



Enhancement of Solubility and Dissolution of Celecoxib by Solid Dispersion Technique

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Abstract

The solid dispersion was defined as the dispersion of one or more active ingredients in an inert carrier or matrix. The purpose of the study was to improve the physicochemical properties of celecoxib like solubility, dissolution properties and stability of poorly soluble drug by forming dispersion with urea as water soluble carrier. The solid dispersion of celecoxib by Physical triturating method, Solvent evaporation and fusion method were prepared using 1:1, 1:3 and 1:5 ratios of drug and polymer (urea). The saturation solubility was carried using USP type XXIV (paddle) type dissolution apparatus. The prepared dispersion showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug. The dispersion with urea (1:5) by fusion method showed faster dissolution rate (79.08%) as compared to other dispersions with urea (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 dispersion of celecoxib: urea prepared as 1:5 ratio by fusion method showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation in this study.

Key words: solid dispersion, water soluble carrier, celecoxib and urea.

Introduction:

The bioavailability can be increased by changing in disintegration and dissolution the aqueous solubility is lesser than 1 µg/ml will definitely create a bioavailability problem and thereby affecting the efficacy of the drug. There is number of methods through which aqueous solubility of the drug can be increased in which solid dispersion is one of the effective and accepted techniques in the pharmaceutical industry. The solid dispersion was defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state by using melting solvent systems. The drug is dispersed in molecular form of carriers which are pharmacologically inert. A number of freely water soluble materials with intrinsic rapid dissolution properties have been used to formulate solid dispersion various formulate solid dispersion. Various sugars, bile acids, surface active agents and polymers have been used as carriers.

The increased dissolution of drugs in solid dispersion may be due to solubility effect of the carrier's reduction in particle size, reduction in aggregation of hydrophobic drugs due to improved humentation. Many poorly water soluble hydrophobic drugs like Digoxin, Warfarin, Griseofulvin^[1], Glibenclamide, Oflaxacin, Spironolactone^[2], and Praziquantel^[3] have been presented in solid dispersion form to improve the solubility and dissolution rate.

Celecoxib is a non-steroidal anti-inflammatory drug, which effectively inhibits the enzyme- Cyclo oxygenated-2 (Cox2) and exhibits pharmacological action of prototypical NSAIDS, includes analgesic and antipyretic activities. The dose of the drugs is between 100 and 400 mg and is depends upon the condition (Anon, 1998; Lane, 1997; Higgins; Anon, 1997) .It is recommended for the condition like osteoarthritis and rheumatoid arthritis in adults. The objective of the present study was the preparation of solid dispersion of

Celecoxib using Urea. It may improve the solubility of practically water insoluble drugs like Celecoxib it may help as to overcome limited dissolution rate and formulation difficulties.

Materials and Methods:

Celecoxib was purchased from (NDDS Zydus Cadila, Ahmedabad), Urea (Nice chemicals pvt.ltd, Cochin), Sodium lauryl sulphate (SLS) (S.d.Fine Chemical, Boisar) and all other required chemicals were analytical grade.

Preparation of solid dispersion:

Physical mixture ^[4, 5]:

The solid dispersion of celecoxib and urea prepared by modifying procedure of Sivashankar;et.al (2002) and Gowthamarajan K;et.al(2002) by mixing Celecoxib and the Urea of different ratio 1:1, :3 and 1:5 respectively by triturating using mortar and pestle for 15 minutes.

Solvent Evaporation ^[4, 6, 7]:

This was prepared by the method published by (Himasankar, K; et.al, Madhusudhan.B; et.al, Saha; et.al, Int.J.Pharm Sci; 2002) and further modified as the Celecoxib and Urea in different proportions were dissolved in sufficient volume of methanol with continuous stirring. The solvent was completely evaporated at 40-45⁰ C with continuous stirring to obtain the dry granules.

Fusion method ^[6]:

The accurately weighed amount of carrier urea was melted in a porcelain dish at 80-85⁰ C in melted polymer .Calculated amount of Celecoxib was added with thorough mixing for 1-2 minutes followed by quick cooling .The ratio of drug and carrier in the ratio of 1:1.,1:3 and 1:5 were prepared by the modified technique.

Evaluation of solid dispersions:

Solubility studies ^[1, 2, 8, and 6]:

The solubility studies on pure drug, physical mixture and solid dispersion prepared by solvent evaporation and fusion method were conducted in a thermostat shaker water bath

by shaking for 96 hrs at 37⁰ C \pm 0.5⁰ C .Finally the solution were filtered by using whatman filter paper (grade41, HiMedia) and after a suitable dilutions of the titrate, the drug concentration was determined spectrophotometrically at 254nm. All solubility measurements were performed in triplicate.

