University of Szeged
Department of Pharmaceutical Technology

Summary of Ph.D. Thesis

Influence of the surface free energy on the parameters of pellets

Zsófia Tüske

Szeged
2006

Introduction

Solid dosage forms (pellets, tablets or capsules) are the most frequently used pharmaceutical dosage forms in therapy. They play an important role in the pharmaceutical industry. In the course of the production of solid dosage forms, numerous problems have to be taken into consideration. The elimination of unfavourable phenomena and the solution of problems are highlighted fields in pharmaceutical technology. The factors influencing the granule/pellet parameters, which pellets may be separate dosage forms or intermediates in tabletting and in capsule filling, and the optimization of these factors are still topics of research. There are many influential factors. The roles of several factors are well known, but the effects of some are not completely solved.

In the course of pelletization, a knowledge of the properties of the active agents and the excipients is very important. The wettability and the surface free energy of solids are momentous physical-chemical parameters in the design of pharmaceutical formulations. This type of information can help in the selection of the components if the interfacial interactions and compatibility of the formulation components are known.

A knowledge of surface free energy is of great significance for an understanding of the interactions between the particles of powders and powder mixtures and the accessories of the equipment in the course of various technological procedures (powder mixing, granulating, pelletizing, capsule filling, tabletting and film coating. In the course of pellet making, the aim is to produce a product with appropriate mechanical properties, which is proof against the mechanical effects experienced during the further processing (capsule filling or film coating).

Aims

Pellets containing metronidazole were produced in a centrifugal granulator from the model active agent. The typically large metronidazole crystals were not ground or milled in order to avoid changes in the surface and the physico-chemical properties of the particles. The part of the surface energy in wet-granulation has been discussed in various papers. Those investigations were made with binary systems (one powder component and binder). The publications tended to select the suitable binder for a model excipient or active agent.

During the building-up of the pellets, the spreading coefficient, the work of adhesion and cohesion, the particle size and the binder solution applied are all determining factors. For a binary system (one powder and binder), connections can be found between the spreading coefficient and the pellet parameters (primarily the friability). For systems containing many components, the selection of a suitable excipient(s)

to produce a product from an active agent is a complex task. There are several factors, which must be considered.

The aims of the present work were as follows:

To review the role of surface free energy as an important physical-chemical parameter during the development of solid dosage forms, especially in the field of wet-granulation.

The aim was to investigate the role of the surface free energy of one- and two-component powder compositions in the pellet production.

The first aim of the study was to investigate the role of surface free energy in the formation of pellets from one- and two-component powder compositions and to choose a suitable excipient (active agent - excipient - binder systems). The surface free energies of the *powder components* were determined.

The second aim was to investigate whether the surface free energy of a powder mixture depends on the proportions of the components, and how the forces of cohesion and adhesion between the particles affect their interactions as functions of the proportions of the components. The surface properties of the *powder mixtures* were investigated.

The third aim was to study the role of surface energy in the formation of pellets from two-component powder compositions containing different amounts of a poorly water-soluble model drug and an excipient, and to look for connections between the properties of the mixtures and the pellet properties.

Surface free energy

The surface free energy of solids can be derived from the contact angle which the different liquids form on the surface of the solid compacts. The theory of calculating the surface free energy of solids is based on the different wetting properties of the different surfaces with the same liquid. On the other hand, the contact angles of different liquids on the same surface are different.

The surface free energy is the surface free energy change when the surface area of a medium is increased by unit area. For solids, the surface free energy is commonly denoted by γ_s and is given in units of energy per unit area, mJ/m^2 (or mN/m).

In the method of Wu, the surface free energy is taken as the sum of dispersive (d) and polar (p) components ($\gamma_s = \gamma_s^d + \gamma_s^p$). The surface free energies of solid materials can be determined by means of contact angle measurements on two liquids with known polarities. They can be assessed by solving two equations 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.

Parameters calculated from surface free energy

The spreading coefficient of a material over the surface of another material (S_{12}) can be determined according to Eq (2):

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

where γ^d is the dispersion solid surface free energy, γ^p is the polar component of the surface free energy and γ is the total surface free energy.

