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TERNARY SOLID DISPERSIONS OF CELECOXIB: FROM PHYSICAL CHARACTERIZATION TO DISSOLUTION ENHANCEMENT

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ABSTRACT
The poor solubility and wettability of a non steroidal anti inflammatory drug, celecoxib leads to poor dissolution and hence, low bioavailability after oral administration. The objective of the present study was to formulate solid dispersions of celecoxib , with water soluble polymers poly vinyl pyrrolidine (PVP K30), poly ethylene glycol (PEG 6000), hydroxypropyl methylcellulose 5cps (HPMC) and a super disintegrant namely pregelatinised starch (PGS) by common solvent and solvent evaporation methods. Solid Dispersions prepared were evaluated for dissolution rate and dissolution efficiency in comparison to the corresponding pure drug. Solid dispersions of celecoxib showed a marked enhancement in dissolution rate and dissolution efficiency. The increasing order of dissolution rate of solid dispersions of celecoxib with various polymers was HPMC > PVP > PEG. Solid dispersions at 2:2:6 ratio of C: HPMC: PGS, a 53.57 fold increase in the dissolution rate of celecoxib was observed. Solid dispersions were characterized by infrared spectroscopy (IR), differential scanning calorimetry (DSC) and X-ray diffractogram (XRD). Solid dispersions in combined carriers gave much higher rates of dissolution than super disintegrant PGS alone. Super disintegrant PGS alone or in combination with hydrophilic polymers could be used to enhance the dissolution rate of poorly soluble drug celecoxib. Finally, *in-vitro* dissolution studies showed that celecoxib release was greatly improved by formation of solid dispersion.

Keywords: *Celecoxib; Solid Dispersions; Dissolution rate; Solubility, Superdisintegrant.*

INTRODUCTION

Celecoxib (C), 4-[5-(4-methylphenyl)-3-(trifluoro-methyl)-1H-pyrazol-1-yl]benzene sulfonamide, is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and anti-pyretic activities, is used in the treatment of rheumatoid arthritis and osteoarthritis[1,2]. Celecoxib is also used in the management of acute pain and dysmenorrhoea, as an adjunct to standard therapy to reduce the number of adenomatous colorectal polyps in patients with familial adenomatous polyposis. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2) and at therapeutic concentrations in humans, celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. Most of the NSAIDs belong to class II category under Biopharmaceutical classification system (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. Rate of absorption and/or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids. To improve the dissolution and bioavailability of poorly water – soluble drugs, various techniques such as solvent evaporation[3], cyclodextrin complexation[4], micronization[5], co-grinding[6], solubilization, salt formation, complexation with polymers[7], change in physical form, use of prodrug and drug derivatization, addition of surfactants have been employed. The present study aims at enhancing the dissolution rate of celecoxib. In the present investigation solid dispersions were prepared by employing common solvent and solvent evaporation methods. Studies were carried out on celecoxib with an objective of enhancing their dissolution rates and bioavailability. Water dispersible super disintegrant PGS, a new class of tablet excipient was evaluated as carrier, alone and in combination with PVP, HPMC, PEG for enhancing the dissolution rate and bioavailability of celecoxib.

MATERIALS AND METHODS

Materials

Celecoxib was a gift sample from M/s.Sigma Laboratories, Mumbai, methanol (Qualigens) and

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polyvinyl pyrrolidone (PVP K30) was a gift sample from M/s. Sun Pharma Ind. Ltd., Mumbai. All other materials used were of pharmacopoeial grade and were procured from commercial sources.

Methods

Preparation of solid dispersions

Preparation Employing Superdisintegrant PGS

Solid dispersions of celecoxib in superdisintegrant PGS were prepared by solvent evaporation method. The required quantities of celecoxib were dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant PGS (passed through 120 No. mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50°C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh no.100. Solid dispersions in the superdisintegrant PGS were prepared at a ratio of C, PGS namely 1:4 respectively.