FT-IR Spectroscopy:

The prepared physical mixture and solid dispersions of the ratios 1:1,1:3 and 1:5 drug and polymer respectively ,were evaluated for its drug polymer interaction by FT-IR spectrum after the translucent pellets were made using KBr (Shimadzu FT-IR 8201 PC) .

Drug content analysis ^[9]:

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% sodiumlaurylsulphate solution and assayed for drug content using a double beam UV/Vis spectrophotometer at 254 nm. All the dispersions should contained 100 \pm 5% of the drug.

In-vitro dissolution studies ^[3, 4, 5, 6, 8, and 10]:

The dissolution studies were performed for all solid dispersions and pure Celecoxib using the dissolution type-II USPXXIV basket method filling in the empty gelatin capsule shell. The 900ml of 1% sodium lauryl sulphate solution used as medium and kept at 37⁰ C \pm 0.5⁰ C. Then rotated the basket with the speed of 50 rotations per minute. At the predetermined time intervals 5ml of test sample were withdrawn, after required dilutions the samples were analyzed by spectrophotometer (Shimadzu) at 254nm.Equal volume of sample a liqueate fresh medium was replaced to maintain sink condition.

Results and Discussion:

Solid dispersion of Celecoxib containing varying concentration of Urea was improved

in an attempt to improve the solubility and dissolution rate of Celecoxib. The Celecoxib, physical mixture and solid dispersion were investigated by analytical method and IR spectra.

Solubility Studies:

The solubility of the Celecoxib was studied using 1% SLS solution. As the solid dispersion is a metastable form and tends to transform into the stable form, the drug concentration may tend to decrease with elapse of time during the solubility test. In order to avoid this problem all the solubility test samples of the different formulations were withdrawn and analyzed at established time (96hrs). This allowed readily to compare the solubility of different solid dispersions.

The solubility of different concentrations of drug and polymer was observed that the prepared with urea 1:5 presented higher dissolution concentration as compared with the other formulations obtained with different ratios (1:1 and 1:3). When concentration of Urea increased, the solubility was observed 267.24 µg/ml in fusion method and solvent evaporation method. But maximum solubility was observed in fusion method 1:5 (Drug: Urea) ratio 267.54 µg/ml (Fig: 1), when compared with that of pure Celecoxib (226.49 µg/ml). Table: 1.

Table: 1 Effect of concentration of Drug: Carrier ratio on Solubility of Celecoxib from prepared Solid dispersions

Method	1:1	1:3	1:5
Physical mixture method	230.26 ± 1.22	233.20 ± 1.9	233.20 ± 1.9
Solvent evaporation method	241.02 ± 1.2	253.20 ± 1.32	259.40 ± 2.11
Fusion method	250.62 ± 7.25	256.27 ± 12.32	267.24 ± 4.92

Drug Content:

The drug content of different concentrations of drug and polymer was estimated spectrophotometrically at 254nm and was tabulated (Table. 2).

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

Method	1:1	1:3	1:5
Physical mixture method	99.93 ± 0.01	99.04 ± 0.03	99.25 ± 0.02
Solvent evaporation method	99.25 ± 0.02	98.93 ± 0.03	98.61 ± 0.03
Fusion method	98.72 ± 0.01	99.15 ± 0.01	99.25 ± 0.02

In-Vitro drug release:

The dissolution profiles of Celecoxib the different solid dispersion and physical mixture were studied. The dissolution rate was significantly increased when the Celecoxib: Urea ratio was at 1:5. The mean percentage of drugs for physical mixture after 60minute was 28.99%, 34.95%, 40.90% and 45.46% for pure drug, 1:1, 1:3 and 1:5 respectively (Fig:1). But in the solvent evaporation method half fold increase in release rate it was observed 37.86, 53.35 and 68.06 respectively (Fig: 2) (This may be due to impact of complexation and bond formation. This may lead improved solubility by reducing particle size). In the fusion method there was two fold increase in release rate as compared to physical mixture and there was slight increase compared to solvent evaporation. It was 54.10, 72.05, 79.08 respectively (Fig: 3). The release kinetics of Celecoxib prepared from different methods of solid dispersions was observed and tabulated (Table.3).