The work of cohesion (W_c) and adhesion (W_a), and the surface free energy may be calculated from each other. Eqs (3) and (4) can be used:

$$W_c = 2\gamma_s \quad (3)$$

$$W_a = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p}\right] \quad (4)$$

Materials and methods

Materials

Metronidazole (Ph. Eur. 4th) was used as the model active agent, which is a drug frequently used in the treatment of various anaerobic infections.

Hydroxypropyl cellulose (Klucel LF) (Hercules Inc., USA) is a partially substituted poly(hydroxypropyl)ether of cellulose. It is used as a binder during wet-granulation. It is freely soluble in water below 38 ºC, forming a smooth, clear, colloidal solution.

Corn starch (Ph. Eur. 4th) occurs as an odourless, tasteless, fine white powder, comprising very small spherical granules whose size and shape are characteristic. It consists of amylose and amylopectin, two polysaccharides based on α-glucose. Starch is used as an excipient primarily in oral solid-dosage formulations, where it is utilized as a binder, diluent and disintegrant.

Microcrystalline cellulose (Vivapur 101) (Rettenmaier & Söhne GmbH & Co., Rosenberg, Germany) is a purified, partially depolymerized cellulose. It is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations.

α-Lactose monohydrate (Ph. Eur. 4th) occurs as white to off-white crystalline particles or powder. It is a disaccharide, consisting of glucose and galactose. It is widely used as a filler or diluent in solid-dosage forms.

The liquids used for contact angle measurements were glycerol (Riedel-de Haën AG, Germany) (γ^d = 32.0 mN/m, γ^p = 31.7 mN/m) and diiodomethane (Sigma, Germany) (γ^d = 50.8 mN/m, γ^p = 0 mN/m).

Methods

The *contact angles were measured* with the Wilhelmy-plate method, and with the sessile-drop method. Compacts of the powders were made in a highly polished stainless steel punch in a Specac hydraulic press (England). Wilhelmy contact angles were determined with a Krüss tensiometer software (Germany) using a Krüss Tensiometer K12. Sessile drop contact angles were measured using a drop shape analyser (OCA 20 Dataphysics Instruments GmbH, Fielderstadt, Germany), using a charging pipette (Hamilton Microliter Syringe).

The *particle size distribution and average size* of the powders were measured with a Laborlux S light microscope and a Quantimet 500 MC (Q 500 MC) image analyser system (Leica Cambridge Ltd., Cambridge, UK).

Pellets were prepared using a *centrifugal granulator* (Freund CF-360, Japan). Powder mixing was performed with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Basel, Switzerland) (50 rpm for 10 min). The binder solution used was in every case a 10% aqueous solution of Klucel LF.

The powder mixtures and the *textures* of the pellets were investigated with a scanning electron microscope (SEM) (Hitachi 2400 S, Hitachi Scientific Instruments Ltd., Tokyo, Japan).

The *friability* was characterized by placing 5.0 g of the pellets in a 122 ml bottle, together with 12 g of stainless steel balls 8 mm in diameter. The bottle was then placed in a rotating shaker mixer (Turbula, Willy A. Bachofen Maschinenfabrik, Basel, Switzerland) (50 rpm for 2 min). The friability percentage was calculated. The *breaking strength and the deformation process* were studied with a modified breaking hardness tester (developed in the department).

Bulk and tapped densities were determined using a STAV 2003 Stampfvolumeter (Engelsmann A.G., Luwigshafen, Germany).

The *porosity* of a sample was determined via the equation

$$\varepsilon = 1 - \frac{\rho_{\text{tap}}}{\rho_{\text{p}}} * 100 \qquad (5)$$

where ε, ρ_{tap} and ρ_p are the porosity, tapped density and pycnometric density, respectively. A Quantachrome SPY-2 stereopycnometer (Quantachrome Corp., Syosset, New York, USA) was used to determine the pycnometric volumes of the samples.

The *compactibility* were tested with a STAV 2003 Stampvolumeter. The Kawakita equation was applied to the data obtained from the tapping test.

The *mathematical evaluation* was carried out with the SPSS for Windows 9.0 package.

