Research Article

PREPARATION AND EVALUATION OF SOLID DISPERSIONS OF CELECOXIB

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ABSTRACT

Celecoxib is a non-steroidal anti-inflammatory drug. The present study was planned to prepare and evaluate the solid dispersions of Celecoxib. Solid dispersions of Celecoxib were prepared by using various hydrophilic carriers like PVP-K-40, PEG 6000, PEG 4000 and Dextrin in various ratios by melt-in solvent method and solvent evaporation technique. The prepared solid dispersions were subjected to solubility studies (in water, 0.1N HCl and phosphate buffer pH 7.4) and drug content uniformity studies. The *in-vitro* release studies were carried out with USP type I dissolution apparatus (100 rpm, 37 ± 2°C) in phosphate buffer pH 7.4 and stability studies were carried out at 40 ± 2°C and 75± 5% RH. The cumulative amount of drug release at the end of 2 hours of Celecoxib: PVP was 96.86%, Celecoxib: PEG-4000 was 97.06 %, Celecoxib: PEG-6000 was 97.32% and Celecoxib: dextrin was 98.05%. Therefore, it can be concluded that the dissolution rate of poorly soluble drug Celecoxib can be significantly enhanced by formulating it into solid dispersions.

Keywords: Celecoxib, solid dispersions, dextrin, melt-in solvent method, solvent evaporation technique, bioavailability.

INTRODUCTION

With recent progress in high throughput screening of potential therapeutic agents the number of poorly water soluble drug candidates has risen sharply and formulating poorly water soluble compounds for oral drug delivery now presents one of the most frequent and greatest challenges to scientists in the pharmaceutical industry[1-4].

As a consequence of extensive research oral drug delivery systems like micelles with surfactants, micro emulsions, self emulsifying or micro emulsifying drug delivery systems (SEDDS/SMEDDS), solid dispersions, microspheres and cyclodextrin inclusion complexes are designed[1]. Celecoxib is a non-steroidal drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, etc. It is a poorly water soluble drug having 97% protein binding and poor bioavailability.

The present study aims to enhance the dissolution rate of poorly water soluble drug Celecoxib by formulating it into solid dispersions using various hydrophilic carriers like PVP-K-40, PEG 6000, PEG 4000 and Dextrin in various ratios by melt-in solvent method and solvent evaporation technique.

MATERIALS AND METHODS

Materials

Celecoxib was obtained from Cheminor drugs limited, Hyderabad. The hydrophilic polymers like PVP-K-40, PEG 6000, PEG 4000, Dextrin and ethanol were obtained from S.D. Fine chemicals ltd., Mumbai.

Methods

1. Calibration curve of Celecoxib

The method of estimation of Celecoxib by UV spectrophotometer at 258.2 nm was standardized and the drug was found to obey Beer-Lambert's law in the concentration range of 2-12 µg/ml.

2. Preparation of solid dispersions of Celecoxib[5-8]

Solid dispersions of Celecoxib were prepared by using PVP-K-40, PEG 6000, PEG 4000 and Dextrin in the ratios 1:1, 1:4, 1:9 individually by melt-in solvent method (fusion method) and solvent evaporation technique. The details of the various formulations prepared are tabulated in table 2.

Table 1: Calibration curve of Celecoxib

Concentration (µg/ml)	Absorbance (nm)
2	0.111
4	0.208
6	0.292
8	0.396
10	0.483
12	0.588

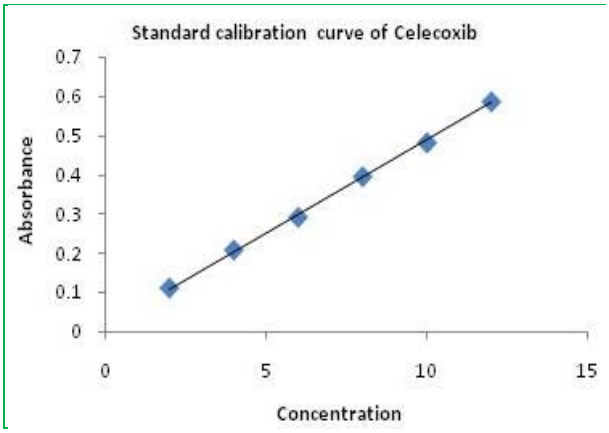

Figure 1: Calibration curve of Celecoxib

Table 2: Various formulations of solid dispersions of Celecoxib

Formulation code	Polymer	Drug:polymer
F1	PEG-4000	1:01
F2		1:04
F3		1:09
F4	PEG-6000	1:01
F5		1:04
F6		1:09
F7	PVP-K-40	1:01
F8		1:04
F9		1:09
F10	DEXTRIN	1:01
F11		1:04
F12		1:09