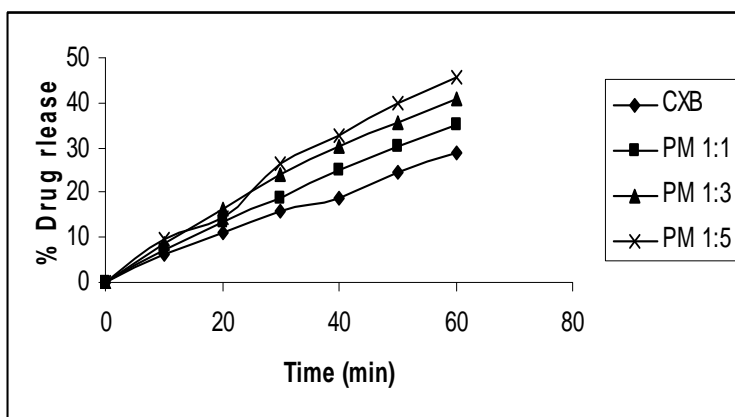


Fig: 1 Physical mixture drug release rate compared with pure drug.

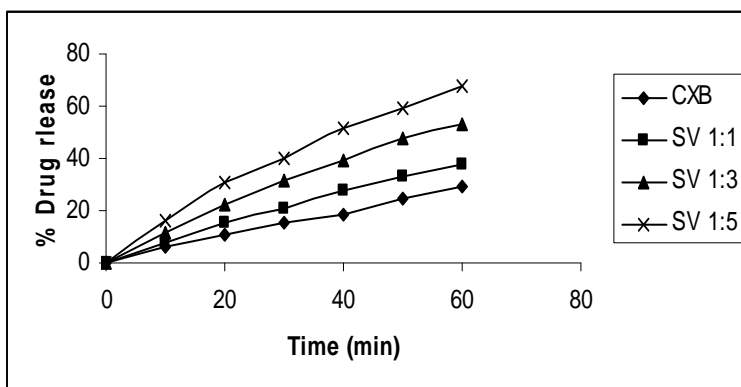


Fig: 2 Solvent evaporation drug release rate compared with pure drug

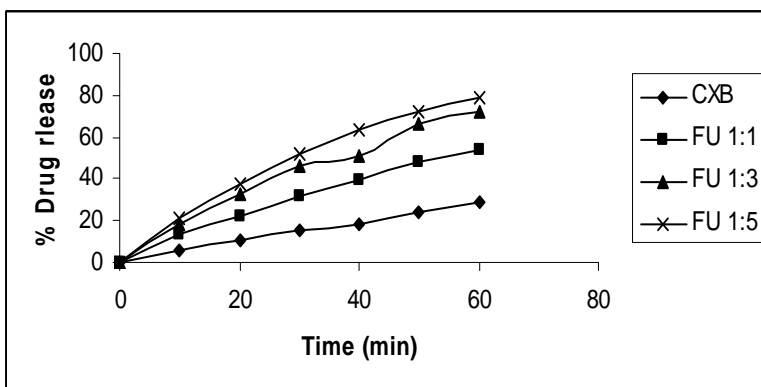


Fig: 3 Fusion method drug release rate compared with pure drug

Table: 3 Kinetics of Celecoxib from prepared Solid dispersions by Fusion Method.

Drug :Carrier	1:1	1:3	1:5
Zero order	0.9967	0.99674	0.9731
First order	0.8513	0.8513	0.8513
Higuchi	0.9928	0.9604	0.9977
Korsmeyer-Peppas	0.999	0.9758	0.9923
Hixson-Crowell	0.9984	0.9578	0.9982

Spectroscopy studies:

The obtained spectrum shows absorbance at 3259.5 cm⁻¹ and 3340.5cm⁻¹ showed the presence of primary amines in the pure Celecoxib (fig .4) and there bands were shifted in the spectra (fusion method1:5) because of the possible hydrogen bonding between the polymer and the drug ,which showed that complex has been formed .The absorbance of the remaining related peaks of the drugs in the spectra 2,3 and 4 showed the presence of drug in the prepared solid dispersion .The FT-IR spectral results showed that drug was not degraded in the presence of Urea or solid dispersion or in complex.

