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Research paper

Design and study of ibuprofen disintegrating sustained-release tablets comprising coated pellets

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Abstract

One challenge in tableting of sustained-release multiparticulates is maintaining the desired drug release after compaction. The aim of this study was to design sustained-release ibuprofen tablets which upon oral ingestion rapidly disintegrate into sustained-release pellets in which the integrity of the pellet core and/or coat is preserved.

First free films composed of Eudragit RS 30D and RL 30D in 4:1 ratio and containing different levels of triethyl citrate (TEC) were prepared and tested to optimize the plasticizer level. Cured Eudragit based pellets with 60% ibuprofen loading which in our previous study showed proper mechanical properties for compression were coated with Eudragit RS 30D/RL 30D (4:1) containing 20% triethyl citrate at different coating levels. The mechanical properties of the coated pellets were tested. Polymer coated pellets were compacted into tablets either alone or with a blend of excipients comprising Avicel, PEG 4000, cross-linked PVP. A 3^2 full factorial design was used to optimize the filler blend composition. Effects of pellet to filler ratio, compression force and granulation of filler on tablet characteristics were investigated.

Results of mechanical test showed that the coating of cured pellets had no significant effect on yield point and elastic modulus of the pellets. In the case of 5% coating level sustained release of ibuprofen over a period of 24 h was achieved. The results obtained from tableting procedure showed that by selecting suitable filler blend (60% Avicel, 10% cross-linked PVP and 30% PEG 4000), compression force, and granulation of filler it was possible to prepare sustained-release tablets containing high ratio of coated pellets (even 80%) with desirable strength, disintegration time, and drug release rate. It was observed that compression force, pellet to filler ratio, composition of filler blend and granulation of fillers had no effect on drug release rate from compacted pellets but had significant influence on tablet strength, friability, and disintegration time. SEM graphs and in vitro release profiles for compacted pellets showed no apparent damage to the coated pellets as a result of the compaction process.

Keywords: Ibuprofen; Eudragit; Pellet; Multiparticulate tablet; Sustained release

1. Introduction

Recently, there has been an increasing interest in the development of multiparticulate dosage form in the shape of tablets rather than hard gelatin capsules. The aim of most studies on the compaction of pellets is to convert multiple-unit dosage form into a single unit dosage form which is able to disintegrate into the primary individual multiparticles [1]. Administration of pellets as a tablet which disintegrates into their subunits upon ingestion combines the advantages of oral multiple-unit dosage forms (e.g. free dispersion in GI-tract to avoid local irritation and dose dumping, and provide uniform absorption and improve bioavailability) with those of tablets.

In our attempts for production of sustained-release Eudragit RS/RL based ibuprofen pellets as a tablet it was shown that the curing process had a significant

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retarding effect on drug release rate from these pellets, but due to presence of high drug loading in these pellets and consequently low polymer content, the polymer matrix could not have a desirable sustaining effect on drug release rate [2] and further coating is required to achieve sustained-release formulation. However alteration of mechanical properties of cured pellets from brittle to plastic makes them a suitable substrate for preparation of multiple-unit tablets either in the form of un-coated or coated pellets, as it can prevent cracking of pellets and/or their coating under the compression force and therefore prevent major changes in the release properties after compression.

It has been shown that the films prepared from acrylic polymers are more flexible and therefore more suitable for the compaction of coated pellets compared to ethylcellulose films [3]. It has been also reported that an aqueous dispersion of Eudragit polymers is more suitable than their solvent-based coatings for pellets which are intended to be compacted [1]. Eudragit RS 30D and RL 30D are widely used as coating materials to sustain drug release. The diffusion rate of dissolved drug molecules through membrane of Eudragit RS 30D is lower than Eudragit RL 30D. The mixed films prepared from two acrylic polymer latexes show intermediate permeability [4].

