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EMPLOYMENT OF COMBINED CARRIERS FOR DISSOLUTION ENHANCEMENT OF CELECOXIB

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ABSTRACT

Solid Dispersions of celecoxib (C) with water soluble polymers polyvinylpyrrolidine (PVP), polyethylene glycol (PEG), hydroxylpropylmethylcellulose (HPMC) and a superdisintegrant namely microcrystalline cellulose (MCC) were prepared by common solvent and solvent evaporation methods employing methanol as solvent. 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. Solid dispersions of C: HPMC: MCC at 2:2:10 ratio showed 7.71 fold increase in the dissolution rate of celecoxib. Solid dispersions in combined carriers gave much higher rates of dissolution than MCC alone. MCC alone or in combination with hydrophilic polymers could be used to enhance the dissolution rate of poorly soluble drug celecoxib.

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

INTRODUCTION

Celecoxib (C), 4-[5-(4-methylphenyl)-3-(trifluoromethyl)- 1H-pyrazol-1-yl] benzene sulfonamide, is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and anti-pyretic activities and used in the treatment of rheumatoid arthritis & osteoarthritis[1,2]. Celecoxib is also used in the management of acute pain and dysmenorrhoea, as an adjunct to standard therapy[3] 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. Celecoxib is absorbed slowly from the gastrointestinal tract, peak plasma concentrations[4] being achieved approximately 4hrs after an oral dose. 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 are controlled by rate of dissolution in gastro-intestinal fluids[5]. The present study aims at enhancing the dissolution rate of celecoxib. In the present investigation solid dispersions[6] 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 MCC, a new class of tablet excipient was evaluated as carrier, alone and in combination with PVP, HPMC, and PEG for enhancing the dissolution rate and bioavailability of celecoxib.

MATERIALS AND METHODS

Celecoxib was a gift sample from M/s. Sigma Laboratories, Mumbai. Methanol (Qualigens) and polyvinylpyrrolidone (PVP K_{30}), HPMC, PEG were procured from commercial sources. All other materials used were of pharmacopoeial grade.

PREPARATION OF SOLID DISPERSIONS

Preparation of Solid Dispersions Employing Superdisintegrant MCC

Solid dispersions of celecoxib (C) in superdisintegrant MCC were prepared by solvent evaporation method. The required quantities of C were dissolved in methanol to get a clear solution in a dry mortar. The superdisintegrant MCC (passed through No.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°C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh no.100. Solid dispersion was prepared with the superdisintegrant MCC at a ratio of C, MCC namely 1:6 respectively.

Preparation of Solid Dispersions Employing Combined Carriers

The required quantities of C and water soluble carriers (PEG, PVP, and HPMC) were dissolved in the solvent to get a clear solution in a dry mortar. The

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superdisintegrant MCC 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 Prepared*

Sl. No.	Composition		
	Drug	Carriers	SD Code
1.	Celecoxib (2)	PEG(2), MCC (10)	C-PEG-MCC, 2210
2.	Celecoxib (2)	PVP (2), MCC (10)	C-PVP-MCC, 2210
3.	Celecoxib (2)	HPMC (2), MCC (10)	C-HPMC-MCC, 2210
4.	Celecoxib (1)	MCC(6)	C-MCC, 16

Estimation of celecoxib

A spectrophotometric 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[7]. 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 range of 0-20 *µg/ml.*

Estimation of celecoxib solid dispersions prepared

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 2.

Table 2. *Celecoxib Content of Various Solid Dispersions Prepared*

Sl.No.	SD Code	Percent Celecoxib Content ($\bar{x}$ ± s.d.)
1.	C-PEG-MCC, 2210	14.23 ± 0.74 (0.824)
2.	C-PVP-MCC, 2210	14.19 ± 0.62 (0.86)
3.	C-HPMC-MCC, 2210	14.22 ± 0.59 (0.88)
4.	C-MCC, 16	14.24 ± 0.52 (1.47)

Dissolution Rate Studies on Solid Dispersions

Dissolution rate of celecoxib was studied using an USP XXIII six station dissolution rate test apparatus (Electro Lab). Paddle 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 given in Table 3. Dissolution rates of celecoxib and its solid dispersions followed first order kinetics Table 4 and dissolution profiles plotted were shown in Fig1 and 2. Dissolution parameters such as $T_{50,}$ $DE_{30,}$ $K_{1,}$ Percent of celecoxib dissolved in 10 minutes are given in Table 5.

Table 3. *Dissolution Profile of Celecoxib Solid Dispersions*

Time (min)	Percent Celecoxib Dissolved ($\bar{x}$ ± s.d., n = 3)				
	C	C-PEG-MCC 2210	C-PVP-MCC 2210	C-HPMC-MCC 2210	C-MCC 16
5	24.42±0.77	50.5±0.07	49.7±0.87	73.6±0.88	38.9±1.11
10	30.37±0.45	58.9±1.87	53.3±1.23	78.7±0.77	52.4±1.23
20	33.86±0.55	62.2±1.12	56.4±0.78	85.1±0.56	56.6±1.45
30	35.13±0.76	66.5±1.78	59.4±1.87	85.9±1.22	60.2±1.33
45	37.83±0.26	80.9±1.23	67.4±1.23	86.9±1.58	61.8±1.87
60	39.41±0.68	84.5±0.98	73.9±1.87	89.1±0.88	65.6±1.36
90	42.66±0.49	88.5±1.20	76.5±1.89	94.9±0.87	70.3±0.56
120	45.75±0.47	99.3±0.89	78.5±0.88	99.7±0.63	75.1±0.88