Preparation Employing Combined Carriers

The required quantities of celecoxib and water soluble carriers (PEG, PVP, HPMC) were dissolved in the solvent to get a clear solution in a dry mortar. The super disintegrant PGS was then added to the drug solution and dispersed. The solvent was then evaporated by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50° C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh No.100. Various solid dispersions prepared with their composition are listed in Table 1.

Table 1: *Composition of Various Solid Dispersions*

Sl. No.	Composition			
	Drug	Carriers	SD Code	Percent Celecoxib Content *(x ± s.d.,)*
1.	Celecoxib (2)	PEG(2), PGS (6)	C-PEG-PGS, 226	19.77 ± 0.78 (0.79)
2.	Celecoxib (2)	PVP (2), PGS (6)	C-PVP-PGS, 226	19.97 ± 0.89 (0.55)
3.	Celecoxib (2)	HPMC (2), PGS (6)	C-HPMC-PGS, 226	19.87 ± 0.99 (0.48)
4.	Celecoxib (1)	PGS(4)	C-PGS, 14	19.88 ± 0.62 (0.91)

Estimation of celecoxib

A spectrophotmetric method based on the measurement of absorbance at 254 nm in water containing 1% SLS was used in the present study for the estimation of celecoxib. The method was validated for reproducibility, accuracy, precision and linearity by analyzing six individually weighed samples of celecoxib. The stock solution of celecoxib was subsequently diluted to a series of dilution containing 5, 10, 15 and 20 *µg/ml* of solution, using water containing 1% SLS. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL-159). The method obeyed Beer's law in the concentration of 0-20 *µg/ml.*

Estimation in solid dispersions

From each batch, 4 samples of 50 mg each were taken and analyzed for the drug celecoxib. 50 mg of dispersions were weighed into a 100 ml volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100 ml volumetric flask. The solution was made up to volume with the solvent. The solution was suitably diluted with 1% SLS and assayed at 254 nm for celecoxib. The results are given in Table 1.

Dissolution Rate S tudies on Solid Dispersions

Dissolution rate of celecoxib were studied using an USP XXIII six station dissolution rate test apparatus (Electro Lab). Paddle stirrer at a speed of 50 rpm and temperature of 37° ± 1°C were used in each test. Drug or solid dispersion of drug equivalent to 100 mg of celecoxib was used in each dissolution rate test. Samples of dissolution medium i.e., water containing 1% SLS (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for celecoxib. The dissolution experiments were conducted in triplicate. The results are shown in Figure 1. Dissolution rates of celecoxib and its solid dispersions followed first order kinetics Table 2. Dissolution parameters such as $T_{50,}$ $DE_{30,}$ $K_{1,}$ Percent of celecoxib dissolved in 10 minutes are given in Table 3.

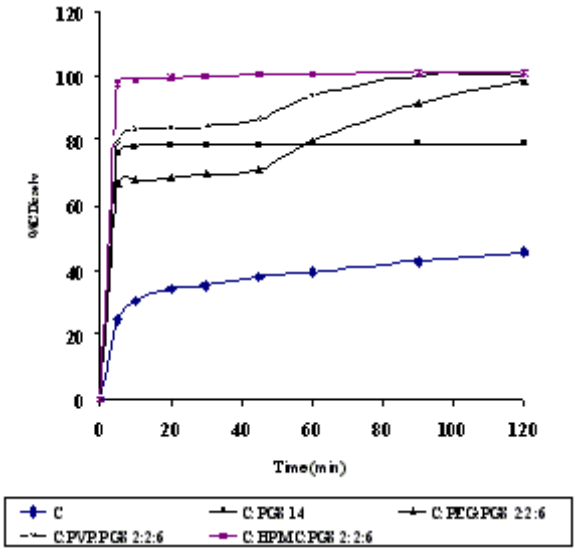

Fig.1: *Dissolution Profiles of Celecoxib and its solid dispersions*

Table 2: *The Correlation Coefficient (r) values of Dissolution Data*

Sl. No.	Solid Dispersion	Correlation coefficient (r) value		
		Zero order	First order	Hixson-Crowell
1.	Celecoxib	0.9435	0.9536	0.990
2.	C-PEG-PGS, 226	0.833	0.908	0.828
3.	C-PVP-PGS, 226	0.899	0.998	0.995
4.	C-HPMC-PGS, 226	0.999	0.999	0.999
5.	C-PGS, 14	0.707	0.859	0.955

