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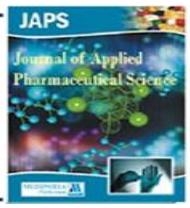

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Prolonged-release solid dispersions of ibuprofen

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ABSTRACT

Ibuprofen (IB) is one of the most important non-steroidal anti-inflammatory drugs used in the treatment of inflammatory chronic diseases. This drug presents, in the pure state, poor physical and mechanical characteristics and their use in solid dosage forms needs the addition of excipients which improve these properties. The selection of the best excipients and the suitable pharmaceutical dosage form to carry ibuprofen are very important for the industrial success of this drug. Thus, in this work, solid dispersions of ibuprofen in cethyl alcohol (SD CA), stearic acid (SD SA) and hydrogenated castor oil (SD HCO) were prepared in order to improve physical and mechanical characteristics of this drug. Physical mixtures with the same composition of solid dispersions were also prepared. Solid dispersions of ibuprofen with stearic acid and hydrogenated castor oil showed better flow characteristics than pure ibuprofen and the respective physical mixtures. Gelatin capsules filled with solid dispersions were submitted to dissolution tests in order to study the influence of the prepared systems in the release profiles of ibuprofen. Prolonged-release of ibuprofen was achieved with the solid dispersions prepared with the different types of excipients.

Keywords: Ibuprofen, Solid dispersions, Physical mixtures, Hydrogenated castor oil, Stearic acid, Cethyl alcohol.

INTRODUCTION

Ibuprofen (IB) is a drug of the anti-inflammatory group (NSAIDs), belonging to the sub-group of drugs derived from propionic acid (Osswald, 2001). It is generally well tolerated, but may trigger headaches, stomach pain, vomiting, diarrhea, stomach and duodenum ulcers (Brunton *et al*., 2007). Thus, arises the need to minimize these adverse effects and prolong its inflammatory action in time. There are two key strategies to alter the release and subsequent absorption of drugs, one is based on its modification and the other is based on the modification of the dosage form (Lachman, 2001). The preparation of solid dispersions is a strategy with the aim of changing the release and subsequent drug absorption. The drug is well dispersed in a matrix of a material that modifies its release, encapsulated in the form of particles or compressed to form tablets. The matrix systems are classified according to their chemical nature and release mechanism. Hydrophilic matrices absorb water and form a gel prior to dissolution (eg. methylcellulose, agar-agar, alginates and carbomer) and hydrophobic matrices originate porous solid structures in which the drug is dispersed. Hydrophobic matrices include the inert matrices, insoluble in gastric juices (e.g. cellulose acetate, ethyl cellulose, etc.), and lipidic matrices which suffer erosion, gastric enzyme lipolysis, or solubilization by ionization (e.g. hydrogenated castor oil, stearic acid and cethyl alcohol).

The choice of a matrix is very important, because this choice will influence the ability of the formulation to control the drug release and thereby sustain the therapeutic action over time (Liberal, 2008; Salomen, Doelker, 1980). Waxes and other related lipidic materials such as cethyl alcohol, stearic acid and hydrogenated castor oil, form matrices that control the release of drugs by diffusion through pores or by erosion (Rowe *et al., 2003*). The term solid dispersion is reflected by the dispersion of one or more active substances in a carrier or inert solid matrix prepared by melting, or by using solvents or by solvent-melting method (definition proposed by Chiou and Riegelman (Chiou & Riegelman, 1971)). Solid dispersions may have several advantages and pharmaceutical applications, the main ones are: the uniform and homogeneous distribution of small quantities of drug in the solid state, the stabilization of unstable drugs, the dispersion of liquid or gaseous compounds and the production of prolonged release systems or the increase of drug dissolution rates.

The combination of a slightly soluble drug in water with a water-soluble matrix results in a rapid-release drug formulation (e.g. solid dispersion of ibuprofen/PEG 4000 or ibuprofen/PEG 8000, to increase the dissolution rate of the drug) (Newa, 2008). Another example is described to obtain solid dispersions of ibuprofen in Poloxamer 407 in order to increase the solubility and consequently the dissolution rate of this drug (Newa, 2008). Moreover, the combination of a water soluble drug with a slightly water soluble matrix sustains the drug release from the matrix. The characteristics of drug release can be altered by changing the ratio between the drug and excipient (Ford, Rubinstein, 1978).

To disperse a drug in an excipient several methods can be used, including the solvent method (Ford, 1986), the fusion method (Sharma, Joshi, 2007; Yi *et al.*, 2008), the solvent-melting method, freeze and spray drying technology (Park *et al., 2009*).

