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FORMULATION STUDIES ON SOLID DISPERSIONS OF CELECOXIB IN SUPERDISINTEGRANTS ALONE AND WITH PVP

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ABSTRACT

The feasibility of formulating the solid dispersions of celecoxib into tablet dosage forms is evaluated. All the tablets formulated employing solid dispersions of celecoxib in superdisintegrants gave rapid and higher dissolution of celecoxib when compared to that of celecoxib plain tablets. The increasing order of dissolution rate of formulated tablets with various carriers was Croscarmellose (CC)>Pregelatinised starch (PGS)> Primojel(PJ)> Crospovidone (CP). The same order of performance was observed in both the series of tablets formulated employing superdisintegrants alone and in combination with PVP. A 10.80 fold increase in the dissolution rate of celecoxib was observed with tablets formulated employing its solid dispersions in CC (CF4) when compared to plain tablets (CF1). A 15.24 fold increase in the dissolution rate of celecoxib was observed with tablets formulated employing its solid dispersions in combined carriers CC and PVP (CF8) when compared to its plain tablets (CF1).

Keywords: Celecoxib; Solid Dispersion; Dissolution rate; Solubility; polyvinylpyrrolidine; superdisintegrants.

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to Pharmaceutical Industry. A number of modern drugs are poorly soluble in water and aqueous fluids. Their absorption and bioavailability require an improvement in the dissolution rate and efficiency. Among the various methods for improving the dissolution rate and bioavailability, solid dispersion technologies were found to be very successful with a number of drugs. Solid dispersions of a number of poorly soluble drugs such as phenylbutazone[1], indomethacin[2], tolbutamide[3], griseofulvin[4], ketoprofen[5], sulfathiazole[6] etc., exhibited faster dissolution rates and improved bioavailability. Water soluble substances such as urea[7-9], polyetheleneglycols[3,10-12], polyvinylpyrrolidon[13-15], sugars such as dextrose[16-19] sucrose[20,21], succinic acid[22], bile acids[19,23], Surfactants[24-27], cellulose polymers such as hydroxypropyl methylcellulose[28], hydroxypropyl cellulose[28] and modified starches such as dextrin[29,30], β-cyclodextrin[29,30] and hydroxyethyl starch[29,30] etc. are used as carriers for preparing solid dispersions.

Most of the Non-steroidal anti inflammatory drugs 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. They need enhancement in solubility and dissolution rate for improving their oral bioavailability.

In the present investigation studies were carried out on solid dispersions of celecoxib using water dispersible superdisintegrants, a new class of tablet excipient, alone and in combination with PVP, for enhancing the dissolution rate. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and anti-pyretic activities in humans. It is used in the treatment of rheumatoid arthritis and osteoarthritis[31]. Celecoxib is also used in the management of acute pain and dysmenorrhoea. The usual dose by mouth is 100 mg two or three times daily. Celecoxib is absorbed from the gastro intestinal tract. Peak plasma concentration occurs at about 2 to 4 hours after ingestion. Rate

of absorption and/or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids[32]. Solid dispersions[33] were prepared by employing common solvent and solvent evaporation method. Water dispersible superdisintegrants, a new class of tablet excipient were evaluated as carriers, alone and in combination with PVP, for enhancing the dissolution rate and bioavailability of celecoxib.

EXPERIMENTAL

Celecoxib was a gift sample from M/s. Sigma Laboratories, Mumbai, methanol (Qualigens) and , polyvinylpyrrolidone (PVP K30) was a gift sample from M/s. Sun Pharma Ind. Ltd., Mumbai. Primojel, crospovidone, croscarmellose, lactose, potato starch, talc, magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

PREPARATION OF SOLID DISPERSIONS

Preparation of Solid Dispersions Employing Superdisintegrants

Solid dispersions of celecoxib (C) in superdisintegrants (crosscarmellose, pregelatinised starch, primojel, crospovidone) were prepared by solvent evaporation method. The required quantity of celecoxib was dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant (passed through 120 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 50^0 C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh no.100. In each case solid dispersions in the superdisintegrants were prepared at a drug:excipient ratio of 1:4.

Preparation of Solid Dispersions Employing Combined Carriers

The required quantities of celecoxib and water soluble carrier (PVP) were dissolved in the solvent to get a clear solution in a dry mortar. The super disintegrant 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 50^0 C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh N0.100. Composition of various solid dispersions prepared is given in Table 1.

