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Review

Direct compression of cushion-layered ethyl cellulose-coated extended release pellets into rapidly disintegrating tablets without changes in the release profile

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ABSTRACT

The aim of this study was to develop and optimize a segregation-free ethyl cellulose-coated extended release multiparticulate formulation to be compressed into tablets without affecting the drug release. Standard tableting excipients (e.g., microcrystalline cellulose, lactose or sorbitol) were layered onto ethyl cellulose-coated propranolol hydrochloride pellets to form a cushion layer in order to eliminate segregation problems normally resulting from particle size difference between coated pellets and excipient powders and second to protect the integrity of the brittle ethyl cellulose coating during compression. The disintegration behavior of the tablets depended strongly on the composition of the cushion layer. Rapid tablet disintegration was obtained with microcrystalline cellulose and the disintegrant sodium croscarmellose. However, the drug release from these cushion-layered pellets still increased upon compression. Incorporation of a glidant into the cushion layer or between the cushion layer and the ethyl cellulose coating reduced the compression effect on drug release markedly. Glidant-containing formulations showed a delayed deformation and damage of the ethyl cellulose-coated pellet upon mechanical stress. In summary, cushion layer based on microcrystalline cellulose facilitated segregation-free compression of a highly compression-sensitive extended release ethyl cellulose-coated pellets into fast-disintegrating and hard tablets without compromising the release properties of the multiparticulates. Directly compressible cushion-layered pellets protected the pellet coating significantly better from damages during tabletting when compared to the conventional compression of blends of coated pellets and excipient powders.

Contents

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1. Introduction

Multiple unit systems such as pellets can be administered orally either filled into hard capsules or compressed into rapidly disintegrating tablets. Pellet compression has received increasing attention since tablets are mechanically stronger, can be divided, be dispersed into water prior to intake and be produced at lower cost when compared to capsules (Chambin et al., 2005).

The major challenge during compression of coated pellets is the stress on the functional polymer coating, which can rupture the coating and hence change the release characteristics of the formulations (Altaf et al., 1998). Compression into a non- or slowly disintegrating tablet because of adhesion of pellets to each other is also undesirable, since slower release due to retarded tablet disintegration could occur (Dashevsky et al., 2004). In addition, segregation of the pellets from other necessary tabletting excipients can occur prior to compression resulting in content uniformity problems.

The extent of coating damage depends strongly on the mechanical properties of the polymer coating (Bodmeier, 1997) and the compression force. Ethyl cellulose coatings are widely used for controlled release dosage forms (Tarvainen et al., 2003). However, ethyl cellulose is a brittle polymer, which easily ruptured under stress leading to a loss of the extended release properties (Dashevsky et al., 2004; Bodmeier, 1997; Bodmeier and Paeratakul, 1994; Bansal et al., 1993). In general, pellets are blended with tableting excipients in powder form and then compressed (Fig. 1). Protection of the ethyl cellulose-coated pellets with admixed tableting excipients could marginally reduce the damage of the coated pellets during compression (Dashevsky et al., 2004; Bansal et al., 1993; Béchard and Leroux, 1992). However, the difference in pellet and excipient particle size increases the risk of segregation during the tableting process and hence of variations in weight and drug content (Lundqvist and Podczeck, 1997; Wagner et al., 1999). Stabilizing or cushioning agents were therefore either granulated or layered onto pellets to avoid segregation during tableting (Chambin et al., 2005; Altaf et al., 1998, 1999; Pan et al., 2010; Haslam, 1998).

Pan et al. compressed a blend of pellet-containing granules and separate tableting excipients, which showed an improved weight and drug content uniformity (Pan et al., 2010). The compressed acrylic polymeric-coated pellets resulted in similar release, however, the tablet hardness was low (30 N). In another approach, small amounts of MCC (10%, w/w) were layered or granulated with pellets in order to achieve a cushioning layer on top of the polymer-coated pellets (Altaf et al., 1998, 1999). The disintegration of the tablets was prolonged and the drug release increased compared to the uncompressed pellets reflecting insufficient protection. To optimize the formulation and therefore the protection properties upon compression, Altaf et al. layered polyethylene oxide (10%, w/w) between ethyl cellulose and microcrystalline cellulose (Altaf et al., 1999). The PEO layer, however, could not sufficiently protect the pellets from rupturing during the compression. Thus, none of the previous approaches was capable of properly protecting coated pellets from the stress during tablet compression in order to maintain the original drug release profile.