The aim of this study was to develop a coating formulation for cured Eudragit based ibuprofen pellets to achieve sustained release of drug over 24 h and to compress these pellets as a tablet. The tablets should disintegrate rapidly into their comprising pellets upon contact with dissolution medium. The influences of inclusion of filler, type of filler, compression force and pellet to filler ratio on the properties of compacts were also investigated.

2. Materials and methods

2.1. Materials

Ibuprofen and microcrystalline cellulose (Avicel® PH101) were provided by Darupakhsh (Tehran, Iran), Eudragit RL PO, Eudragit RS PO, Eudragit RL 30D and Eudragit RS 30D were gifts from Rohm Pharma GmbH (Darmstadt, Germany), polyvinylpyrrolidone (PVP K30) and cross-linked povidone (PVP XL) were supplied by Fluka (Switzerland), polyethylene glycol (PEG 4000), magnesium stearate, talc and triethyl citrate were obtained from Merck (Germany).

2.2. Methods

2.2.1. Preparation of cured pellets

Cured pellets containing 60% ibuprofen, 27% Eudragit RS/RL (1:1), 10% Avicel and 3% PVP K30 were prepared based on the procedure described by Abbaspour et al. [2]. Briefly, the components were mixed and kneaded to make a wet mass with suitable consistency. The wet mass was then extruded through a 1 mm screen at 120 rpm and spheronized at 1000 rpm for 2 min. The obtained pellets were dried at 40 °C for 10 h; those pellets in the range of 850–1180 μm were cured at 60 °C for 24 h and then were allowed to cool at the ambient temperature for at least overnight. Then they were kept in tightly closed containers until use.

2.2.2. Coating procedure

2.2.2.1. Preparation of free films. This part of study was performed in order to optimize the percent of plasticizer in coating formulation. It has been shown that Eudragit RS 30D is less permeable than Eudragit RL 30D and they can be mixed in any proportion to achieve intermediate permeability [4]. The 4:1 ratio of Eudragit RS 30D and Eudragit RL 30D was used for film preparation based on some preliminary studies performed in our laboratory. Free films composed of Eudragit RS 30D and Eudragit RL 30D in 4:1 ratio and different percents of TEC (10%, 20%, 30% w/w based on dry polymer) as plasticizer were prepared. The dispersions were diluted with distilled water to achieve 10% (w/v) dry polymer content. The plasticizer was added to dispersions by stirring 5 h prior to film preparation. Samples equal to 30 mL of resulted dispersions were poured into leveled flat-faced Teflon plates (casting area = 10 × 10 cm). The plates were placed in an oven at 40 °C for 48 h and then were transferred to a desiccator with 100% relative humidity (RH) resulted by water at room temperature for 10 h, to make the films flexible enough to be removed intact from the plate [5]. The softened films were then cut carefully with a sharp scalpel into several strips of 10 mm width and at least 50 mm length and then peeled off from the plate. Free films were stored in a desiccator with 50% RH resulted from a saturated solution of magnesium nitrate hexahydrate at room temperature until mechanical tests were performed [5].

2.2.2.2. Mechanical tests of free films. The thickness of the film strips was measured at five different points using a micrometer (Mitutoyo, Japan) and the mean thickness was calculated. Specimens with an average thickness of 250–300 μm were selected. Films with air bubble, nicks or tears and having mean thickness variations of greater than 5% were excluded from analysis.

Each specimen was placed between two grips of a Material Testing Machine (Hounsfield, England) fitted with a 1 kN load cell. The initial distance between two grips (initial length of the film specimens) was 30 mm and the speed of grip separation was set at 10 mm/min. The extension – force graphs, stress at break (the tensile stress at which the specimen ruptures), and % elongation (or % strain at break) were obtained with a computer system attached to the apparatus (QMAT, Hounsfield, England). The experiment was repeated 5 times for each formulation and the mean value was reported.

2.2.2.3. Coating of the pellets. Ten percent (w/v) of coating formulation containing Eudragit RS 30D and Eudragit RL 30D in 4:1 ratio was prepared. Triethyl citrate was added