



ENHANCEMENT OF CELECOXIB SOLUBILITY BY SOLID DISPERSION USING MANNITOL

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ABSTRACTS

Bioavailability can be increased by changing in disintegration and dissolution the aqueous solubility is lesser than 1 μ g/ml will defiantly create a bioavailability problem and thereby affecting the efficacy of the drug. There are number of methods through which aqueous solubility of the drug can be increased in which solid dispersions is one of the effective and accepted technique in the pharmaceutical industry. The purpose of the study was to improve the physicochemical properties of celecoxib a poorly water soluble drug by forming dispersion with mannitol as water soluble carrier. The solid dispersion of celecoxib by physical triturating, solvent evaporation and fusion method were prepared using 1:1, 1:3 and 1:5 ratios of drug and polymer (mannitol). The prepared dispersions showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug. The dispersions with mannitol (1:5) by fusion method showed faster dissolution rate (82.46%) as compared to other solid dispersions with mannitol (1:1 and 1:3) whichever prepared by physical mixture and solvent evaporation method. The FT-IR shows the complexation and there were no interactions. Finally, solid dispersions of celecoxib: mannitol prepared as 1:5 ratio by fusion method showed excellent physicochemical characteristics and was found to be described by dissolution kinetics and was selected as the best formulation in the study.

Keywords: Solid dispersion, Celecoxib, Mannitol

INTRODUCTION

Celecoxib (CXB) is an anti-inflammatory, analgesic and antipyretic drug used in treatment rheumatoid arthritis, osteoarthritis¹. The aqueous solubility of CXB is 3 to 7 μ g/ml when determined at pH 7.0 at 40 $^{\circ}$ C. The peak plasma concentration is reported three hours after oral dosing. CXB is evenly distributed *in-vivo* and has a volume of distribution of 455 \pm 166 in humans². This larger volume of distribution and low aqueous solubility may be related to the lipophilic nature of CXB and be reflective of low bio availability. Different approaches are reported to improve the solubility of CXB. Use of co-solvent like ethanol, ethylene glycol, propylene glycol and polyethylene glycol has been tried³. Deposition of drug on the surface of an inert carrier leads to reduction in the particle size of drug.

There by providing faster rate of dissolution. Various hydrophilic materials with high surface area can be utilized to deposit the drug on their surface. The selection of carrier and method of preparation are critical factors influencing the properties of the drug incorporated in the solid dispersion. Solid dispersion techniques can be used to increase dissolution and bioavailability of several insoluble drugs^{4,5} Dissolution rate of griseofulvin was increased by depositing it on the surface of disintegrants such as primogel, starch, Nymcel^{6,7}. Solvent deposition technique was used to enhance the dissolution rate and anti-inflammatory effect of piroxicam. The poor aqueous solubility of the drug gives rise to difficulties in the pharmaceutical formulation of dosage forms and may lead to variable bio availability. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently improve the bio availability of poorly soluble drugs. The drug is dispersed in molecular form in a pharmacologically inert carrier which freely water soluble with intrinsic rapid dissolution properties. This technique improves the poor aqueous solubility and low dissolution rates by solubilising effect of carriers, reduction in particle size, reduction in aggregation of hydrophobic drugs due to improved humectation.

MATERIALS AND METHODS

Materials

Celecoxib by Zydus Cadila, Ahmedabad. Mannitol from Nice chemicals Pvt. Ltd., Cochin, Sodium lauryl sulphate was donated by S.D. chemicals Ltd., Boisar and Methanol obtained from Qualigens, Mumbai.

Preparation of solid dispersions

Solid dispersion of Mannitol and CXB were prepared in the molecular ratios of 1:1, 1:3, 1:5 of drug: carrier. Three techniques used for preparation were

Physical mixture^{8,9}

Physical mixtures were prepared by homogeneous blending of previously sieved and weighed celecoxib and mannitol in a mortar and pestle. The physical mixtures were subsequently stored at room temperature in desiccator over anhydrous CaCl₂ until use.