3. Evaluation of solid dispersions of Celecoxib

The following parameters were evaluated for the prepared solid dispersions of Celecoxib.

(a) Micromeritic properties

The solid dispersions of the various formulations were evaluated for angle of repose, bulk density, tapped density and compressibility index.

Table 3: Micromeritic properties of solid dispersions of Celecoxib

Formulations	Angle of repose (°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)
F1	28^0 .28´±0.53	0.428±0.009	0.614±0.008
F2	27^0 .35´±0.97	0.444±0.007	0.606±0.006
F3	22^0 .96´±0.83	0.455±0.005	0.614±0.009
F4	23^0 .93´±0.78	0.478±0.003	0.568±0.006
F5	29^0 .82´±0.85	0.463±0.002	0.586±0.004
F6	27^0 .96´±0.65	0.454±0.004	0.547±0.005
F7	24^0 .29´±0.89	0.466±0.005	0.584±0.003
F8	25^0 .13´±0.42	0.466±0.001	0.574±0.002
F9	26^0 .48´±0.84	0.433±0.002	0.566±0.004
F10	27^0 .96´±0.65	0.453±0.004	0.547±0.005
F11	28^0 .90´±0.83	0.468±0.005	0.624±0.009
F12	26^0 .73´±0.76	0.458±0.003	0.578±0.006

(b) Dissolution rate/*in-vitro* drug release

The *in-vitro* release studies were carried out by USP type I dissolution apparatus (100 rpm, 37 ± 2^{o}C) in phosphate buffer p^H 7.4. A sample of the sample solution was withdrawn from the dissolution testing apparatus hourly for 8hrs and the samples were replaced with fresh dissolution medium to maintain sink conditions. Absorbance of these solutions was measured at 258.2 nm using UV-Visible spectrophotometer.

Table 4: *In-vitro* drug release profile of formulations F1 to F12

Time	Cumulative % Drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
5	4.5	5.4	7.2	3.15	3.6	4.5	3.6	3.6	5.4	4.05	4.5	7.2
10	7.20	9.00	11.70	3.6	6.48	10.81	4.5	5.4	9.01	6.3	8.1	12.6
20	18.00	19.81	22.52	3.11	14.42	19	19	12.6	1.71	9.91	15.3	20.7
30	22.52	20.72	27.02	13.52	22.53	25.23	17.1	18.02	27.03	14.4	23.4	32.4
40	26.12	29.72	35.13	18.02	28	31.54	22.5	22.5	33.3	19.8	29.5	40.5
50	36.02	38.73	43.33	27.03	32.44	38.74	27.9	27.03	36.9	28.2	35.13	47.7
60	45.04	49.54	52.34	36.04	37.84	46.85	33.3	31.53	46.85	37.8	39.16	57.6
70	53.15	53.15	54.05	45.05	46	56.76	38.7	35.1	55.86	46.5	47.7	63.07
80	58.55	62.15	63.06	54.06	58.57	62.17	52.2	45.05	59.46	55.3	16.2	71.1
90	64.86	66.66	71.17	63.07	64	70.28	64.8	55.86	66.67	64.8	69.3	77.4
100	72.17	72.07	73.87	67.58	71.18	74.78	72.08	64.8	73.88	71.1	75.6	81.9
120	74.84	78.8	85.58	72	76	80	75.6	78.3	83.79	75.6	81.9	88.2