The aim of this work was therefore to develop a formulation approach allowing the segregation-free compression of coated pellets into tablets with sufficient hardness, disintegration behavior (<15 min) and without significant changes in the release profile. This was achieved by layering excipients directly onto the coated pellets followed by compression of theses pellets without further addition of tabletting excipients.

2. Materials and methods

2.1. Materials

Sucrose beads (Suglets sucrose spheres NF, 710–850 μm, NP Pharm, Bazainville, France); hydroxypropylmethyl cellulose (HPMC, Methocel® E5, Colorcon, Orpington, UK); polyvinylpyrrolidone (Kollidon® 90 F, BASF AG, Ludwigshafen, Germany); hydroxylpropyl cellulose (HPC, Klucel®EF-PHARM, Hercules Incorporated, Wilmington, USA); ethyl cellulose (Ethocel 10 cP, DOW, Midland, USA); microcrystalline cellulose (Avicel® PH-101 and PH-200, FMC BioPolymers, Cork, Ireland); lactose monohydrate (SorboLac® 400, Meggle, Wasserburg, Germany); sorbitol (Roquette, Tunbridge Wells, Lestrem, France); magnesium stearate (MgSt) (Herwe®-chemisch-technische Erzeugnisse GmbH, Sinsheim-Dühren, Germany); croscarmellose sodium (Ac-Di-Sol®, FMC BioPolymer, Cork, Ireland); sodium stearyl fumarate (PRUV®, JRS Pharma Gmbh & Co, Rosenberg, Germany); propranolol hydrochloride (BASF AG, Ludwigshafen, Germany).

2.2. Methods

2.2.1. Preparation of drug cores

Propranolol HCl was layered onto 600 g sucrose cores (710–850 μm) from an isopropanol/water (50:50, w/w) solution of 18% (w/w) solids content with HPMC as binder (10%, w/w based on drug) to achieve a 10–30% (w/w) drug content based on the resulting drug pellets in a fluidized bed coater (Aeromatic Strea-1, Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland) under the following conditions: inlet temperature 45–50 °C, product temperature 40–45 °C, outlet temperature 35–38 °C, air flow rate 50–70 m^3 h, atomizing air pressure 1.3 bar, spray nozzle diameter 1.2 mm.

2.2.2. Preparation of coated pellets

Drug layered pellets were coated with ethyl cellulose from an isopropanol/water (88:12, w/w) solution of 6% (w/w) solids content in a fluidized bed coater Glatt GPCG-1 to a theoretical coating level of 2 mg/cm^2. The coating conditions were: batch size 800 g, inlet temperature 40–45 °C, product temperature 40 °C, air flow 60–65 m^3 h; nozzle diameter 1.2 mm, spray pressure 1.5 bar.

2.2.3. Preparation of top-coated pellets

2.2.3.1. Seal coating. The HPMC seal coating was sprayed onto ethyl cellulose-coated pellets from an ethanolic suspension of 6% (w/w) solids content to a coating level of 2–3% (w/w).

2.2.3.2. Glidant layer. Magnesium stearate was sprayed onto ethyl cellulose or HPMC seal-coated pellets from an ethanolic suspension of 6% (w/w) solids content with HPMC as binder (25% based on magnesium stearate) to a coating level of 1–3% (w/w).

2.2.3.3. Cushion layer (directly compressible pellet system). Tableting excipients were layered directly onto the ethyl cellulose or onto the seal/glidant-coated pellets prior to compression (Fig. 1). The tableting excipients (filler, disintegrant and optionally glidant) were sprayed from an ethanolic suspension of 18% (w/w) solids content with PVP, HPC or HPMC as binder (10% based on coated pellets) to a coating level of 20–100% (w/w).

The coatings were performed in a rotary mini coater (self-built) at a batch size of 40 g, inlet and product temperature of 20–25 °C, air flow of 9–11 m^3 h, nozzle diameter of 0.75 mm and spray pressure of 0.8–1.8 bar.