Solvent evaporation^{8, 10, 11}

The required amounts of CXB and carrier was dissolved in methanol and allowed to stand overnight. The solvent was removed at 60 $^{\circ}$ C under vacuum until the solid dispersion was dry. The dried mass was pulverized, passed through 44-mesh sieve and stored in a desiccator over anhydrous CaCl₂ until used for further studies. This mass was hand filled into zero-size hard gelatin capsules just before the dissolution studies.

Fusion method¹⁰

The solid dispersions were prepared by heating accurately weighed amounts of mannitol and drug in a closed teflon container in an oil bath at 80 $^{\circ}$ C. The mixtures were stirred repeatedly and after 10 min cooled either at room temperature.

Evaluation of solid dispersions

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors¹². Solubility studies on pure drug, physical mixture and solid dispersions were conducted in thermostatic shaker bath (Labline, Chennai) for 96 hrs at 37 $^{\circ}$ C \pm 5 $^{\circ}$ C, finally the solutions were filtered using whatmann filter paper (grade 41 Himedia) and the filtrate was diluted (10 μ g/ml) for determining drug concentration by spectrophotometrically (Elico SC164), the absorbance was measure at 254 nm. All solubility measurements were performed in triplicate.

FT-IR spectroscopy

IR spectrum of powder CB and its different solid dispersions of the ratios 1:1, 1:3 and 1:5 drug and polymer respectively, were recorded using Jasco FT/IR 5300 infrared spectrophotometer by KBr disc

method. The scanning range was 4000 to 450 cm^{-1} and the resolution was 4 cm^{-1}

Drug content analysis

An accurately weighed quantity of solid dispersion equivalent to 100 mg of celecoxib was taken into a 100 ml volumetric flask and dissolved in acetonitrile. Five ml of the filtrate was diluted to 100 ml with 1 % sodium lauryl sulphate solution and assayed for drug content using a double beam UV/Vis spectrophotometer at 245 nm. All the dispersions contained 100 ± 5 % of the drug.

In-vitro release

In-vitro dissolution studies were conducted in 900 ml of water with 1% sodium lauryl sulphate solution using USP XXII dissolution type II apparatus (Electrolab) at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ at speed of 50 rotations per minute for the different ratios of solid dispersion. At the specific

predetermined time intervals 5ml samples were withdrawn by replacing the equivalent quantity of fresh medium to maintain sink condition. The aliquots were diluted and analyzed by spectrophotometrically at 254 nm.

RESULTS AND DISCUSSION

Solubility studies

The solubility of different concentrations of drug and polymer was observed that the prepared with mannitol 1:5 presented higher dissolution concentration as compared with other formulations 1:1, 1:3. When mannitol concentration was increased, the solubility was also increased in fusion and solvent evaporation method. But maximum solubility was in fusion method, 1:5 (drug: Mannitol) ($289.09 \mu\text{g}/\text{ml}$) when compared with pure drug ($226.49 \mu\text{g}/\text{ml}$) Table 1.

Table1: Phase solubility study of Celecoxib

Methods	Drug: Mannitol (Conc. $\mu\text{g}/\text{ml}$)		
	1:1	1:3	1:5
Physical mixture method	230.04 ± 7.00	237.09 ± 5.22	230.20 ± 7.23
Solvent evaporation method	245.13 ± 2.50	260.10 ± 2.59	272.26 ± 2.42
Fusion method	268.14 ± 2.90	275.65 ± 4.92	289.09 ± 5.00

Pure drug $266.49 \pm 9.8013 \mu\text{g}/\text{ml}$

Table: 2 Effect of concentration of Drug: Carrier ratio on %drug content of Celecoxib from prepared solid dispersions

Method	1:1	1:3	1:5
Physical mixture method	100.13 ± 0.016	100.04 ± 0.030	99.99 ± 0.020
Solvent evaporation method	101.05 ± 0.020	99.93 ± 0.032	100.61 ± 0.032
Fusion method	99.98 ± 0.016	99.8 ± 0.016	100.25 ± 0.020