Table 3: *Dissolution Parameters of Celecoxib and its Solid Dispersions in Superdisintegrant*

Sl. No.	Solid Dispersion	Dissolution Parameter			
		T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	No. of folds increase in K_1
1.	Celecoxib	>120	28.8	0.0035	-
2.	C-PEG-PGS, 226..	4	80.2	0.115	31.98
3.	C-PVP-PGS, 226..	2.5	90.9	0.179	49.89
4.	C-HPMC-PGS, 226	2	91.85	0.193	53.57
5.	C-PGS, 14	4.5	76.56	0.063	17.54

Characterization of Solid Dispersion

Fourier T ransform Infrared (FTIR) Spectroscopic Analysis

FTIR was used to assess the interaction between carrier and drug molecule in the solid state. The IR spectra were recorded using an FTIR spectro-photometer (Thermo Nicolet Nexus 670 Spectrometer). The moisture free samples were scanned over the frequency range of 4000 - 400 cm^{-1}. FTIR spectra of celecoxib and solid dispersions of celecoxib with HPMC and PGS are shown in Figure 2. The spectra of pure drug showed peaks at 3234.02 cm^{-1}, 3339.2 cm^{-1} (N-H stretch) 1374.54 cm^{-1} (C-N stretching of 3° amine), 1348.25 cm^{-1} (S=O stretch), 1016.04 cm^{-1} (C-F stretch). The FTIR spectra of solid dispersions of celecoxib prepared using HPMC, PGS showed peaks at 3349.4 cm^{-1}, 3344.17 cm^{-1} (N-H stretch) 1374.19 cm^{-1} (C-N stretching of 3° amine), 1348.25 cm^{-1} (S=O stretch), 1016.04 cm^{-1} (C-F stretch), almost all the bands of celecoxib, without affecting its peak position and trends, which indicated the absence of well defined interactions between celecoxib, MCC and HPMC.