Results and discussion

Role of surface free energy in selection of a suitable excipient

The role of the surface free energy in the selection of a suitable excipient was investigated through studies on pellet samples containing different fillers. The first sample (Sample 1) consisted only of metronidazole and no excipient. The other pellet samples consisted of the active agent (75%) and one of the selected excipients (25%) (Sample 2: Vivapur 101, Sample 3: corn starch, Sample 4: α-lactose monohydarte).

When the spreading coefficient of a binder over the substrate (S_{12}) is positive, the formation of dense, non-friable pellets can be expected (for two-component compositions, i.e. substrate + binder). However, the spreading coefficient results alone cannot predict the granule properties, especially in complex systems. Other factors play important roles, e.g. the particle size, the proportions of the components and the attractive effect (adhesion, cohesion) between the particles.

The results are partly in accordance with the spreading coefficient data (*Table 1.*). The friability of Sample 1 is higher than expected (24%). The lowest friabilities of Sample 2 and Sample 3 are connected with the higher spreading coefficients of Klucel LF over the powders used in these compounds. The friability of Sample 4 meets expectations.

Table 1.

Parameters of metronidazole and pellets

	Friability (%)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Porosity (%)
Metronidazole	-	0.64 (± 0.00)	0.75 (± 0.00)	47.71 (± 0.10)
Sample 1	24.4 (± 0.2)	0.54 (± 0.00)	0.57 (± 0.00)	60.36 (± 0.12)
Sample 2	13.5 (± 1.4)	0.52 (± 0.01)	0.55 (± 0.00)	62.40 (± 0.02)
Sample 3	11.5 (± 1.7)	0.62 (± 0.00)	0.66 (± 0.00)	54.48 (± 0.07)
Sample 4	19.9 (± 2.0)	0.63 (± 0.01)	0.67 (± 0.01)	54.51 (± 0.03)

In spite of the fact that the binding agent spreads over the metronidazole (S_{12} = 12.2 mN/m) and low friability is expected, the mechanical properties of granules containing only metronidazole are influenced by the work of cohesion of the binder, which coats the particles in several layers and is partly enclosed among

the crystals. Samples 2 (S_{12} = 12.9 mN/m) and 3 (S_{12} = 13.3 mN/m) consist of powders with similar spreading coefficients; in both cases, the particle sizes of the excipients are smaller than that of the metronidazole. The small particles fill in the small holes and the binder is spread over the particles only in a thin layer because of the larger surface. For Samples 2 and 3, therefore, the work of adhesion is determining, which is larger than the work of cohesion of the binder. For Sample 4 (S_{12} = 5.2 mN/m), the situation is similar to that for Samples 2 and 3, and the recrystallization of α-lactose monohydrate exerted a favourable influence on the parameters.

If the work of cohesion of the binder is lower than that of the substrate and the work of adhesion between the particles, then the optimal amount of the binding agent is that which coats the particles in only one uniform and continuous layer.

Effect of proportion of excipient on surface free energy of powder mixtures

Investigations were made of whether the surface free energy of a powder mixture depends on the proportions of the components, and how the forces of cohesion and adhesion between the particles affect their interactions as functions of the proportions of the components. Metronidazole - corn starch powder mixtures were investigated (*Table 2.*).

Table 2.

Compositions of the powder mixtures

	Mix25	Mix35	Mix50	Mix65	Mix75
Metronidazole	750 g	650 g	500 g	350 g	250 g
Corn starch	250 g	350 g	500 g	650 g	750 g

The surface free energy data for the mixtures showed a transition between that of the active agent and that of the excipient. The results for Mix50 were different from the characteristic tendency in this case.

In order to obtain additional information, and to explain the slight deviations in the γ_s data, larger masses of the powder mixtures were also investigated. Determination of the compactibility of powders and powder mixtures provides information on the cohesiveness (and the adhesion properties). Mix65 had the highest value of the constant 1/b, indicating the highest cohesiveness. The values for the other mixtures vary with the W_a and W_c data.

W_a and W_c indicate that the attraction is strongest between the corn starch particles (W_c = 124.5 mN/m) and weakest between the metronidazole crystals (W_c = 113.3 mN/m). The metronidazole - corn starch W_a is intermediate between the two other data (W_a = 118.4 mN/m).

