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Evaluation of powder, solution and suspension layering for the preparation of enteric coated pellets

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ABSTRACT

Gastro-resistant pellets were prepared by use of three different drug loading techniques (powder layering, solution layering and suspension layering) and two different enteric coating techniques (powder layering and suspension layering). Pellets produced by different layering techniques were compared in terms of morphological characteristics, content of drug, release properties and stability. Drug loaded pellets produced by the use of powder layering had much more pronounced surface roughness in comparison to other tested techniques. Higher weight gains of enteric polymer were needed to achieve the same level of gastric resistance when powder layering was employed to apply enteric layer than when it was applied by suspension layering. Both tested techniques of enteric coating application enabled complete dissolution of drug in buffer stage of dissolution test. Suspension layering proved to be superior to other techniques both in drug loading and enteric layering phase.

1. Introduction

Drug loading of pellets can be carried out by means of solution, suspension and dry powder layering or by incorporation into pellets' core by means of direct pelletization techniques like extrusion and spheronization (Huyghebaert et al., 2005; McConnell et al., 2009; Nastruzzi et al., 2000). Each of these techniques has its advantages and drawbacks. A particular technique is chosen on the basis of characteristics of active substance and finished product. Solution or suspension layering is known to be able to give smooth layers, but to achieve this it is sometimes required to incorporate high concentrations of binders which reduce potency of the final product. Moreover, process length can be prolonged due to high amounts of solvent that need to be removed (Suhrenbrock et al., 2011). During these processes solid state transformations of drug can occur or solvents can impact the morphology of pellets making them inappropriate for functional coating (Nikowitz et al., 2013; Lust et al., 2013; McConnell et al., 2009). These obstacles can be overcome by using powder layering technique. During powder layering pellet cores are intermittently or concurrently treated with micronized drug and adhesive solution — binding liquid. This layering technique requires smaller amounts of solvents which reduce process time, but with prospect of obtaining pellets of rough and uneven surface (Cao et al., 2012). Pellet layering processes can be performed in conventional coating pans or fluid-bed apparatuses equipped with bottom or tangentional spraying systems.

Drug-loaded pellets can be coated with insoluble and/or pH-dependent coating to obtain finished product with tailored release profile. Application of functional coating can be carried out by means of various techniques which include powder layering and spray coating of suspension containing dissolved polymer. If functional film is applied to pellet cores by the use of powder layering micronized polymer is part of powder phase and liquid plasticizer has a function of adhesive solution. The process consists of two steps: application of dry powder to pellets and film formation or curing which takes place at elevated temperatures needed for softening and coalescence of polymer particles (Kablitz and Urbanetz, 2007). Although, the importance of coating quality rises with the amount of functionality it provides, release profile of finished product does not always depend only on type and amount of applied functional coat and processing conditions, but on properties of core as well (Kállai et al., 2010; Liu et al., 2009).

Model drug in this study was duloxetine hydrochloride which undergoes degradation in acidic environment. It is freely soluble in a mixture of water and isopropanol (1:1), soluble in ethanol, slightly soluble in isopropanol, sparingly soluble in water and undergoes degradation in acidic environment. To prevent loss of drug and subtherapeutic drug plasma levels due to degradation in the stomach, it has to be formulated like a gastro-resistant dosage form. Furthermore, to ensure adequate stability of the finished product, contact between acid labile drug and acidic enteric polymer has to be prevented by a barrier layer of adequate thickness (Marjo et al., 2011; Jansen et al., 1998). Therefore, if duloxetine pellets are produced by means of layering, finished pellets contain at least three layers: drug layer, barrier layer and layer of enteric coating.