Table-1:Various solid dispersions composition

Sl. No.	Composition		
	Drug	Carriers	SD Code
1.	Celecoxib (1)	PJ (4)	C-PJ, 14
2.	Celecoxib (1)	CP(4)	C-CP, 14
3.	Celecoxib (1)	CC(4)	C-CC, 14
4.	Celecoxib (1)	PGS(4)	C-PGS, 14
5.	Celecoxib (1)	PJ(3.2) PVP (0.8)	C-PJ-PVP
6.	Celecoxib (1)	CP(3.2) PVP (0.8)	C-CP-PVP
7.	Celecoxib (1)	CC(3.2) PVP (0.8)	C-CC-PVP
8.	Celecoxib (1)	PGS(3.2) PVP (0.8)	C-PGS-PVP

Figure in parentheses( ) indicate ratio

Estimation of celecoxib

Spectrophotometric method based on the measurement of absorbance at 254 nm in water containing 1% sodium lauryl sulphate was used in the present study for the estimation of celecoxib[34]. 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 2, 4, 6, 8 and 10 *µg/ml* of solution, using distilled water containing 1% sodium lauryl sulphate. The absorbance of these solutions was measured in UV-VIS spectrophtometer (ELICO SL-159). The method obeyed Beer's law in the concentration range of 0-10 *µg/ml.*

Estimation of celecoxib in solid dispersions

From each batch, 4 samples of 50 mg were taken and analyzed for celecoxib. 50 mg of dispersion was weighed and transferred 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 distilled water containing 1% sodium lauryl sulphate and assayed at 254 nm for celecoxib. The results are given in Table 2.

Table-2: Celecoxib Content of Various Solid Dispersions

S. No.	SD Code	Percent Celecoxib Content ($\bar{x}$ ± s.d.,)
1.	C-PJ, 14	19.6 ± 0.27 (0.76)
2.	C-CP, 14	19.7 ± 0.32(1.73)
3.	C-CC, 14	19.5± 0.10 (0.86)
4.	C-PGS, 14	19.6 ± 0.71 (0.55)
5.	C-PJ-PVP	19.5± 0.62 (1.04)
6.	C-CP-PVP	19.4± 0.29 (0.58)
7.	C-CC-PVP	19.5± 0.22 (0.69)
8.	C-PGS-PVP	19.8± 0.37 (0.88)

Formulation of Tablets by Direct Compression Method

Solid dispersions of celecoxib (C) in superdisintegrants and combined carriers exhibited several times higher dissolution rates and dissolution efficiency values than the corresponding pure drugs. The feasibility of formulating these solid dispersions into tablet dosage forms is evaluated. As the superdisintegrants employed as carriers in solid dispersions lose their swelling characteristics when dried during wet granulation method, these dispersions were formulated into compressed tablets by direct compression method. All these solid dispersions in superdisintegrants and combined carriers were found to be sufficiently free flowing for direct compression. Tablets each containing 100 mg of celecoxib were prepared as per the formulae given in Table 3.

Table-3: Formulae of Celecoxib Tablets Prepared Employing its Solid Dispersions in Super Disintegrants

Ingredient (mg/Tablet)	Formulation								
	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6	CF_7	CF_8	CF_9
Celecoxib	100	-	-	-	-	-	-	-	-
C-PJ 14	-	500	-	-	-	-	-	-	-
C-CP 14	-	-	500	-	-	-	-	-	-
C-CC 14	-	-	-	500	-	-	-	-	-
C-PGS 14	-	-	-	-	500	-	-	-	-
C-PJ -PVP	-	-	-	-	-	500	-	-	-
C-CP- PVP	-	-	-	-	-	-	500	-	-
C-CC- PVP	-	-	-	-	-	-	-	500	-
C-PGS-PVP	-	-	-	-	-	-	-	-	500
Lactose	400	-	-	-	-	-	-	-	-
Potato Starch	25	25	25	25	25	25	25	25	25
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total Weight (mg)	535	535	535	535	535	535	535	535	535

All ingredients were blended in a closed dry plastic container. The blend of powders was compressed into tablets to a hardness of 6-8 kg/sq.cm. On a 'Cadmach' single punch tablet machine. In each case 50 tablets were prepared.