Differences can be seen in the scanning electron micrographs of the mixtures containing different amounts of corn starch, in the different mixtures the interactions (adhesion and cohesion) being manifested differently. In Mix25 (*Figure 1.*) and Mix35, the metronidazole crystals are covered by one layer of corn starch particles. In Mix50, the corn starch particles are to be seen mainly on the surface of the metronidazole and there are a few corn starch aggregates among the metronidazole crystals. In Mix65, the corn starch particles are partly situated on the metronidazole surface and partly form aggregates. The amount of aggregates is larger here. In Mix75 (*Figure 2.*) the corn starch particles can be seen forming a few smaller aggregates around the metronidazole. A transition can be observed between Mix50 and Mix65. Accordingly, for a corn starch content over 50%, the cohesion between the corn starch particles is determinative.

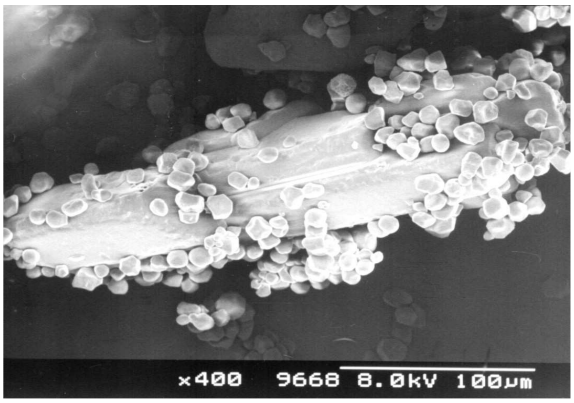

Fig. 1. SEM micrograph of Mix 25 (400×)

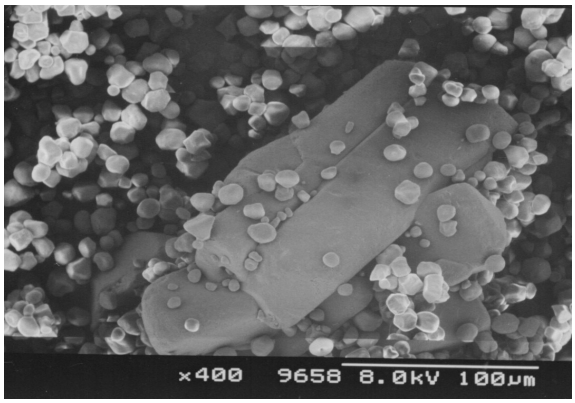

Fig. 2. SEM micrograph of Mix 75 (400×)

Investigations of pellets prepared from powder mixtures

The pellet samples were denoted P25-P75, similarly to the notations of the mixtures. First, the probable spreading of the binding agent on the surface of the mixtures was investigated. The probable mechanical properties of the pellets were estimated from the S data. It may be stated that S_{12} increased as the corn starch content of the mixtures was elevated. For this reason, the spreading of the binder over the surface of the powder mixtures becomes increasingly favoured. The pellet friability tended to increase as the corn starch content was increased, in contrast with the prediction made from the S data. The breaking strength exhibited a decreasing tendency, in accordance with the friability data. For more complex systems, S cannot be utilized to predict the mechanical properties of the pellets. For the samples investigated here, it may be stated that, as the γ_s values of the mixtures increased and the binder - mixture S values increased (the corn starch content increased), the mechanical properties of the pellets produced (friability and breaking strength) became more unfavourable. The bulk and tapped densities of the pellets decreased and the porosity increased as the corn starch content increased, and the granules had a looser, more porous structure. Consequently, in contrast with the predictions from the S values, pellets with a more porous and looser texture and with unfavourable mechanical properties can be produced as the S_{12} values increase. The pellets

containing less corn starch (P25 and P35) proved to be ideal compositions. The compositions of these pellets were homogeneous. In these cases, the work of cohesion of the corn starch was not dominant.