MATERIALS AND METHODS

Materials

Ibuprofen (Lot No. 0507939, Roig Farma, Spain), cetyl alcohol (Lanette 16) (Lot No. S383040010, José M. Vaz Pereira SA, Portugal), stearic acid (Lot No. 062,821, Acofarma, Spain), hydrogenated castor oil (Cutina HR®) (Lot No. CG42720170, José M. Vaz Pereira SA, Portugal), monosodium phosphate (Lot No. 0194, José M. Vaz Pereira, SA, Portugal), disodium phosphate anhydrous (Lot No. 130470JR, José M. Vaz Pereira, SA, Portugal), propylene glycol (Lot No. VF251920D4, José M. Vaz Pereira, SA, Portugal) and chloroform (Lot No. 7B128128C, Pronolab, José M. Vaz Pereira, SA, Portugal). Gelatin capsules No. 0 (Lot No. 9328900023, Guinama, Spain)

Methods

Preparation of solid dispersions containing ibuprofen

Solid dispersions at a 1:2 ratio of ibuprofen/excipient were prepared using the fusion method. This ratio was used to make certain that the excipient contained the ibuprofen, in order to obtain the sustained release of the ibuprofen. Excipient melting (variable temperature according to the melting point of the excipients) on a hot plate under stirring was used, followed by addition of ibuprofen to the excipient cast, slow cooling for solidification of the mass, and grinding. Gelatin capsules No. 0 were filled with these solid dispersions (method - capsule filling plate).

Preparation of physical mixtures containing ibuprofen

For a total amount of 120 g and respecting the weight ratio of 1:2 ibuprofen:excipient, physical mixtures were also prepared, using a Turbula WAB T2F (Switzerland) for 15 minutes.

Determination of particle size distribution

The test was performed in the Retsh AS 200 Digit (Germany), for the dry sieving. Sieves with the following mesh diameter were chosen: 1000µm, 500µm, 355µm, 180µm, 125 µm and 90µm. Samples were weighed (50 g) and subjected to a 2.0 mm amplitude vibration, for two cycles of 5 minutes. Tests were performed in triplicate, with the result being the average of the obtained values.

Determination of flow velocity and repose angle

For these tests, a Granulate Flow Tester, Erweka Type: GT / GTB (Germany) was used. A funnel with a metal tip with a hole of 15 mm and 50 g of solid dispersions of ibuprofen were used. The tests were performed in triplicate, with the result being the average of the obtained values.

Determination of ibuprofen content using UV-VIS spectrophotometry

For the determination of ibuprofen content in solid dispersions and lipid microparticles, 75 mg of each sample was dissolved in chloroform (50 ml) and analyzed by UV-VIS spectrophotometry (UV-VIS spectrophotometer JASCO V-650, Japan) at 272 nm. The accuracy, repeatability, specificity, and linearity of the spectrophotometric method were previously evaluated.

Capsules Mass Uniformity test

Mass uniformity test of gelatin capsules filled with the solid dispersions and lipid microparticles was performed. Twenty individually weighed units of capsules containing solid dispersions or lipid microparticles were taken at random and the average mass was determined.

Release / dissolution in vitro

For these determinations, were used gelatin capsules containing solid dispersions and capsules containing only pure Ibuprofen. Dissolution tests were performed under the following conditions:

- Dissolution apparatus - SOTAX AT7 (Switzerland);
- Basket method;
- Agitation speed - 100 rpm;
- Temperature - 37 ± 0.5 º C;
- Dissolution liquid - pH 7.4 buffer phosphate solution (Portuguese Pharmacopoeia VIII);

- Dissolution liquid volume - 500 ml;
- Sample bulk - 10.0 ml;
- Collection times - 30, 60, 120, 240, 360, 600 minutes.

Samples were assayed in triplicate in a UV-VIS spectrophotometer at 272 nm, using pH 7.4 buffer phosphate solution as a blank.

RESULTS AND DISCUSSION

Determination of particle size distribution

Figure I show the particle size distribution of the different solid dispersions of ibuprofen. As can be seen, solid dispersions of ibuprofen in hydrogenated castor oil and stearic acid presented a higher percentage of particles with average size higher than 1000 μm. The solid dispersion of ibuprofen in cethyl alcohol showed a higher percentage of particles between 500 and 1000 μm.

