



Research paper

Role of surface free energy and spreading coefficient in the formulation of active agent-layered pellets

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ABSTRACT

Formulation of layered pellets can be a useful method for the preparation of multiparticulate systems. The aims of this work were to study the properties of hydrophilic active agent (pirenzepine dihydrochloride) layers formed on different pellet cores, the efficacy of layering and the connection between the core and the layers. The carrier pellets were prepared from mixtures of a hydrophilic (microcrystalline cellulose) and a hydrophobic (magnesium stearate) component in different ratios. These cores were coated in a fluid bed apparatus with an aqueous solution of active agent, with or without the addition of hydroxypropyl methyl cellulose (HPMC) as an adhesive component. The wettability of the pharmaceutical powders was assessed by means of Enslin number and contact angle measurements, and the surface energy was determined. Spreading coefficients of the components were also calculated and correlated with pellet properties such as the content of active agent, the friability and the morphological appearance of the layered product. An increased friability of the layer formed and the lower effectiveness of the process were experienced with a reduction in the wetting of the core. The efficiency of layering on a less polar core could be increased by the addition of HPMC, but the sensitivity of these pirenzepine layers to mechanical stress was higher. The type of the abrasion of these particles was dissimilar to that for samples prepared without HPMC. Peeling of the layers containing HPMC was observed for hydrophobic cores, but this phenomenon was not detected for the hydrophilic ones. These results can be explained by the spreading coefficients, which revealed an insufficient adhesion of layers for the samples that exhibited peeling.

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1. Introduction

Multiparticulate drug delivery systems possess many advantages in comparison with single-unit dosage forms, such as more predictable gastric emptying and more uniform drug dispersion in the gastrointestinal tract, with less interindividual and intraindividual variability in bioavailability [1–4].

Commonly used and intensively investigated drug-loading processes for the formulation of multiparticulate systems include powder layering and solution/suspension layering [5–8], in which active agents are deposited onto mainly inert cores in some layers. Layering on cellulose or sugar (non-pareil) spheres is a process that can lead to the uniform distribution of a drug on a carrier excipient. The fluid layering technique can be useful for active agents or intermediates dispersed in liquids. In the event of intermediates, the separation of solid components, such as nanocrystals, is not

necessary. A poorly soluble model drug was formulated as a muco-adhesive nanodispersion, which can be used directly as a layering dispersion for sugar spheres in a fluidized bed coater [9].

A great variety of techniques make use of different cores for formulation: drug-containing matrix cores or layered cores for further coating [10,11]. The surface polarity of the core, and hence the adhesion between the core and the evolving layer, can differ. At the beginning of film coating, initially droplets hit the core surfaces where they need to adhere. During continuous drying, these deposits form a layer, to which the next droplets need to adhere, i.e. during any layering process, initially adhesion between the core and the layering material must take place. In this study, this last-mentioned process was investigated. In the majority of the processes, adhesion must occur between the already deposited and dried layering material and the further layering material. Several adhesive components, e.g. polymers, can be used to ensure appropriate binding of the layers. Before choosing the types and the amounts of the ingredients, it is reasonable to evaluate the effects of the core properties on the formulation of a drug-layered product.

Knowledge of the wettability and surface free energy of pharmaceutical solids is important in the design of pharmaceutical

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formulations [12–14]. The method of assessing the surface free energy (γ) indirectly from wettability measurements is widely used [15–17]. In the method of Wu and Brzozowski [18], the surface free energy is taken as the sum of the dispersive (γ^d) and the polar (γ^p) components. The surface free energies of solid materials can be determined by means of contact angle measurements, using two liquids with known polarities. They can be assessed by solving an equation with two unknowns:

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

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 a material (1) over the surface of another material (2) can be determined according to [19]:

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

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.

