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REVIEW

Investigation for the quality factors on the tablets containing medicated pellets

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Abstract Sustained and controlled pellets are considered as one of the ideal dosage forms. Due to the large coverage area of pellets, loaded drugs can be absorbed completely in the body and bioavailability is improved correspondingly. Coated pellets-containing tablet is a special oral formulation consisting of various pellets with different release rate. Desired rate of drug release rate can be achieved by adjusting the proportion of pellets. However, this formulation faces strict requirements in the process of preparation. Several factors will influence release behavior of tablets, including pellet cores, coating, and tabletting. Therefore, these factors will be investigated sufficiently in this review to provide valuable information for manufacturing process.

Contents

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1. Introduction

Orally sustained and controlled drug delivery systems are usually used to improve release behavior of drugs to meet different conditions in the body, which includes single unit dosage forms (SUF) and multiple unit dosage forms (MUFs) (Abdul et al., 2010). The latter consists of pellets, granules, microparticles and minitablets. Compared with SUF, MUFs present several advantages (Liu et al., 2012): (i) The multiparticulates spread uniformly throughout the gastrointestinal tract (GIT), which can reduce local irritation of active ingredient, enhance drug absorption and lower the fluctuation of peak plasma. (ii) MUFs possess constant transit time in the GIT, which can avoid dose bumping and improve safety. (iii) The defect of individual unit has no serious effect on efficacy. (iv) Inter- and intra-individual variations in the bioavailability caused for instance by food effects can also be reduced.

Pellets are a class of globular entity consisting drugs and excipients, which normally are no more than 2.5 mm in diameter. Coated pellets have effects of sustained release and masking taste. Tablets consisting coated pellets can contain incompatible drugs or drugs with different release rates. In contrast with pellet-containing capsules, tablets are more tamper resistant, easier to swallow and of lower cost in industrial production. With the application of coated pellets-containing tablets, tablets will be completely disintegrated into pellets and drug can be subsequently released from the pellets (Table 1). In fact, the MUF should not fuse into the non-disintegrating matrix during compaction and then disintegrate rapidly into the individual pellets in GIT. Compaction process has no effect on the release characteristics.

Compared with the preparation of common tablets, the technologies of pellet-containing tablets are more complex. At present, available tablets in the market mainly include proton pump inhibitors and some drug with narrow therapeutic window (Table 1). The key point in the preparation of coated pellet-containing tablet is to ensure the integrity of the coating film, which must be able to withstand the compression force. Many studies (Altaf et al., 1998; Miller et al., 1999) showed that coating films usually suffer from damages in the compression process, which will influence drug release behavior. Current researches mainly focus on the optimization for type and diameter of pellet cores, type and dosage of coating polymers and plasticizer, buffer excipients, as well as technological parameters (Fig. 1). All of these will be discussed specifically in this review and put forward corresponding solutions.

2. Formulation factor

2.1. Pellet core

Core features of coated pellets are essential to the tabletting of coated pellets. Cores, with good elasticity and toughness, ought to meet the requirements of deformation during tabletting, which can reduce undesirable effects following elastic recovery on coating films and ensure intact coating films. Determinant factors of tensile strength contain core composition, size, porosity, and so on. Coated cores with good tensile strength can withstand pressure in the tabletting process and maintain intact coating film.

2.1.1. Core composition

Pellets itself must have certain tensile strength, and thus maintain release behavior of pellets following tabletting. The first issue to be considered is the composition of pellets. Components of pellets include diluents and adhesive, such as lactose, starch, microcrystalline cellulose (MCC), hydroxymethyl cellulose, polyvinyl alcohol, Polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).

Due to the good rheological properties that enhance the plasticity of other excipients and produce bonding effects, MCC is called balling promoter and applied widely. The mechanism of tabletting with MCC-containing pellets was studied

Table 1 Overview of marketed tablets containing coated pellets.

Trade name	API	Therapeutic role	Formulation	Manufacturer
Betaloc ZOK	Metroprolol succinate	Hypertension	Multi-unites sustained pellet-containing tablet	AZN
Harnal D	Tamsulosin Hydrochloride	Hyperplasia of prostate	Multi-unites sustained pellet-containing disintegrating tablet	Astellas
Losec MUPS	Omeprazole Magnesium	Peptic ulcer	Multi-unites enteric pellet-containing tablet	AZN
Nexium	Esomeprazole magnesium	Peptic ulcer	Multi-unites enteric pellet-containing tablet	AZN
Prevacid	Lansoprazole	Peptic ulcer	Multi-unites enteric pellet-containing disintegrating tablet	Takeda