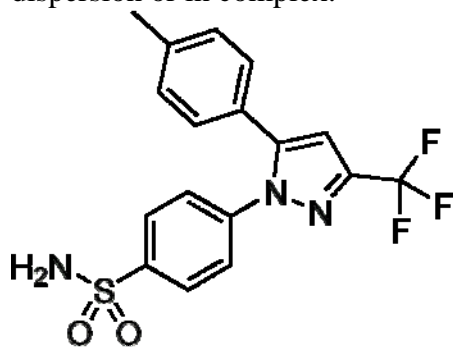


Fig. 4: Celecoxib

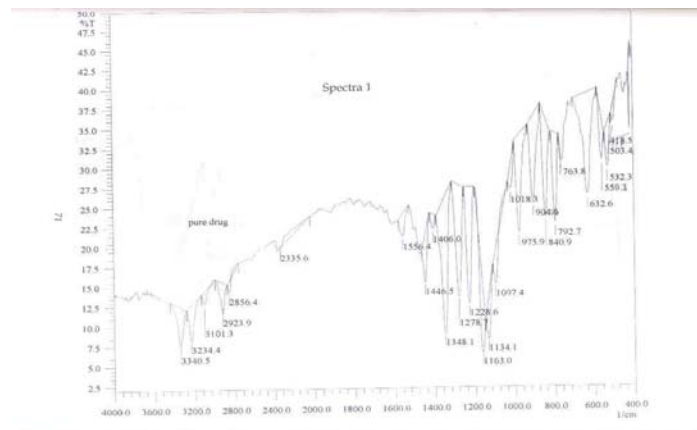


Fig. 5: 1:5 Physical Mixture

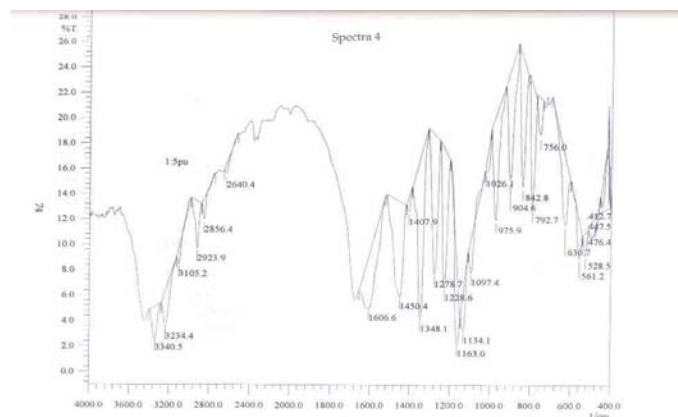


Fig. 6: 1:5 Solvent evaporation

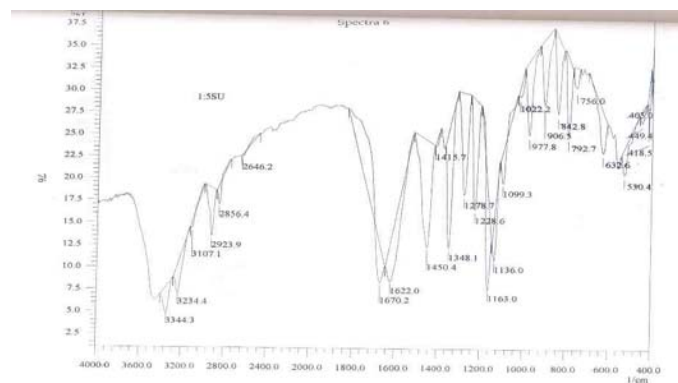
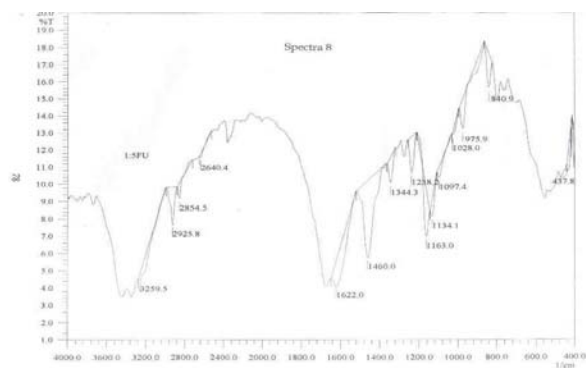


Fig. 7: 1:5 Fusion method



Conclusion:

The prepared solid dispersions were extended to various characterizations. IR shows there was no degradation of drugs. The solubility and dissolution studies showed there is a possibility of improved solubility of Celecoxib through solid dispersion with Urea. A maximum increase in dissolution rate was obtained with Celecoxib: Urea solid dispersion with a weight ratio of 1:5. Though Urea dispersion by fusion showed faster dissolution rate when compared with that of pure drug.

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