In this study, pellet cores with various levels of hydrophilicity were prepared from mixtures of microcrystalline cellulose as a hydrophilic [20] and magnesium stearate as a hydrophobic [21] components in different ratios. These cores were layered with an aqueous solution of a water-soluble active pharmaceutical ingredient. A fluid bed apparatus with a Wurster column was applied for the layering. The effectiveness of layering, the mechanical properties of the evolved layer and the product, and the connection between the core and the layer were evaluated. The results of wetting and surface free energy studies were used to understand the formation of the layer. In the second part of the work, different concentrations of a binding polymer were applied in the layering liquid. The same properties of these products were analysed and compared with those of the previously made products. The novelty of the present approach was to study the effects of cores with different hydrophilicity on layering and mechanical properties of the developing pellets. While the methods of drug layering onto inert cores [22], and the importance of wetting and so the surface free energy in the formulation of different solid dosage forms have been extensively studied [14,23] and documented, the effects of hydrophilicity of the core on the properties of the drug-layered product have received little attention to date. This study is a new approach to this technique. The mechanism of layering, the role and the effect of surface properties of cores with different hydrophilicity were in the middle of attention in this study. Our present aim, therefore, is to improve the understanding of the mechanism of layering on pellet cores with differing surface free energies. The problems that may occur during layering in case of cores with different hydrophilicity and the possible solutions to improve the efficacy of layering were studied.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) (Avicel PH 101, FMC Europe N.V., Brussels, Belgium) with a mean particle size of 50 μm was applied as the hydrophilic component of the core pellets, and magnesium stearate (Mg-st) (Pharma VEG Ch/3043, Baerlocher,

Unterschleissheim, Germany) with a mean particle size of 10 μm as the hydrophobic one. Different binary powder mixtures containing these materials were prepared for the production of cores. Pirenzepine dihydrochloride (PHCl) (Ph. Eur., TEVA Gyógyszergyár Zrt., Debrecen, Hungary) has antimuscarinic effect; it is a white powder which is freely soluble in water (1–10 ml of water per gram of PHCl). It was chosen as model drug and was applied in a 10% aqueous solution as layering liquid.

In the second part of the work, the adhesive component was hydroxypropyl methyl cellulose (HPMC) (Pharmacoat 606, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan). It was applied in concentrations of 2% and 5% (i.e. 20% and 50% HPMC based on the PHCl mass) in the layering liquid, which also contained 10% PHCl.

2.2. Preparation of core pellets

Core pellets were prepared by an extrusion–spheronization process. MCC and Mg-st (0, 5, 10, 15, 20, 25, 30, 35 and 40 w/w%) were blended for 5 min in a tumbling laboratory mixer (LM20, Bohle, Ennigerloh, Germany). The dry powder mixture was then loaded into the gravimetric powder feeder (K-CL-KT 20, K-Tron Soder, Niederlenz, Switzerland) of the extruder. The extrusion took place at a constant powder feed rate of 33 g/min. A twin-screw extruder (Micro 27GL-28D, Leistritz Extrusionstechnik GmbH, Nuremberg, Germany) equipped with an axial screen with dies 1 mm in diameter and 2.5 mm in length was used for extrusion, at a rotation speed of 100 rpm. Deionized water was used as granulation fluid and was supplied by a membrane pump (Cerex EP-31, Bran and Luebbe, Norderstedt, Germany) with a flow-through metering device (Corimass MFC 081/K, Krohne, Duisburg, Germany). The quantity of water was appropriate with which nearly spherical pellets developed. This quantity was different for every sample depending on the composition. The water content based on the dry mass continuously decreased with increasing amount of Mg-st (Table 1).

Batches of 300 g of wet extrudate were spheronized in a spheronizer (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate 300 mm in diameter. Constant operational parameters were used for all batches as follows: spheronization was performed at room temperature for 5 min, at a rotation speed of 750 rpm. The resultant pellets were dried at 60 °C in a ventilated air oven (Heraeus ET 6130, Kendo, Hanau) for 4 h, the moisture content was <2.5% in every sample.

2.3. Layering of core pellets

The layering solution was sprayed onto core pellets 0.8–1.2 mm in diameter, obtained as a sieve fraction, in a fluid bed apparatus (Strea-1, Niro-Aeromatic AG, Switzerland) with a Wurster column 19.5 cm high and 5 cm in diameter. The distance between the bottom of the chamber and the tube was 15 mm. Two hundred grams of liquid was used for 200 g of pellets in every case. Constant operational parameters were used for the layering for all batches as follows: inlet air temperature: 55 °C; atomizing air pressure: 2 bar;

Table 1
Water contents of binary powder mixtures of MCC and Mg-st.

Mixture	Water content based on dry mass (%)
MCC pure	159.2
5% Mg-st	144.1
10% Mg-st	139.8
15% Mg-st	137.5
20% Mg-st	131.9
25% Mg-st	128.4
30% Mg-st	118.6
40% Mg-st	112.8

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