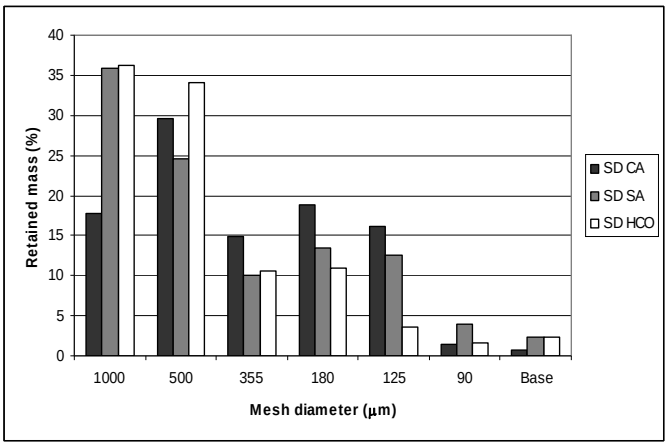

Fig. 1: Size distribution of the solid dispersions of ibuprofen (SD CA- solid dispersions of cetyl alcohol; SD SA - solid dispersions of stearic acid; SD HCO - solid dispersions of hydrogenated castor oil).

Determination of flow velocity and repose angle

The Ibuprofen pure powder did not flow. Also, physical mixtures of ibuprofen with each excipient did not flow. In all cases, the particles of the physical mixtures stay sticked to the funnel wall. The solid dispersion of ibuprofen in cethyl alcohol (SD CA) did not show flowability. On the other hand, the solid dispersion of ibuprofen in stearic acid (SD SA) showed a flowability of 6.0 ± 0.28 s and a repose angle of 44.5 ° ± 0.31. Similarly, the solid dispersion of ibuprofen in hydrogenated castor oil (SD HCO) presented a flowability of 5.3 ± 0.06 s and a repose angle of 41.9 ° ± 1.22. Despite the flowability presented by these solid dispersions, the respective values of repose angle suggested poor flow characteristics. The higher percentage of smaller particles presented by cethyl alcohol solid dispersions, had influence on its lack of flowability.

Determination of ibuprofen using UV-VIS spectrophotometry

For ibuprofen UV-VIS spectrophotometry determination, several validation parameters were evaluated. The method showed good linearity (coefficient of determination of 0.999), accuracy (101.30%±2.55) and repeatability (CV = 0.34%) within the range of concentrations assayed. In assessing the specificity it was verified that stearic acid and cethyl alcohol showed some absorbance at 272nm. Thus, for the calculations of ibuprofen released, the absorbance of these two excipients was subtracted to the absorbance values corresponding to solid dispersions.

Figure 2 presents the content of ibuprofen in the solid dispersions prepared with the different types of excipients, cethyl alcohol, stearic acid and hydrogenated castor oil (Cutina HR®).

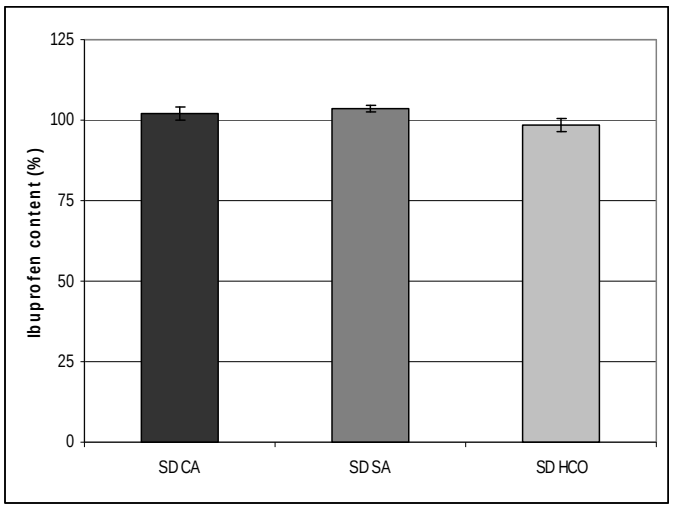

Fig. 2: Ibuprofen content in solid dispersions (SD CA- solid dispersions of cetyl alcohol; SD SA - solid dispersions of stearic acid; SD HCO - solid dispersions of hydrogenated castor oil).

The results of the determination of ibuprofen content in the different solid dispersions showed percentages of drug around 100% in all cases.

Mass Uniformity of gelatin capsules

Table I show the values of mass uniformity of gelatin capsules prepared with the different solid dispersions.

Table. 1: Results of mass uniformity of capsules prepared with ibuprofen and the different solid dispersions.

