.

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

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

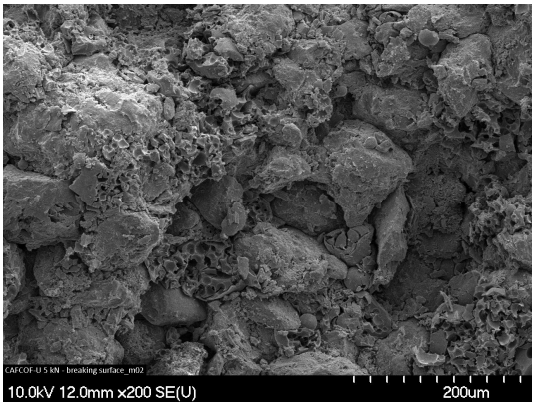
flowability of the gum base, and the die was filled unevenly during compression. Magnesium stearate applied as an additive promoted the flowability somewhat, but not perfectly.

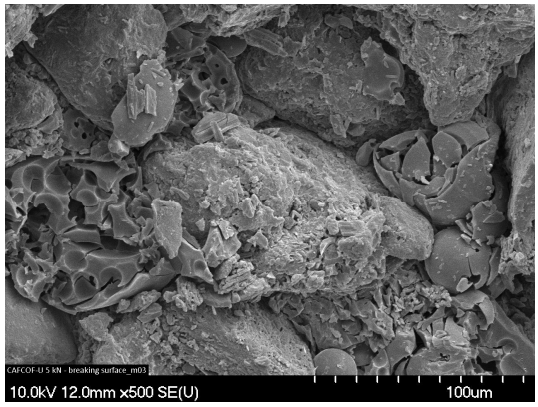
The surface free energy of caffeine and the polarity also proved to be rather high. A high polarity is generally very good as concerns the dissolution of an API from a tablet. There was seen to be a difference in the effects of the two types of magnesium stearate. In the event of higher surface area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

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.

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. The SEM photos 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). (Fig. 15) This explains why there was no difference in dissolution rate.





Magn. 200x *Magn. 500x*

Figure 15: Breaking surface of Cafcof-U tablet
Compression force 5 kN

We expect fast effect when a dosage form used in the oral cavity. The total quantity of active ingredient dissolved within 30 minutes from the tablets. The chewing result of a significant amount of drug released in the first five minutes, but we found that the later release was characterized by matrix systems kinetics (Korsmeyer-Peppas).

5. CONCLUSIONS, PRACTICAL USEFULNESS

During my work I was looking for the answers how to solve the frequently problems occurring in the pharmaceutical industry. My attention primarily used to overcome friction occuring during the production of solid dosage forms. The friction can be observed during capsules filling and during compression which not only makes it difficult to manufacture, but also affects the product quality parameters. Because the magnesium stearate is the most commonly used lubricant to overcome the friction, I tried to gain more knowledge about the applicability of that material.

In case of the products introduced in Section I, the manufacturing problems have been encountered when using the magnesium stearate with high specific surface area. The magnesium stearate with low specific surface area had to be used to eliminate the dissolution problems.

Based on the experiments, 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.

The manufacturing problems and measurement results presented in Chapter I point out that it has to be examined during the development what type of magnesium stearate application is required. So in further productions the lubricant-related manufacturing problems can be avoided. The surface properties of components / granules is needed to know. These properties must be investigated previously.

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 useful suggestions for the industry based on the results of Section I are as follows:

- It is suggested to create a database, in which the test results of the surface properties for each material are available. It can reduce the number of experiments and development time.
- Using the correct type of magnesium stearate might helps to increase the similarity between the dissolution profiles of the original and the generic products.

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 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.

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.

The useful suggestions for the industry based on the results of Section II related to the directly compressible medicated chewing gums are as follows:

- Unnecessary to apply high compression forces.
- It is suggested to use magnesium stearate with high specific surface area.
- Appropriate pressing tools should be used.
- Because of the elastic recovery pay attention the size of the blister cavity during packaging.

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.

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

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