Evaluation of Tablets

The tablets were evaluated for hardness, friability, disintegration, content of active ingredient and dissolution rate. Disintegration times were determined in 'Thermonic' tablet disintegration test machine (USP) using distilled water. Hardness of the tablets was tested using a 'Monsanto' hardness tester. Friability of the tablets was determined in a 'Roche' friabilator. The results are given in Table 4.

Table-4: Evaluation of Tablets of Celecoxib Tablets

Sl. No.	Tablet Formulation	Drug Content (mg/tablet)	Hardness (Kg/sq.cm)	Friability (%)	Disintegration Time (min)
1.	CF_1	98.9	7.5	0.42	4.0
2.	CF_2	99.4	8.5	0.11	2.0
3.	CF_3	99.5	7.5	0.52	2.5
4.	CF_4	99.3	7.5	0.35	1.5
5.	CF_5	99.6	8.0	0.45	1.5
6.	CF_6	99.7	7.5	0.32	1.5
7.	CF_7	98.9	8.5	0.30	2.0
8.	CF_8	99.1	7.5	0.35	1.5
9.	CF_9	99.2	7.5	0.38	1.5

Content of Active Ingredient

Ten tablets were weighed, powdered and mixed thoroughly. Four samples of tablet powder, each equivalent to 20 mg drug were weighed accurately and taken in a boiling test tube. In each case, celecoxib present in the tablet powder was extracted with 4 x 10 ml quantities of methanol and the extracts were collected into a 100 ml volumetric flask. The volume was made up to the mark with methanol. The solution was subsequently diluted with distilled water containing 1% sodium lauryl sulphate and assayed for celecoxib at 254 nm. The results are given in Table 4.

Dissolution Rate Study on Celecoxib Tablets

Dissolution rate of celecoxib tablets was studied using an USP XXIII 6 station dissolution rate test apparatus (Electro Lab) with a paddle stirrer. The dissolution rate was studied in 900 ml of distilled water containing 1% sodium lauryl sulphate at a speed of 50 rpm and a temperature of $37^0 \pm 1^0$C. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 μ) at different time intervals, suitably diluted, and assayed for celecoxib at 254 nm. The dissolution experiments were conducted in triplicate. The dissolution profiles of various tablets are shown in Fig. 1.

Table-5: The Correlation Coefficient (r) Value in the Analysis of Dissolution Data of Celecoxib Tablets as per Zero Order and First Order Models

Tablet Formulation No.	Solid Dispersion Employed	Correlation Coefficient (r) Value	
		Zero Order	First Order
CF1	Pure drug	0.9447	0.9700
CF2	C-PJ 14	0.8475	0.9719
CF3	C-CP 14	0.8526	0.9728
CF4	C-CC 14	0.7284	0.9830

CF5	C-PGS 14	0.7757	0.9761
CF6	C-PJ PVP	0.7541	0.9632
CF7	C-CP PVP	0.8092	0.9583
CF8	C-CC PVP	0.5645	0.9018
CF9	C-PGS PVP	0.6778	0.9434