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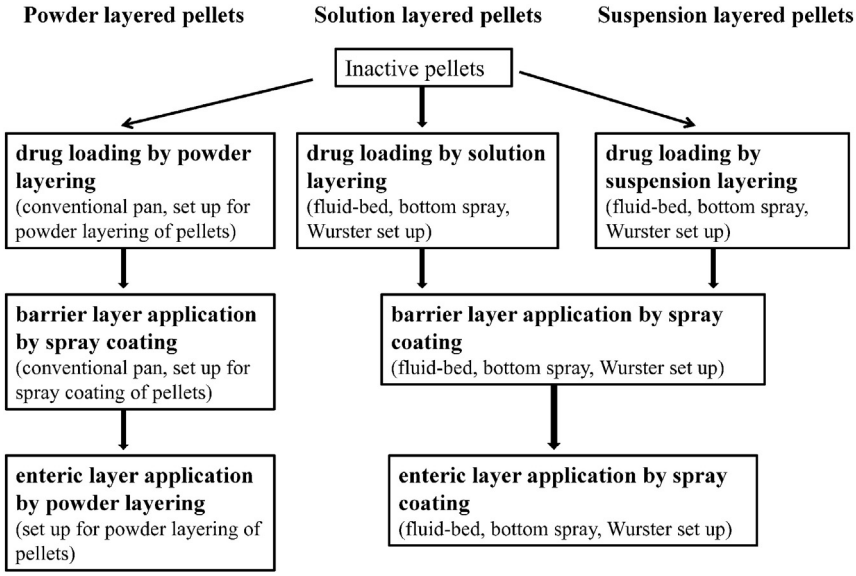

Fig. 1. Schematic overview of the processing steps for obtaining different multiparticulate formulations.

The objectives of our study were:

- To evaluate different techniques of loading a model drug onto inactive pellets: powder layering, solution layering and suspension layering
- To evaluate different techniques for applying enteric coating onto pellets containing drug layer and barrier layer, namely powder layering and spray coating of suspension containing dissolved polymer.

Products obtained by different manufacturing techniques will be compared in terms of assay, acid resistance, dissolution and stability so to establish the superior formulation technique.

2. Materials and methods

2.1. Materials

Duloxetine hydrochloride of particle size distribution d (90) < 10 μm (JiuZhou, China), non-pareil seeds 20–25 mesh (JRS Pharma, Germany), povidone K-30 (ISP, Switzerland), hypromellose 3 cp (Taian Ruitai Cellulose Co. Ltd., China), triacetin (Eastman Chemical B.V., Switzerland), talc (Imerys Talc, Italy), hypromellose acetate succinate MF (Shin-Etsu, Japan), hypromellose acetate succinate LF (Shin-Etsu, Japan), triethyl citrate (Jungbunzlauer, Germany), polysorbate 80 (Oleon, Belgium), castor oil (Henry Lamotte Oils, Germany), hypromellose 6 cp (The Dow Chemical Company, United Kingdom), hydroxypropylcellulose EXF (Ashland, The Netherlands), isopropanol (Brenntag-CEE, Germany) and ethanol concentrated (Swan Lake, Serbia) were used in performed experiments. All other reagents were of analytical grade.

2.2. Methods

2.2.1. Preparation of coated pellets

Fig. 1 shows a schematic overview of the processing steps for obtaining different multiparticulate formulations presented in this paper. Formulations are designated according to layering technique used for drug loading.

All powder layering experiments were carried out in GS 25 HT/PRA/M (IMA, Italy) coating machine in configuration with perforated immersion swords for processing pellets. The system has been described in detail by Nastruzzi et al. (2000). Application of barrier coating on powder layered pellets was performed also in GS 25 HT/PRA/M by the use of spray coating. All other spray coating experiments were performed on fluid-bed apparatus Glatt GPCG2 (Glatt GmbH, Germany) fitted with Wurster partition and a bottom spray two-fluid nozzle with 1.2 mm orifice (Düsen Schlick GmbH, Germany). In all experiments target level of drug in drug loading phase was 31% and level of barrier coating was 25% in relation to weight of drug loaded pellets. Target weight gain in enteric layer application was 60% in relation to weight of barrier layered pellets when enteric layer is applied by powder layering and 40% when it is applied by spray coating.

The formulation of product and production process parameters for all coating experiments presented in this work were set on account of preliminary experiments which were carried out with the basic principles of pellet layering in mind, that is to minimize agglomeration of pellets during production process and to minimize use of excipients to shorten time of production.

Table 1
Formulations of coating liquids and powders used in drug loading, barrier and enteric coating of powder layered pellets.

Material (%)	Drug loading by powder layering	Application of barrier layer by spray coating	Application of enteric layer by powder layering
Liquid phase			
Povidone K-30	5	/	/
Hypromellose 3 cp	/	7	/
Talc	/	8	/
Triacetin	/	1	/
Triethyl citrate			35
Polysorbate 80	/	/	4.5
Castor oil	/	/	7.5
Water[a]	/	42	/
Ethanol concentrated[a]	95	42	53
Powder phase			
Model drug	85	/	/
Talc	15	/	20
Hypromellose acetate succinate	/	/	80

[a] Solvent that disappears during coating process.