The pellet particles produced differed in composition, particularly in the event of a higher corn starch content. Some particles contained more metronidazole, and others less. The distribution of the components was not homogeneous. The pellet parameters were also influenced by the amount of the binder solution. The same quantity of binder solution was used for pelletization in every case. Compositions containing more small corn starch particles possess a larger surface area. Above a critical limit, the amount of the binder solution was not sufficient to ensure the coverage of the particles. For this reason, the mechanical properties of the pellets containing higher quantities of excipient were unfavourable.

Summary

Major conclusions:

- The build-up of the pellets, their structure and the interactions between the powder particles can be studied according to a new aspect by using the surface free energy data.
- If the work of cohesion of the binder is lower than that of the substrate and the work of adhesion between the particles, then the optimal amount of the binding agent is that which coats the particles in only one uniform and continuous layer.
- Differences can be seen in the scanning electron micrographs of the mixtures containing different amounts of corn starch, the interactions (adhesion and cohesion) being manifested differently in the different mixtures. For a corn starch content over 50%, the cohesion between the corn starch particles is determinative. The corn starch particles attract one another rather than the metronidazole crystals, and form small aggregates.
- The pellet friability tended to increase as the corn starch content was increased, in contrast with the prediction made from the S data. The breaking strength exhibited a decreasing tendency, in accordance with the friability data. Thus, the mechanical properties of the pellets became more unfavourable as S_{12} increased.
- The bulk and tapped densities of the pellets decreased as the corn starch content was increased. The pellets had a looser, more porous structure. An increasing tendency can be detected in the porosity results as the corn starch content was increased.
- The pellet particles produced differed in composition, particularly in the event of a higher corn starch content. Some particles contained more metronidazole, and others less. The distribution of the components was not homogeneous. This was due in great part to the W_a and W_c between the particles, similarly as observed for the powder mixtures.

- Above a critical limit, the amount of the binder solution was not sufficient to ensure the coverage of the particles. For this reason, the mechanical properties of the pellets containing higher quantities of excipient were unfavourable.
- Consequently, in contrast with the predictions from the S values, pellets with a more porous and looser texture and with unfavourable mechanical properties can be produced as the S_{12} values increase. The pellets containing less corn starch (P25 and P35) proved to be ideal compositions. The compositions of these pellets were homogeneous.

Practical usefulness:

The use of the surface free energy may be a new aspect in the selection of suitable excipients in the course of pelletization. The suitable excipients can be selected on the basis of the binder - substrate spreading coefficient values. The choice of an excipient with a higher S value is suggested, instead of an excipient with a low spreading coefficient. In this case the given binder will spread on the surface of the excipient. The interactions between the particles can be investigated by evaluating the W_a and W_c data.

If the work of cohesion of the binder is lower than that of the substrate and the work of adhesion between the particles, then the optimal amount of the binding agent is that which coats the particles in only one uniform and continuous layer. The mechanical properties of the pellets are in this case optimal.

Investigation of the scanning electron micrographs of the powder mixtures used during the pelletization can prognosticate the problems arising during the pellet making. Inhomogeneous distribution in the powder mixture can produce pellet particles with different compositions.

The spreading coefficient results alone cannot predict the granule mechanical properties, especially in complex systems. Other factors play important roles, e.g. the particle size, the proportions of the components, the amount of the binder and the attractive effect between the particles. However, the use of S values and other factors can complement one other and they can therefore be applied in the course of the industrial development.

The structure and the mechanical properties of the pellets are determinative from the aspect of the further processing. The pellets need a certain mechanical strength in order to resist the force arising during the further processing in the course of the coating of the particles, during capsule filling or also during tabletting.

The data calculated from the surface free energy give important information for the practice of pelletization. This information can be used during the development of a new pharmaceutical dosage form. Furthermore, it is of value during the industrial processing in order to solve different technological problems which may arise during that stage.

