Application of inert spheres for formulation of multiparticulates dosage form

Doctoral theses

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Introduction

The pharmacokinetic properties of an active pharmaceutical ingredient (API) can be improved with the choice of an adequate dosage form. One such choice seems to be the formulation of multiparticulate dosage form comprising pellets, which proved to be successful in the improvement of the efficacy and toleratibility of numerous compounds (e.g.: antiarrhythmics). Consequently, there is a growing interest toward the application of inert pellets as starting excipients for pharmaceutical pellet manufacturing. They serve as alternatives to develop and adapt a relatively simple manufacturing technology compared to pellet agglomeration.

Several materials have been investigated to develop and produce inert cores as starting excipients for pharmaceutical pellet manufacturing with various particle sizes. These include inert cores based on saccharose and microcrystalline cellulose. Sugar spheres have been used as inert cores for a long time and are monographed in the major pharmacopoeias [Eur. Ph., USP]. Microcrystalline cellulose (MCC), the gold standard for extrusion-spheronization, is widely used, but possesses various disadvantages, such as drug adsorption to the surface, its chemical incompatibility with a number of drugs, and its lack of disintegration when used in matrix pellets.

Isomalt, a polyol produced from sucrose. This sugar alcohol is interesting for pharmaceutical purposes because of its multiple potential health benefits. It is suitable for diabetics, non-cariogenic (tooth-friendly). Another advantage of this polyol is that it does not contain a carbonyl group (Maillard reaction is impossible), hence it is chemically more stable than related saccharides. Recently, isomalt became important in pharmaceutical development used as tablet or granule excipient.

Purpose of research

- investigate the application possibility of isomalt as a starter pellet and to compare the most important characteristics of this core to the commonly used sugar and microcrystalline cellulose based inert spheres,

- different type of inert pellet cores as started excipients for the production of layered structured pellets. The application of fluidization process in the layering process of various drugs exhibiting different solubility charcteristics on inert cores. The formation of coating polymers with different ratios of Eudragit RS (ERS) and Eudragit RL (ERL) on the surface of the drug layered pellets,

- nondestructive control of the drug layering and the coating process (NIR spectroscopy and image analysis),

- investigate and compare the effect of the three cores on the in vitro drug release of various drugs exhibiting different solubility charcteristics, when they were coated with a permeable membrane. For a better understanding of the drug release of the mentioned dosage form I aimed to simulate the effect of the osmolality in the gastrointestinal tract using glucose as an osmotically active agent.

Methods

Manufacture of drug layered and coated pellets

Sugar, MCC and isomalt inert cores were layered with various model drugs (metoprolol-tartarate, ibuprofen-sodium, diclofenac-sodium) exhibiting different solubility properties, and were coated with different ratios of ERS and ERL (0:100 and 50:50 and 100:0 ratio) in a bottom spray configured fluidized bed apparatus (Aeromatic Strea I., Aeromatic-Fielder AG).

Characterization methods – Physical properties of pellets

Particle shape, size, and particle size distribution were determined using a computer image analysis (IA) system, which consist of a stereomicroscope (SMZ 1000 type, Nikon), a fibreoptic light source (Intralux 5000-1 type, Volpi) a digital camera (Coolpix 4500 type, Nikon) and the software Image Pro Plus 4.5.(Media Cynerbetics). Changes occurring in the shape parameters of inert cores during fluidization and/or in contact with water were evaluated by IA system. Surface morphology examination was carried out by means of scanning electronmicroscopy (SEM, *JEOL JSM-6380 LA type*). The tensile strength of pellets was determined using a texture analyser (TA-HDi®plus Texture Analyser) operating with a 5 kg load cell. True density of pellets was measured with a helium pycnometer (*Ultrapycnometer 1000*), apparent volume prior to and following settling was determined using a STAV 2003 type settling apparatus equipped with an Omron HFCX-A4 counter. NIR spectroscopic examinations using a Hitachi U-3501 spectrophotometer were also performed in order to follow layering and coating process.

