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Research paper

Fast dispersible/slow releasing ibuprofen tablets

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Abstract

Eight formulations were developed containing ibuprofen in the form of orally disintegrating tablets. To prevent bitter taste and side effects of the drug, the drug was associated with Phospholipon 80H, a saturated lecithin, by wet granulation. The granules were then coated using different film forming agents (Kollicoat SR 30, Amprac 01, Kollidon 90F, Eudragit RD 100) obtaining four lots 1–4. Coated granules were then formulated with a sweetener (Aspartame), a mannitol-based diluent (Pearlitol SD 200) and Kollidon CL (1-4K) or Explotab (1-4E) were added as superdisintegrants and compacted under low compression force. The eight lots of tablets, 1-4K and 1-4E, were assessed if suitable as oral disintegrating tablets by determination of a range of technological parameters. Wetting and disintegregation time matched with the requirements of EP IV Ed., for almost all these formulations. Dissolution profiles suggested that the combined action of the hydrophobic lecithin and the coating delay the release of the drug from tablets with respect to when it is free or in the form of simple granules. By an appropriate combination of excipients it was thus possible to obtain orally disintegrating tablets and a delayed release of ibuprofen using simple and conventional techniques.

Keywords: Orally disintegrating tablets; Ibuprofen; Lecithin; Taste masking; Slow release; Gastroprotection; Fast dispersing tablets

1. Introduction

Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally disintegrating tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration [1–3], since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and travelling patients. The advantages of this new type of solid dosage form are widely recognized, since the term "oro-dispersible tablet" appears in the European Pharmacopoeia (Suppl. 4.1, IV Ed.) defined as "*uncovered tablet for buccal cavity, where it disperses before ingestion*". These tablets display a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption [4,5]. To fulfil these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid de-aggregation of the matrix. Different technological techniques, such as freeze drying or moulding or direct compression [6–8], are currently employed to prepare the formulations of this type present on the pharmaceutical market.

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In this paper a simple compression technology was employed for preparing fast disintegrating tablets containing ibuprofen. Traditional compression in fact involves a limited number of process steps and low costs, resulting in fully automated production and packaging lines; it also allows the presence of high doses of both active agent and excipients [9]. Since too high mechanical resistance of the tablet does not usually favour rapid de-aggregation, to combine these two opposite prerequisites into the same formulation we coupled mechanical resistance of the final tablet, to be inserted and taken from usual blister packs, together with the presence of a (super)disaggregant agent to improve oral dispersibility.

Ibuprofen is widely available as *over the counter* formulations throughout Europe for a number of non-serious, self-limiting conditions involving mild to moderate fever and pain. This drug is sometimes associated with a "peppery" taste that limits its use as an effective analgesic and antipyretic drug, e.g. in children. Formulations where ibuprofen was associated with hydroxypropyl beta cyclodextrin, for the entrapment of ibuprofen to reduce its bitter taste, and sweeteners to mask the sour taste and make it more palatable, have been described [10,11]. Moreover, previous results showed that ibuprofen (and its salts) irritates the throat much more than the mouth, and that its quality in the throat is characterized primarily as sting/prick, itch and tickle (often leading to cough) [12].

In addition to its bitter and irritating taste, ibuprofen displays significant risks of gastrointestinal side effects, when chronically administered in the elderly. The developed formulations aimed also to minimize the gastrolesivity of the drug and to improve its palatability by a close association with a lecithin, as excipient, and the presence of sweet-taste additives, such as aspartame and mannitol. Fast dispersibility of the tablet, guaranteed by the presence of a superdisaggregant, and slow release of the drug were tested by the measurement of a number of technological parameters.

2. Materials and methods

2.1. Materials

All the materials used in the present research were commercial samples. *Active agent*: ibuprofen (Welding GmbH, Hamburg, Germany); *protective agents*: Phospholipon 80H (*hydrogenated phosphatidylcholine, 60%*) (Phospholipid, Koln, Germany); Lipoid *S75* (*phosphatidylcholine, 71%; phosphatidylethanolamine, 7.6%*) (Lipoid, Ludwigshafen, Germany); *film forming agents*: Kollicoat SR 30D (*30% w/w aqueous dispersion polyvinyl acetate 27%, Povidon 2.5%, SDS 0.3%*) (Eigenmann & Veronelli, Rho, Italy), Amprac 01 (*pregelatinised starch acetate*) (Rofarma, Gaggiano, Italy), Kollidon 90F (*water soluble high PM PVP polymer, with a water content around 19% w/w*) (Basf, Ludwigshafen, Germany), Eudragit RD 100 (*copolymers of acrylate and methacrylates esters with quaternary ammonium groups in combination with 10% sodium carboxymethylcellulose*) (Rofarma, Gaggiano, Italy); de-aggregating agents: Explotab (*sodium starch glycolate*) (Loxer, Monaco, France), Kollidon CL (*crospovidone*) (Basf, Ludwigshafen, Germany). Aspartame (ACEF, Fiorenzuola d'Arda, Italy), Pearlitol SD200 (*spray dried mannitol*) (Faravelli, Milan, Italy); *lubricant*: magnesium stearate (Faravelli, Milan, Italy) were of pharmaceutical grade, according to EP IV Ed.

2.2. Preparation of the tablets

The preparation of the tablets was carried out according to three different steps.

2.2.1. Granulation

Each phosphatidylcholine (Phospholipon 80H; Lipoid S75) was mixed with ibuprofen in the weight ratio 1:4. The mixture was kneaded in the presence of an amount of water sufficient to homogenize the mass using a laboratory kneader (LK5 Erweka Italia, Seveso, Italy) which was then extruded through a steel grid (2.8 mm) (wet granulator Mod. FGS, Erweka Italia, Seveso, Italy). The final granulate was dried at 45 °C (Drier Mod FD 600 F8/5, Vismara, Milano, Italy) up to a humidity content 3–5% and sieved, selecting particle size $\leqslant$600 μm. The two materials were identified as A (Phospholipon 80H) and B (Lipoid S75).

2.2.2. Film formation

This and the following steps were carried out only with lot A (see Section 3).

Four commercial coating materials (Kollicoat SR 30D, Amprac 01, Kollidon 90F, Eudragit RD 100) were sprayed as aqueous suspension on the granulate particles. The aqueous coating processes were preferred, since they represent an alternative to organic solvent-based film coating for environmental, economic and safety reasons, and all the materials proposed match these needs quite well.

A 20% *w/w* suspension was prepared in water containing each of the four film forming agents that differ in the nature and concentration of the four filming materials (Kollidon R 30D – 2%; Amprac 01 – 2.8%; Kollidon 90F – 0.7%; Eudragit RD 100 – 1.5%, respectively). Each suspension was sprayed onto granules, previously prepared and the filmed granules were simply indicated as 1, 2, 3 and 4, according to the film agent (in order). The whole process was carried out on a "pan" (Mod. VNF 50, Nicomac). Starting from these intermediate formulations we prepared the final tablets.

2.2.3. Compression

Filmed granules were mixed with appropriate amounts of diluent (spray dried mannitol, size < 200 μ), disaggregating agent and lubricant (magnesium stearate). The addition of 10% *w/w* of a disaggregating agent (Kollidon CL-K and Explotab-E) generated two new series of tablets (1K, 2K,