Table 5: Curve Fitting Analysis for Different Formulations

Formulations	Zero order (r^2)	First order (r^2)	Higuchi's plot (r^2)	Korsmeyer's peppas plot	
				(R^2)	n
F1	0.855	0.979	0.971	0.991	0.981
F2	0.841	0.985	0.973	0.99	0.982
F3	0.827	0.961	0.983	0.997	0.99
F4	0.889	0.96	0.925	0.904	0.974
F5	0.896	0.963	0.959	0.996	0.987
F6	0.883	0.854	0.978	0.484	0.985
F7	0.891	0.918	0.908	0.964	0.964
F8	0.892	0.886	0.907	0.988	0.979
F9	0.866	0.96	0.949	0.702	0.968
F10	0.902	0.952	0.926	0.964	0.98
F11	0.698	0.095	0.75	0.841	0.796
F12	0.857	0.982	0.99	0.996	0.977

Table 6: Stability studies of solid dispersions of Celecoxib

Formulation	Condition	25±2◦C/60±5%RH			30±2◦C/60±5%RH			40±2◦C/75±5%RH		
		1M	2M	3M	1M	2M	3M	1M	2M	3M
F3	Physical Appearance	No change in physical appearance			No change in physical appearance			No change in physical appearance		
F6										
F9										
F12										
F3	Moisture Content	1.6	1.6	1.6	1.7	1.8	1.8	1.8	1.9	1.9
F6		1.5	1.5	1.6	1.6	1.7	1.6	1.8	1.8	1.9
F9		1.6	1.7	1.5	1.6	1.6	1.7	1.9	1.8	1.4
F12		1.6	1.8	1.4	1.2	1.3	1.4	1.8	1.8	1.9
F3	Drug Content (%)	96.86	96.8	96.72	96.8	96.74	96.6	96.62	96.6	96.52
F6		97.06	97	96.89	97.02	96.82	95.2	96.32	96.21	96
F9		97.32	97.32	97.3	97.32	97.2	97.13	97.1	97.09	96.89
F12		98.05	97.89	97.83	98.01	97.82	97.68	97.56	97.14	96.9