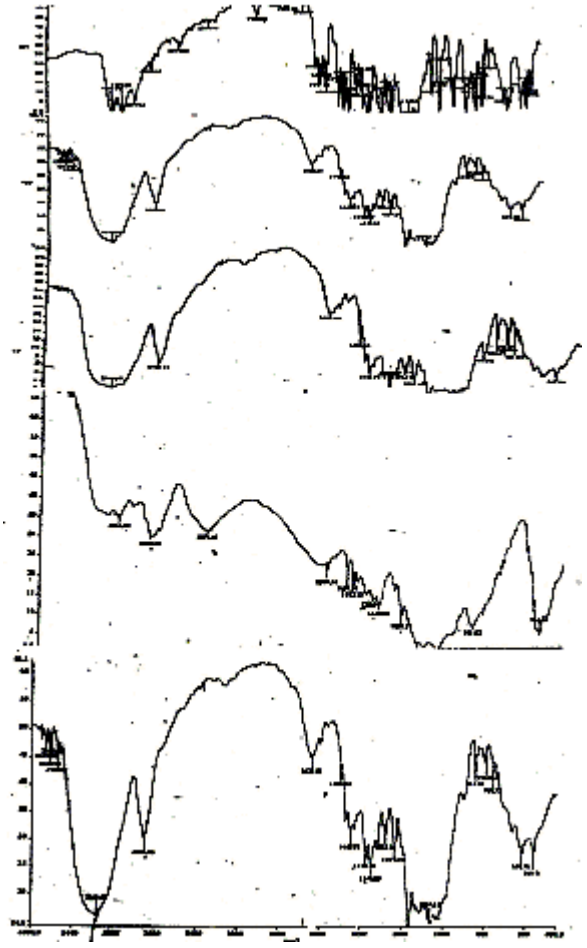

Fig. 2 : *FTIR spectra of (i) Celecoxib (ii) Celecoxib-HPMC (iii) Celecoxib-HPMC-PGS (iv) Celecoxib-HPMC-DCP (V) Celecoxib-HPMC-MCC (From top to bottom)*

Powder X-ray Dif fraction (XRD) Analysis

The Physical state of celecoxib in various solid dispersion preparations was evaluated by X-ray diffraction study. The XRD patterns of the solid dispersions prepared by celecoxib, HPMC and PGS are shown in Figure 3. The diffraction spectrum of celecoxib showed that the drug was crystalline in nature as demonstrated by numerous peaks. The prominent peaks for celecoxib pure were clearly seen at the same positions in solid dispersions but with decreased intensities. It has been observed that the diffraction patterns of the solid dispersions are somewhat diffused compared to diffraction patterns of celecoxib. It also indicates that the crystallinity of the solid dispersions is less than that of the celecoxib.

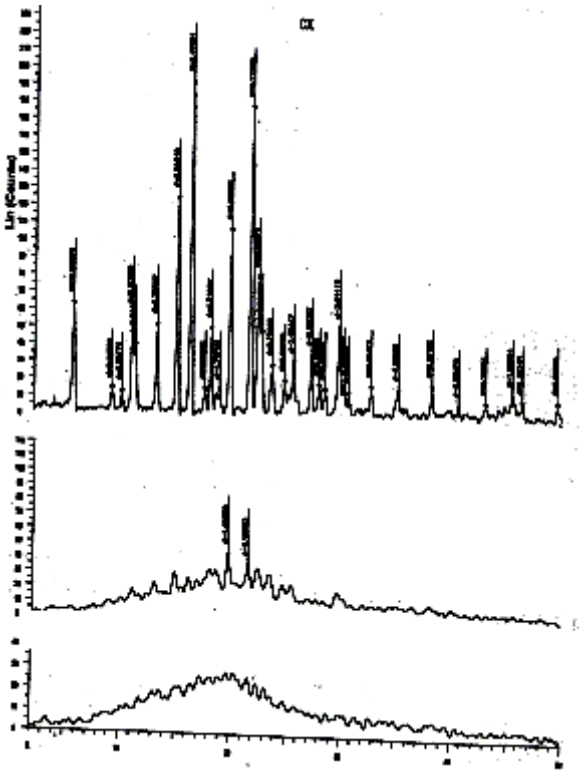

Fig. 3 : *X-Ray Diffractograms of (i) Celecoxib (ii) Celecoxib-HPMC (iii) Celecoxib-HPMC-PGS (From top to bottom)*

Differential Scanning Calorimetric (DSC) Analysis

The DSC thermograms were recorded using a differential scanning calorimeter (DSC 823E, Mettler Toledo Star System). Approximately 2-5 mg of each sample was heated in a pierced aluminum pan from 50°C to 400°C at a heating rate of 10°C/min under a stream of nitrogen. The DSC thermograms of pure celecoxib, solid dispersions prepared using HPMC and MCC are shown in Figure 4. The DSC thermogram of celecoxib exhibits exothermic peak from 155.47°C to 167.84°C corresponding to its melting point. Solid dispersion of celecoxib, PGS showed exothermic peak from 154.75°C to 168.24°C, which shows a weak interaction in the solid dispersion.