Characterization methods – Dissolution studies

The dissolution test was carried out using a Hanson SR8 type apparatus (USP method 1). The concentration of released drug was measured UV-spectrophotometrically. The osmolality of media was determined by an osmometer (Knauer-OSMO, model 2320), applying the freezing point

depression method. IA was used to determine the swelling properties of coated pellets during drug dissolution.

Drug release kinetic study

Since the shape of the dissolution curves of present study were different the Weibull distribution function was used for the characterization of the dissolution profile of pellets:

$$M_t = M_\infty \left[1 - e^{-\left(\frac{t-t_0}{\tau_d}\right)^\beta} \right] \qquad (1)$$

where M_t is the percentage of the dissolved drug at time t, M_∞ is the drug infinite concentration, t_0 is the lag-time of the dissolution, β is the shape parameter of the curve, and the τ_d represents the time (h) when 63.2% of drug has been dissolved. The statistical analysis of data was performed using the TableCurve®3D v4.0 (Systat Software Inc.). The effect of the independent variables on response y was modeled by the following polynomial equation:

$$y = b_0 + b_1 x_1 + b_2 x_2 + b_{11} x_1^2 + b_{22} x_2^2 + b_{12} x_1 x_2 \qquad (2)$$

where x are the factors (x_1: coating system - ratio of the film forming polymers; x_2: osmolality of medium) and b parameters mark the coefficients characterizing the main (b_1, b_2), the quadratic (b_{11}, b_{22}), and the interaction effects (b_{12}).

Table I. Independent variables and their variation interval: factors and their coded levels

Coded value	Actual values	
	x_1 :coating system - amount of film forming polymer (%)	**x_2 :osmolality of medium (Osmol/kg)**
-1	Eudragit RS : Eudragit RL (100:0)	0.106
0	Eudragit RS : Eudragit RL (50:50)	0.483
1	Eudragit RS : Eudragit RL (0:100)	0.706

Results and conclusion

A. Isomalt as new inert core

There was no substantial difference in the shape characteristics (roundness, aspect ratio, Feret diameter, size distribution) of different types of inert cores. The tensile strength of sugar and isomalt cores is lower than that of MCC pellets, but there was no attrition observed during fluid bed layering. Results show that the new pellet core, similarly to the prevoiusly used pellet cores, exhibits adequate shape, particle size distribution and mechanical properties in view of further processing.

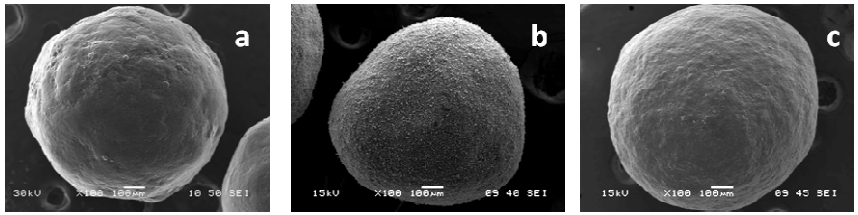

Fig.1. Scanning electron micrographs of pellets based on sugar (A), isomalt (B) and MCC (C)

B. Fluidization process monitoring

The layering of inert cores and coating of drug loaded pellets can be well monitored by nondestructive near-infrared spectroscopy and image analysis.

C. Dissolution studies

Results of dissolution study prove that, in case of a water-soluble drug the only factors effecting drug release are the composition of the coat and the osmolality of the dissolution medium. The type of starter inert core does not play a major role. On the other hand, in case of a poorly water soluble drug (diclofenac sodium) aside the previously listed factors, the type of inert starter core is also

important. With the help of following the particle size changes occuring during the drug release from pellets produced with permeable coats, I concluded that the rate of swelling is indipendent of the neutral pellet core and that the cracking of the coat does not play an important role during drug release. In case of layered pellets made of isomlat and sugar inert cores an additional osmotic pressure is formed during dissolution, which enhances the drug release.