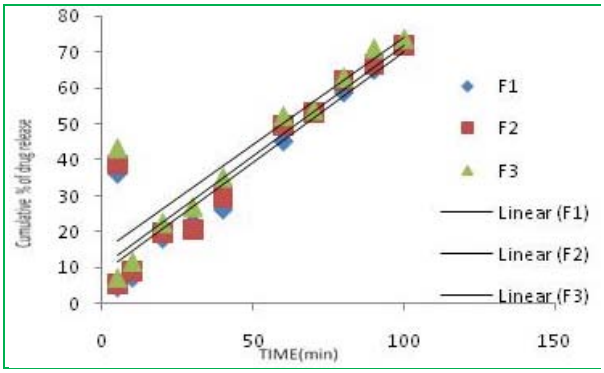

Figure 2: *In-vitro* drug release profile of formulations F1 to F3

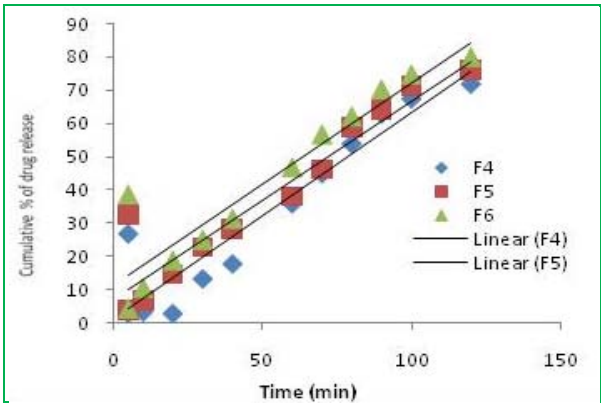

Figure 3: *In-vitro* drug release profile of formulations F4 to F6

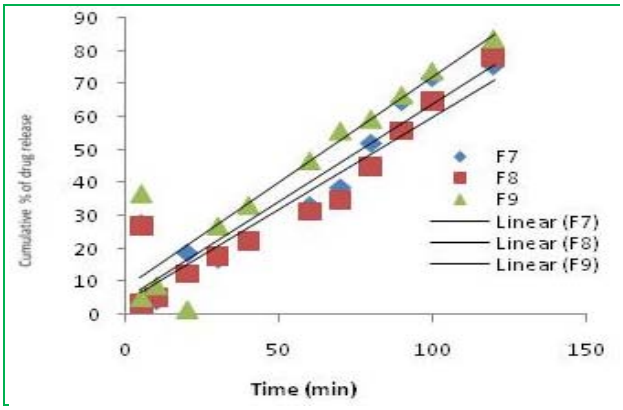

Figure 4: *In-vitro* drug release profile of formulations F7 to F9

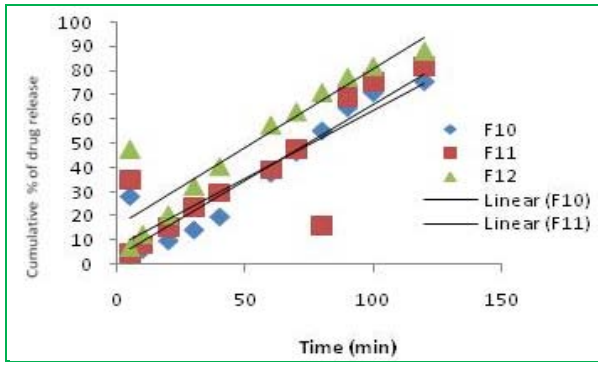

Figure 5: *In-vitro* drug release profile of formulations F10 to F12

Kinetic modeling of drug release[9-11]

The dissolution profile of all the batches was fitted to zero-order, first order, Higuchi, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release.

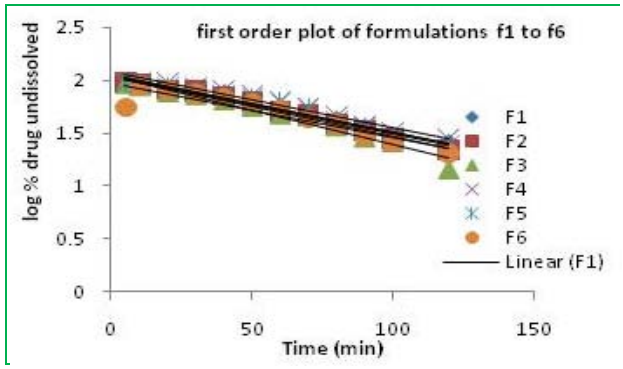

Figure 6: First order plot of solid dispersions of Celecoxib of formulations F1 to F6

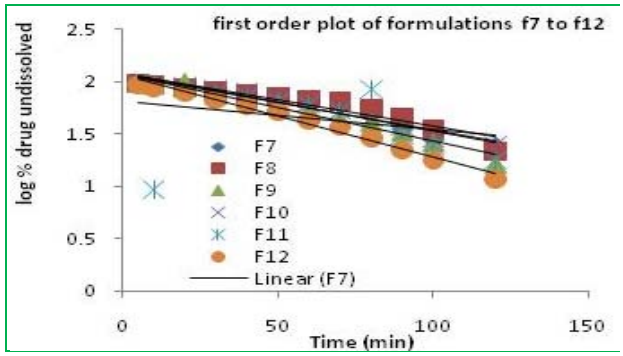

Figure 7: First order plot of solid dispersions of Celecoxib of formulations F7 to F12

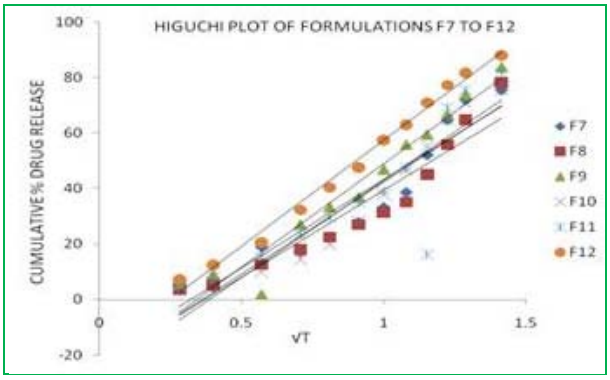

Figure 8: Higuchi plot of solid dispersions of Celecoxib of formulations F1 to F6