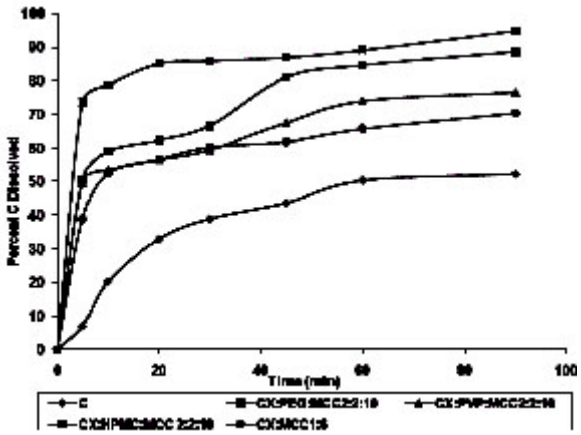

Fig.1 : *Dissolution Profiles of Celecoxib and its solid dispersions*

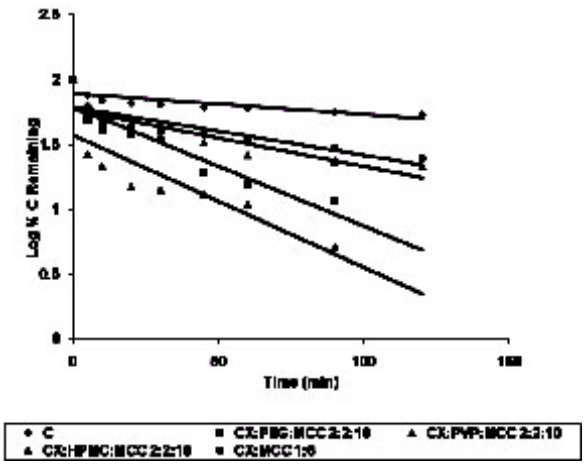

Fig.2 : *First Order Dissolution Plots of Celecoxib and its Solid Dispersions*

Table 4: *Analysis of Dissolution Data*

Sl. No.	Solid Dispersion	Correlation coefficient (r) value		
		Zero order	Fist order	Hixson-Crowell
1.	Celecoxib	0.943	0.953	0.990
2.	C-PEG-MCC, 2210	0.770	0.931	0.969
3.	C-PVP-MCC, 2210	0.720	0.870	0.953
4.	C-HPMC-MCC, 2210	0.608	0.846	0.953
5.	C-MCC, 14	0.721	0.852	0.934

Table 5: *Dissolution Parameters of Celecoxib and its Solid Dispersions in Superdisintegrants*

Sl. No.	Solid Dispersion	Dissolution Parameter			
		T_{50} (min)	DE_{30} (%)	K (min^{-1})	No. of folds increase in K
1.	Celecoxib	>120	28.8	0.0035	-
2.	C-PEG-MCC, 2210	5	54.97	0.0211	6.02
3.	C-PVP-MCC, 2210	5	50.32	0.01	2.85
4.	C-HPMC-MCC, 2210	3.5	74.62	0.027	7.71
5.	C-MCC, 16	9	48.48	0.0085	2.42

Analysis of Dissolution Data as per Hixson-Crowell's cube root law

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.3) 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 (0.846 to 0.931) 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. For evaluation of *in vitro* dissolution data, Khan[9] suggested a parameter called 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.

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

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.

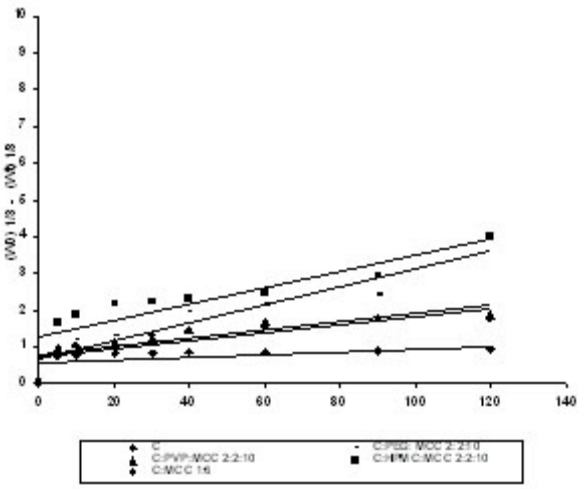

Fig. 3 : *Hixson-Crowell Dissolution Plots of Celecoxib and its Solid Dispersions*

RESULTS AND DISCUSSION

All the dissolution parameters given in Table 2 indicated rapid and higher dissolution of celecoxib from all solid dispersions when compared to pure drug. Celecoxib-HPMC-MCC (2:2:10) solid dispersion gave rapid and higher dissolution than the pure drug. A 7.71 fold increase in the dissolution rate of celecoxib was obtained with this solid dispersion when compared to pure drug. Combined carriers gave much higher enhancement in the dissolution rate of celecoxib than water dispersible carriers alone. Solid dispersions of superdisintegrants gave rapid and higher dissolution of celecoxib when compared to pure drug as well as its solid dispersion in water soluble PVP. 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-MCC solid dispersion gave a 7.71 fold increase in the dissolution rate of celecoxib whereas solid dispersion of celecoxib in MCC alone (C-MCC 16 solid dispersion) gave only

2.42 fold increase. Thus combination of superdisintegrants with water soluble carrier HPMC resulted in a greater enhancement in the dissolution rate of celecoxib.

CONCLUSION

Thus superdisintegrant MCC 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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