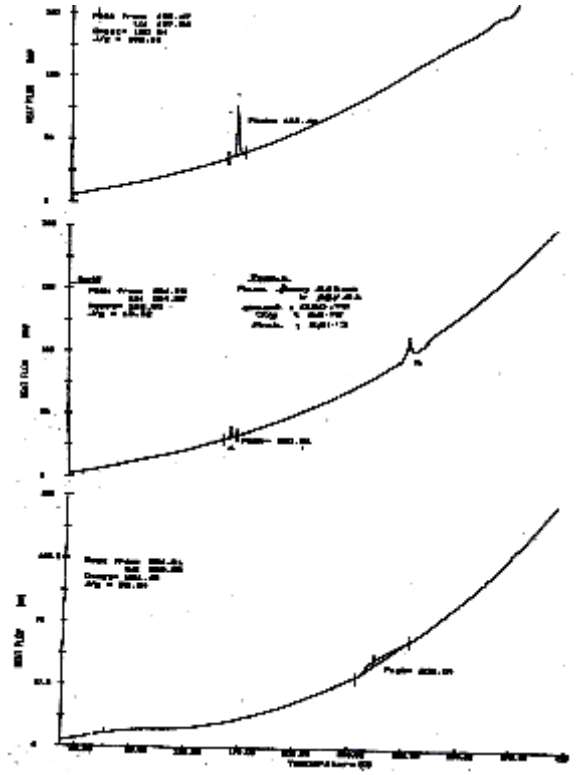

Fig. 4: *Differential Scanning Calometry of (i) Celecoxib (ii) Celecoxib-HPMC (iii) Celecoxib-HPMC-PGS (From top to bottom)*

Analysis of Dissolution Data of Solid Dispersions

The dissolution data of celecoxib and their solid dispersions were also analyzed as per Hixson-Crowell's[8] cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is given by the following equation. $(W_o)^{1/3} - (W_t)^{1/3} = Kt$, where W_o is initial mass and W_t is the mass remained at time 't'. The cube root equation is applicable to the dissolution of monodisperse powder consisting of uniform sized particles. A plot of $(W_o)^{1/3} - (W_t)^{1/3}$ versus time will be linear when dissolution occurs from monodisperse particles of uniform size. Hixson-Crowell plots of the dissolution data were found to be linear (Fig.5) with all solid dispersions. This observation indicated the drug dissolution from all the solid dispersions is occurring from discretely suspended or deposited (monodisperse) particles. This might have also contributed to the enhanced dissolution rate of the solid dispersions. The correlation coefficient (r) values of the first order release model are found to be (0.850 to 0.999) slightly higher when compared to the Hixson-Crowell's cube root model. Hence the release of drug from the preparations followed predominantly first order kinetics compared to Hixson-Crowell cube root law. Correlation coefficient values in the analysis of dissolution data as per zero order, first order and Hixson-Crowell cube root are given in Table 3. Another parameter suitable for evaluation of *in vitro* dissolution has been suggested by Khan [9] Dissolution efficiency (DE). DE is defined as the area under the dissolution curve up to a certain time 't' expressed as percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency (DE)} = \frac{\int_o^t y.dt}{y_{100}t} 100$$

The index DE_{30} would relate to the dissolution of drug from a particular formulation after 30 minutes and could be compared with DE_{30} of other formulations. Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations.

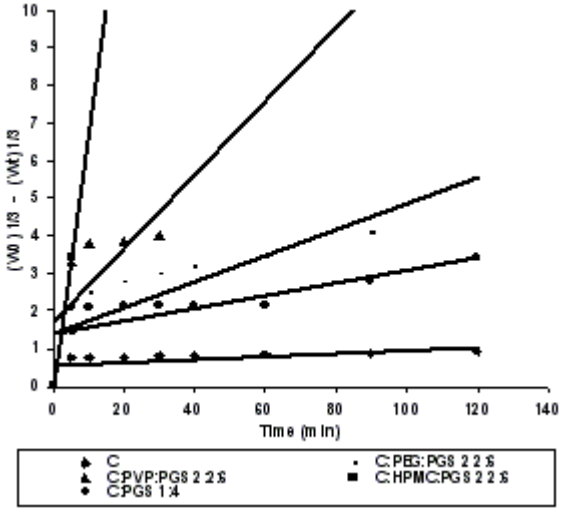

Fig. 5: *Hixson-Crowell Dissolution Plots of Celecoxib and its Solid Dispersions*