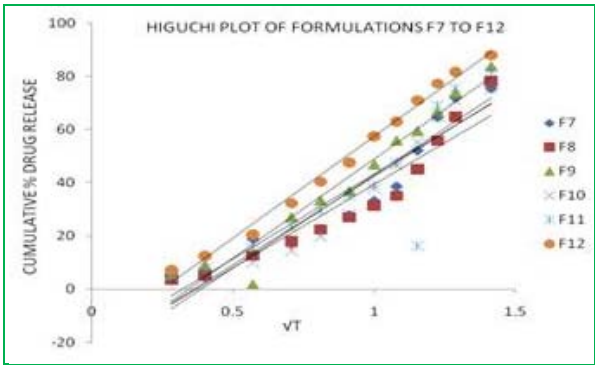

Figure 9: Higuchi plot of solid dispersions of Celecoxib of formulations F7 to F12

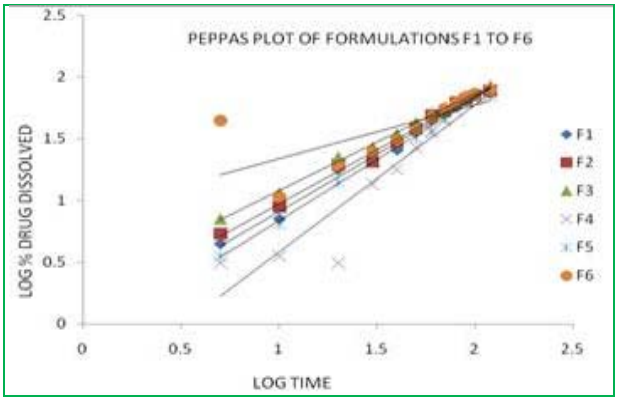

Figure 10: Peppas plot of solid dispersions of Celecoxib of formulations F1 to F6

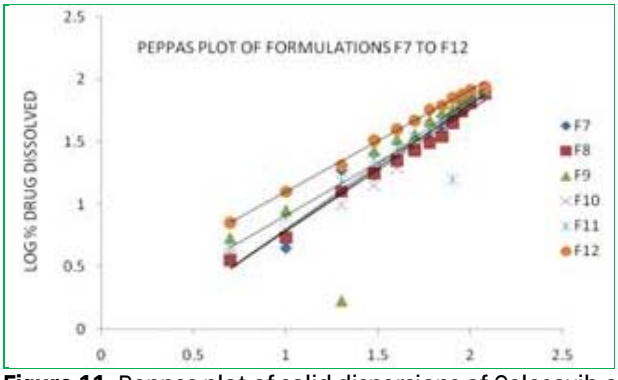

Figure 11: Peppas plot of solid dispersions of Celecoxib of formulations F7 to F12

c) Stability studies of solid dispersions of Celecoxib

The evaluated solid dispersions of Celecoxib were then subjected to stability studies for a period of 3 months under different conditions of temperature and relative humidity. The results of stability studies are tabulated in table 6.

RESULTS AND DISCUSSION

In the present study solid dispersions of Celecoxib could be successively prepared by melt-in solvent method and solvent evaporation technique by using various soluble carriers such as PVP-K-40, PEG 6000, PEG 4000 and Dextrin which are biocompatible and bio degradable in nature. Three different ratios of drug: polymer (1:1, 1:4, 1:9) were taken.

The prepared solid dispersions were subjected to solubility studies in distilled water, 0.1N HCl and phosphate buffer of pH 7.4. Enhancement of solubility in comparison to pure drug was observed for all formulations. Among all the formulations drug: carrier in the ratio 1:9 showed higher solubility as compared to other ratios. The solubility of different carriers are dextrin > PVP-K-40 >PEG 6000> PEG 4000.

Solid dispersions of Celecoxib also showed high dissolution rates in comparison to pure drug. The formulations containing drug and carrier in 1:4 ratios have higher dissolution rates. The dissolution rate of carriers are dextrin > PVP-K-40> PEG 6000>PEG 4000

Stability studies were carried out at 40 ± 2°C and 75 ± 5% RH, for a period of 45 days and formulations did not show any physical change and neither was there any change in drug content.

CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In the present study it can be concluded that the dissolution rate of poorly soluble drug Celecoxib can be significantly enhanced by formulating it into solid dispersions.

In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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