Drug release kinetic study

The kinetic parameters (τ_d, β, t_0), that were calculated using the Weibull distribution function. Coated pellets prepared by layering the drug onto sugar or isomalt cores demonstrated similar drug dissolution profiles and kinetic parameters. In case of pellets coated with Eudragit RS polymer, drug release started later (t_0>0) by increasing osmolality in the dissolution medium, especially for diclofenac sodium layered MCC pellet cores. A surface plot was fitted onto τ_d parameters applying the polynomial equation (Eq. 2) and it is shown in Figure 2. The results show that the effect of the two independent factors on τ_d are very similar for isomalt and sugar, but were different in case of MCC. It can be seen that in case of high permeable coats, drug release rate is not as pronouncedly affected by the change in the osmolality of the medium as in case of coats exhibiting lower permeability. The strength of this effect is not only determined by the permeability of the coat it also varies with the type of starter core (water soluble or water insoluble):

$$\tau_{d,sugar} = 1.14 - 1.79x_1 + 0.73x_2 + 1.33x_1^2 - 0.65x_1x_2 \qquad \text{R=0.993}$$

$$\tau_{d,isomalt} = 1.50 - 2.04x_1 + 1.07x_2 + 1.12x_1^2 + 0.04x_2^2 - 0.925x_1x_2 \qquad \text{R=0.986}$$

$$\tau_{d,MCC} = 27.69 - 17.14x_1 + 19.13x_2 - 0.41x_1^2 + 1.77x_2^2 - 10.03x_1x_2 \qquad \text{R=0.990}$$

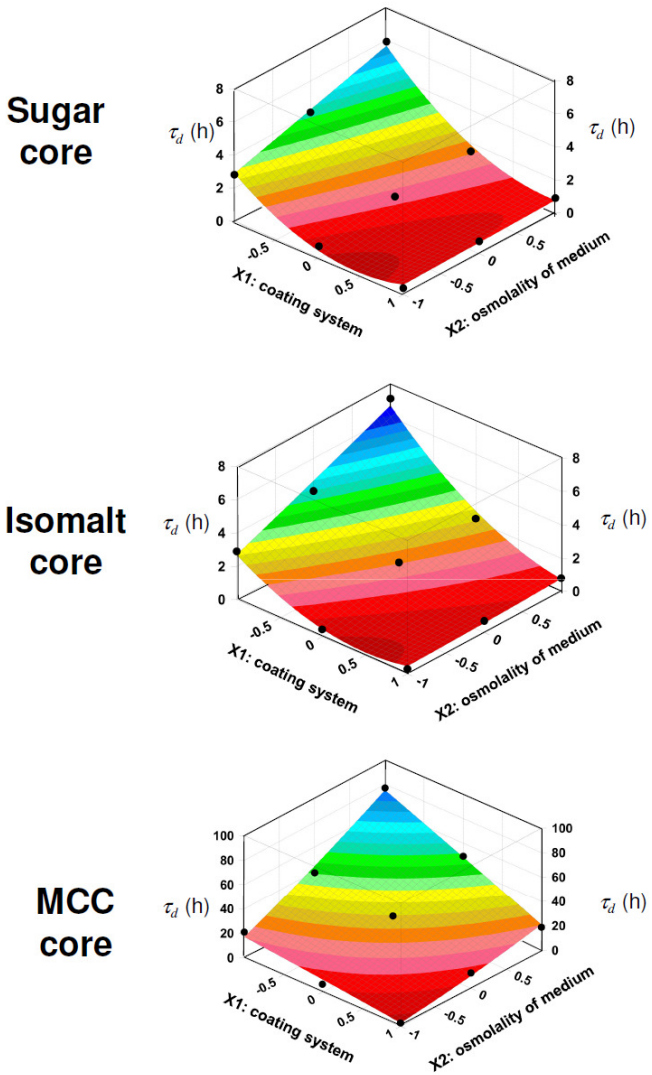

Fig.2. Fitted polynomial equations and surface plot of the effects of polymer type and osmolality on the dissolution (τ_d demonstrates time value when 63.2% of drug is dissolved)

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