RESULTS AND DISCUSSION

All the dissolution parameters given in Table 3 indicated rapid and higher dissolution of celecoxib from all solid dispersions when compared to celecoxib pure drug. Celecoxib-HPMC-PGS (2:2:6) solid dispersion gave rapid and higher dissolution than the pure drug. Combined carriers gave much higher enhancement in the dissolution rate of celecoxib than water dispersible carriers alone. Solid dispersions of superdisintegrants and combined carriers gave rapid and higher dissolution of celecoxib when compared to pure drug. In each case, the K_1 and DE_{30} values were increased. All the solid dispersions in combined carriers gave much higher rates of dissolution, several times higher than the dissolution rate of pure drug. C-HPMC-PGS solid dispersion gave a 53.57 fold increase in the dissolution rate of celecoxib whereas solid dispersion of celecoxib in PGS alone (C-PGS 14 solid dispersion) gave only 17.54 fold increase. Thus combination of superdisintegrants with water soluble carrier HPMC resulted in a greater enhancement in the dissolution rate of celecoxib.

The dissolution data were fitted into zero order, first order and Hixson-crowell models to assess the kinetics of mechanism of dissolution. The kinetic model that best fits the dissolution data was evaluated by comparing the correlation coefficient (r) values obtained in various models. The model that gave higher 'r' value is considered as the best fit model. The correlation coefficient (r) values obtained in the analysis of dissolution data as per different models are given in Table 2. The 'r' values were higher in the first order model than those in the zero order models with all the solid dispersions of celecoxib, indicating that the dissolution of celecoxib from all the solid dispersions followed first order kinetics with correlation coefficient value above 0.9. First order plot is Figure 6.

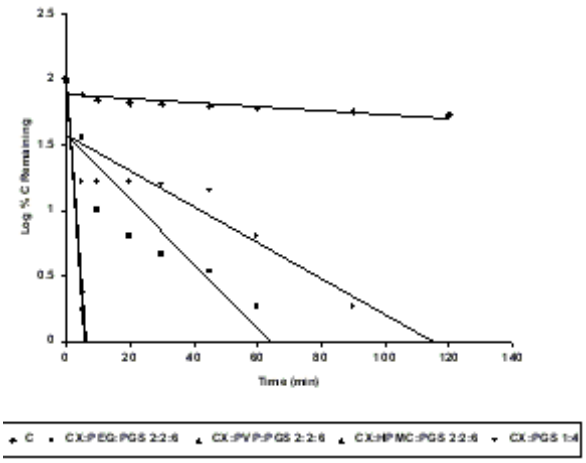

Fig. 6 : *First Order Dissolution Plots of Celecoxib and its Solid Dispersions*

The increasing order of dissolution rate of celecoxib from solid dispersions observed with various hydrophilic polymers was HPMC > PVP > PEG. The increasing order of dissolution rates of celecoxib is comparable with solid dispersions of atorvastatin-beta cyclodextrin[10] complexation, curcumin-cellulose acetate solid dispersion[11], etodolac solid dispersion with cyclodextrin [12]. The solid dispersions of celecoxib provide rapid dissolution rate by one or more of the following mechanisms such as particle size reduction, improvement of wettability of particles, conversion of crystalline drug into amorphous form and solubilizing effect of the carriers by promoting through increase in effective surface area.

CONCLUSION

Thus superdisintegrant PGS was found to be useful as a carrier in celecoxib solid dispersions alone and in combination with HPMC to enhance the solubility, dissolution rate and dissolution efficiency.

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