ANNEX

Publications related to the Ph.D. thesis

Publications

I. Bajdik J., ***Tüske Zs.***, Hódi K., Erős I.: A felületi jelenségek szerepe a szilárd anyagok feldolgozása során. I. rész. A jelenségek elméleti háttere Acta Pharm. Hung. 73 (2003) 80-85

II. ***Tüske Zs.***, Bajdik J., Hódi K., Erős I.: A felületi jelenségek szerepe a szilárd anyagok feldolgozása során. II. rész. A szilárd anyagok határfelületi jelenségeinek kísérleti vizsgálata. Acta Pharm. Hung. 73 (2003) 86-91

III. J. Bajdik, K. Pintye-Hódi, O. Planinšek, ***Zs. Tüske***, L. Tasic, G. Regdon jr., S. Srčič, I. Erős: Surface treatment of indomethacin agglomerates with eudragit. Drug Dev. Ind. Pharm. 30 (2004) 381-388 IF.:0.917

IV. Hódi K., ***Tüske Zs.***, Bajdik J.: Szilárd gyógyszerformák előállításának fizikai kémiai alapjai. Acta Pharm. Hung. 74 (2004) 90-101

V. ***Zs. Tüske***, G. Regdon jr., I. Erős, S. Srčič, K. Pintye-Hódi: The role of the surface free energy in the selection of a suitable excipient in the course of a wet-granulation method. Powder Technol. 155 (2005) 139-144 IF.:0.986

Abstracts

I. ***Tüske Zsófia***: Diclofenac-Na tartalmú pelletek előállítása és vizsgálata. Tudományos Diákköri Konferencia, Szeged, 2001, február 15-17.

II. ***Tüske Zsófia***: Diclofenac-Na tartalmú pelletek előállítása és vizsgálata. XXV. Országos Tudományos Diákköri Konferencia, Pécs, 2001, április 4-7.

III. ***Tüske Zsófia***: A felületi energia szerepének tanulmányozása a pelletkészítés során. VI. Clauder Ottó Emlékverseny, Budapest, 2002. szeptember 26-28.

IV. Bajdik János, Hódi Klára, ***Tüske Zsófia***, Erős István: Felületi jelenségek szerepe a porok feldolgozásában. XIV. Országos Gyógyszertechnológiai Konferencia, Héviz, 2002. november 8-10.

V. Kása Péter, ***Tüske Zsófia***, Hódi Klára, Erős István: Összetétel és készítési paraméterek befolyása a pelletkészítésben. XIV. Országos Gyógyszertechnológiai Konferencia, Héviz, 2002. november 8-10.

VI. ***Tüske Zsófia***, Hódi Klára, Bajdik János, Erős István, Srčič Stane: Az adhézió és a felületi energia szerepe a szilárd gyógyszerformák formulálása során. XIV. Országos Gyógyszertechnológiai Konferencia, Héviz, 2002. november 8-10.

VII. ***Tüske Zsófia***, Erős István, Hódi Klára: A felületi szabadenergia szerepe centrifugál-granulátorban történő pelletelőállítás során. Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium 2003. Eger, 2003. szeptember 22-23. pp.6

VIII. ***Tüske Zsófia***, Erős István, Hódi Klára: A felületi szabadenergia szerepe nedves granulálással előállított pelletek formulálása során. Congressus Pharmaceuticus Hungaricus XII. Budapest, 2003. május 8-10. pp.91.

IX. ***Zsófia Tüske***, István Erős, Klára Pintye-Hódi: The effect of the surface free energy on the production of pellets. International Congress for Particle Technology (PARTEC 2004), Nuremberg, Germany, 16-18.03.2004

X. ***Tüske Zsófia***: Felületi szabadenergia meghatározó módszerek összehasonlítása. Gyógyszer az ezredfordulón V. Az európai csatlakozás küszöbén-Továbbképző konferencia, Sopron, 2004, március 25-27. pp.5.

XI. ***Tüske Zsófia***: A felületi szabadenergia szerepe a megfelelő segédanyag kiválasztásában pelletelőállítás során PORANAL IX. Szemcseméret-analitikai, Környezetvédelmi és Portechnológiai Szimpózium, Balatonfüred, 2004. szeptember 5-7. pp. 22-23.

XII. ***Zsófia Tüske***, István Erős, Klára Pintye-Hódi: Investigation of the surface free energy of metronidazole - corn starch mixtures and of pellets made from the mixtures. 6th Central European Symposium on Pharmaceutical Technology and Biotechnology, Siófok, Hungary, 25-27. 05. 2005

Abstract in: Eur. J. Pharm. Sci., 25 Suppl. 1, S1-S226 (2005) P-92 IF.:1.949