Drug content analysis

The drug content¹³ of different concentrations of drug and polymer was estimated spectrophotometrically at 254 nm as was tabulated table:2

Spectroscopy studies

IR spectra of pure drug and different solid dispersions were compared to confirm the presence of drug. Absorbance at 3288.4 cm^{-1} and 3340.5 cm^{-1} showed the presence of drug. These bands were shifted in the solid dispersion method (fusion method) due to possible hydrogen bonding between the carrier and drug which showed that complex has been formed and indicates that the drug was not degraded in the presence of mannitol or solid dispersions or in complex.

In-vitro drug release

The dissolution profile of celecoxib the different solid dispersions and physical mixture were studied. The dissolution rate was significantly increased when the celecoxib: Mannitol ratio was 1:5. The mean percentage of drugs for the pure drug after 60 minutes was 28.99% (SD=1.5) physical mixture (36.05 %, 45.78% and 49.68%), solvent evaporation (51.25%, 63.34% and 72.84%), and fusion method 68.43%, 72.46% and 82.46%) for the ratios of 1:1, 1:3 and 1:5 respectively. The dispersions show increased dissolution that is 2, 3 and 9 fold increase in dissolution respectively at the end of 1hour. In-vitro drug dissolution was 49.68% (SD= 4.5) for the ratio of 1:5 from physical mixture whereas solvent evaporation (1:5) and fusion method (1:5) dispersion dissolved 72.80% (SD=00) and 82.46% (SD=00) of CXB respectively. (Fig .1) and it was adopted in various kinetic models (Table.3).

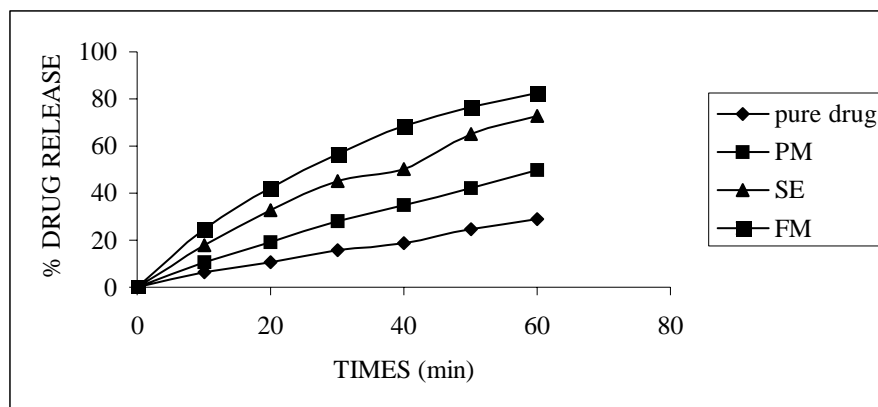


Fig. 1: In-vitro dissolution profile of celecoxib. (Ratio 1:5) of PM- Physical Mixture, SM- Solvent Evaporation, FM- Fusion Method

Table 3: *In-vitro* release kinetics of ratio (1:5) of various solid dispersion methods Pure, (PM) -Physical mixture, (SE) - Solvent evaporation and (FM)-Fusion method

Drug: carrier	Pure	PM	SE	FM	
Zero order	-	0.9963	0.9971	0.9851	0.9664
First order	-	0.8513	0.8513	0.8513	0.8513
Higuchi	0.9787	0.9933	0.9872	0.9951	-
Korsmeyer-Peppas	0.9967	0.9992	0.9925	0.9927	-
Hixon-Crowell	0.9945	0.9991	0.9858	0.9968	-

CONCLUSION

The solid dispersion of CXB was prepared to improve the solubility and dissolution rate. Analytical method of IR spectrum was conformed the drug carrier interaction or complex and showed that the drug was not degraded. A maximum increase in dissolution rates was obtained with the ratio of 1:5 but fusion method showed faster dissolution rate when compared with that of the pure drug and other complexes.

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