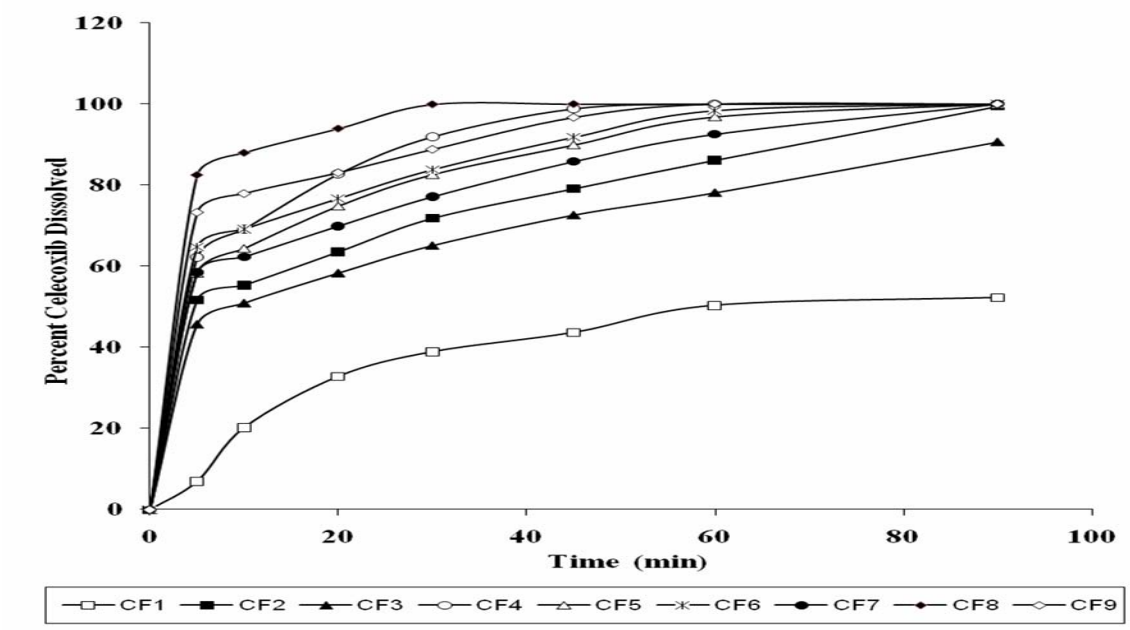

Fig.-1: Dissolution Profiles of Celecoxib Tablets Formulated Employing Celecoxib and its Solid Dispersions in Superdisintegrants

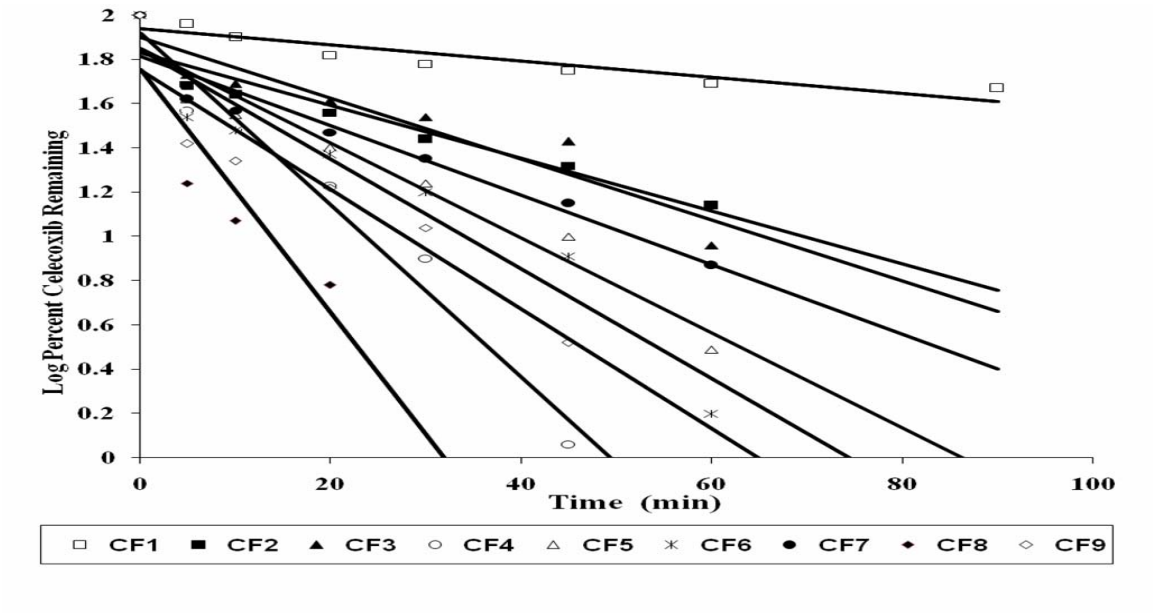

Fig.-2: First Order Dissolution Plots of Celecoxib Tablets Formulated

Table-6: Dissolution Parameters of Celecoxib Tablets formulated Employing Solid Dispersions of Celecoxib

S. No.	Formulation	Dissolution Parameter				Increase in K_1 (No. of Folds)
		T_{50} (min)	T_{90} (min)	DE_{30} (%)	K_1 (min^{-1})	
1.	CF 1	59.5	> 90	23.66	0.0083	-
2.	CF 2	4.55	85.50	55.62	0.0275	3.31
3.	CF 3	9.55	89.65	50.64	0.0220	2.65
4.	CF 4	3.50	29.50	70.56	0.0897	10.80
5.	CF 5	4.50	45.50	64.53	0.0494	5.95
6.	CF 6	3.50	44.55	67.62	0.0570	6.86
7.	CF 7	4.05	58.50	61.51	0.0361	4.34
8.	CF 8	2.50	12.4	83.72	0.1265	15.24
9.	CF 9	3.10	32	74.19	0.0623	7.50

RESULTS AND DISCUSSION

All formulated tablets were of good quality fulfilling official (I.P.) and other requirements with regard to content of active ingredient, hardness, friability and disintegration time. All the tablets formulated employing solid dispersions in superdisintegrants gave rapid and higher dissolution of celecoxib when compared to that of celecoxib plain tablets (i.e. tablets formulated employing celecoxib and lactose as diluent, CF1).