Capsules	Average (mg)	Maximum	Minimum	SD	CV (%)
IB	415,52	398,43	437,72	11,82	2,85
SD CA	399,08	376,58	419,60	12,21	3,06
SD SA	415,25	401,57	428,23	5,59	1,35
SD HCO	435,64	411,65	453,88	9,04	2,07

(SD CA- solid dispersions of cetyl alcohol; SD SA - solid dispersions of stearic acid; SD HCO - solid dispersions of hydrogenated castor oil).

As can be seen in Table I, the mass of capsules was within the limits of Portuguese Pharmacopoeia VIII.

Release/Dissolution *in vitro*

After the preparation and characterization of capsules with the different solid dispersions, *in vitro* dissolution studies were performed. Some validation parameters of the method for ibuprofen determination (UV-VIS spectrophotometry) were evaluated. The method showed good linearity (coefficient of determination of 0.9994), accuracy (100.43%±1.97) and repeatability (CV = 0.18%) within the range of concentrations studied. In assessing the specificity it was verified that the

excipients did not interfere in the absorbance at 272nm, but empty gelatin capsules absorb in this wavelength, so this value was subtracted to the results of absorbance.

Figure 3 show the dissolution profiles of gelatin capsules containing pure ibuprofen and solid dispersions of this drug in cethyl alcohol, stearic acid and hydrogenated castor oil.

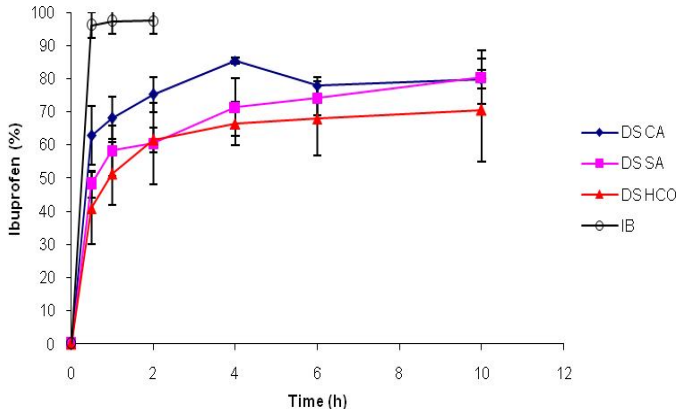

Fig. 3: Dissolution profiles of solid dispersions of ibuprofen with different excipients (SD CA- solid dispersions of cetyl alcohol; SD SA - solid dispersions of stearic acid; SD HCO - solid dispersions of hydrogenated castor oil).

As can be seen in Figure 3, about 95% of pure ibuprofen was dissolved in the first 30 minutes of the dissolution test. Solid dispersion of cethyl alcohol showed a higher percentage of ibuprofen released (62.8%) after 30 minutes, followed by solid dispersion of stearic acid (48.1%) and solid dispersion of hydrogenated castor oil (41.0%). After 10 hours of testing, the amount of ibuprofen released from the solid dispersions of cethyl alcohol and stearic acid was almost identical (80%), while the solid dispersion of hydrogenated castor oil released 70.5% of drug. However, the solid dispersion of hydrogenated castor oil showed a dissolution profile similar to the solid dispersion of stearic acid (*Similarity factor* = 58.7) (Guidance for Industry, 1997). Comparing the solid dispersion of cethyl alcohol (SD CA) and the solid dispersion of hydrogenated castor oil (SD HCO) it can be concluded that this two types of solid dispersions presented different profiles (*Similarity factor* = 40.0).

CONCLUSIONS

The results of this work showed that the type of excipients and the prepared solid dispersions have influence in the physical and mechanical properties, as well as, in the dissolution profiles of ibuprofen. Solid dispersions of ibuprofen in stearic acid and hydrogenated castor oil showed better flow characteristics than pure ibuprofen and the respective physical mixtures. Prolonged-release of ibuprofen was achieved with the preparation of solid dispersions using cethyl alcohol, stearic acid and hydrogenated castor oil. Solid dispersions of ibuprofen in hydrogenated castor oil showed better flow characteristics and a more prolonged release of ibuprofen.

LIST OF ABBREVIATIONS

IB – Ibuprofen
PEG – Poly(ethylene glycol)
SD CA – Solid Dispersions of Cetyl Alcohol
SD HCO – Solid Dispersions of Hydrogenated Castor Oil
SD SA – Solid Dispersions of Stearic Acid
UV-VIS – Ultraviolet-Visible

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