The dissolution data were fitted into zero order, first order models to assess the kinetics and 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 5. The 'r' values were higher in the first order model than those in the zero order models with all the tablet formulations prepared from solid dispersions of celecoxib indicating that the dissolution of celecoxib from all the solid dispersions followed first order kinetics. Celecoxib dissolution from all the tablets followed first order kinetics with correlation coefficient 'r' above 0.9018 (Table 5). The first order dissolution plots of various tablets are shown in Fig.2. The dissolution parameters estimated from the dissolution data of various tablets are summarized in Table 6. All dissolution parameters (K_1, DE_{30}, T_{50} and percent dissolved in 10 min) indicated rapid and higher dissolution of celecoxib from tablets formulated employing its solid dispersions when compared to plain tablets, CF1.

The dissolution rate (K_1) of celecoxib from the tablets formulated employing solid dispersions in superdisintegrants was found to be several times higher (2.65 – 15.24 fold increase) with various tablets when compared to plain tablets (Table 6). Tablets formulated with solid dispersions in croscarmellose sodium (CC) alone (CF4) and in combination with PVP (CF8) gave highest enhancement in the dissolution rate of celecoxib from tablets. A 10.8 and 15.24 fold increase in the dissolution rate was observed with formulations CF4, CF8 respectively when compared to plain tablets CF1.

The increasing order of dissolution rate of Celecoxib from the tablets observed with various superdisintegrants was CC> PGS>PJ>CP. The same order of performance was observed in both the series of tablets formulated (i.e. employing superdisintegrants alone, superdisintegrants with PVP). The increasing order of dissolution rates of tablets formulated from solid dispersions of celecoxib are comparable with solid dispersions of Nifedipine-Crospovidone[35], Nilvadipine-Croscarmellose sodium[36], Nilvadipine- crosspovidone[36], Ibuprofine-PVP [37], Rofecoxib-PVP[37] .

The tablets formulated from solid dispersions of celecoxib provide rapid dissolution rate by one or more of the following mechanisms.

Particle size reduction: Solid dispersions achieve faster dissolution rates as the drug undergoes micronization while depositing over the surface of the excipient. As celecoxib and carriers (CC, CP, PJ, PGS) are dispersed at molecular level in a solid dispersion it releases very fine particles of the drug when the carrier molecules readily dissolve in the aqueous fluids.

Improving the wettability of the particles: Wetting of powders is the primary condition for them to disperse and dissolve in body fluids[38]. The presence of water-soluble carrier (PVP) improves the wettability of hydrophobic drug particles.

Conversion of crystalline drugs into amorphous form: Solid dispersions of celecoxib may convert a crystalline drug into amorphous form. Since the amorphous form is the highest energy form of a pure compound it produces faster dissolution. Solubilizing effect of the carriers (PVP, PJ,CP,CC,PGS)

CONCLUSION

The dissolution rate and dissolution efficiency of celecoxib could be enhanced several times by their solid dispersion in super disintegrants alone and in combination with PVP. Superdisintegrants particularly croscarmellose sodium, pregelatinized starch, primojel and crispovidone were found to be good carriers giving solid dispersions with enhanced dissolution rate and efficiency. These solid dispersions in superdisintegrants could be compressed into tablets. Celecoxib tablets formulated employing their solid dispersions in super disintegrants also exhibited enhanced dissolution rate and efficiency, several times higher than those of plain tablets. These tablets were quite stable with regard to various other characteristics and enhanced dissolution rate. Thus, solid dispersion in superdisintegrants is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of celecoxib. Superdisintegrants are inert safe and non-toxic excipients that are currently used in compressed tablet formulations as disintegrants. These can be used as efficient carriers in solid dispersion techniques to enhance the dissolution rate of insoluble and poorly soluble drugs.

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