ORIGINAL ARTICLE

Enhancement of Solubility and Dissolution Rate of Poorly Soluble Antihypertensive Drug using Solid Dispersion Technique

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Abstract

Aim: To develop and evaluate solid dispersions of carvedilol to enhance solubility and dissolution rate using different hydrophilic carriers. **Materials and Methods:** Estimation of carvedilol was carried out using validated UV method. Solubility studies of pure drug were evaluated in the presence of different hydrophilic carrier with selected weight ratios in 0.1 N hydrochloric acid (HCl). Solid dispersions of carvedilol were prepared successfully using different hydrophilic carriers (mannitol, lactose, and polyethylene glycol [PEG] 4000) as solubilizer by solvent evaporation method. The prepared solid dispersions were evaluated for their physicochemical and micrometric characteristics such as physical appearance, Fourier transform infrared (FTIR), flow properties, drug content, and *in vitro* drug release studies. **Results and Discussion:** This research work has been made to enhance the solubility of pure drug of carvedilol using different hydrophilic carriers by converting pure drug into micronized form by solid dispersion technique. The FTIR spectroscopy was used to confirm compatibility and to rule out any possible interaction between drug and hydrophilic carriers used. Nine solid dispersion formulations (CMSD1, CMSD2, CMSD3, CLSD1, CLSD2, CLSD3, CPSD1, CPSD2, and CPSD3) consisting pure drug of carvedilol with mannitol, lactose, and PEG 4000 used as solubilizer in the ratios of 1:1, 1:2, and 1:4, respectively, were prepared. *In vitro* drug release from solid dispersions was carried out in 0.1N HCl, and the data obtained were fit into different equations and kinetic models to explain release kinetics. A 4.13, 4.60, and 10.7 folds increase in the dissolution efficiency (DE_{20}) of carvedilol was observed with solid dispersions CMSD3, CLSD3, and CPSD3, respectively. Carvedilol with PEG 4000 in 1:2 and 1:4 ratio formulations showed better solubility and emerged to be an ideal formulation for carvedilol solid dispersions. **Conclusion:** From the study results, it can be concluded that optimized solid dispersion formulations have better solubility as compared to pure drug. The solubility of carvedilol was increasing with increase in the concentration of hydrophilic carriers. The developed solid dispersion of carvedilol with PEG 4000 found useful to enhance solubility of carvedilol.

Key words: Carvedilol, lactose, mannitol, polyethylene glycol 4000, solid dispersions, solubility, solvent evaporation technique

INTRODUCTION

Carvedilol is an antihypertensive agent used in the treatment of hypertension, congestive heart failure, cardiac arrhythmias, and angina pectoris.[1] It is a nonselective β-adrenergic blocker with selective α-adrenergic blocking.[2] The chemical structure of carvedilol is shown in Figure 1.

Carvedilol beingas class II compound as per Biopharmaceutical Classification System (BCS). Carvedilol shows very poor bioavailability and significant first pass metabolism.[3,4] The aqueous solubility of carvedilol is the rate limiting factor for

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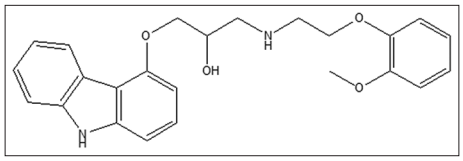

Figure 1: Chemical structure of carvedilol

many of the researchers; enhancement of aqueous solubility was achieved by increasing the surface area of the drug which includes micronization,[5] cyclodextrin complexation,[6] use of hydrophilic polymers,[7,8] and using porous silica.[9] The most industrially acceptable method for enhancement of aqueous solubility and dissolution rate is the preparation of solid dispersion with best suitable carriers. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by different techniques, i.e. melting (fusion), solvent, or melting-solvent method. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in enhancement of aqueous solubility and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. The main objective of this study was made an attempt to prepare carvedilol solid dispersions using hydrophilic carriers such as mannitol, lactose, and polyethylene glycol 4000 (PEG 4000) with different ratios using solvent evaporation method.

MATERIALS AND METHODS

Materials

Carvedilol was gift sample from Aurobindo Pharma Ltd., (Hyderabad, India). Mannitol was procured from and PEG 4000 was procured from Signet Chemical Corporation., Mumbai. Lactose was procured from Molychem, Mumbai. All other reagents used were of analytical grade procured from commercial source.

Analytical method for carvedilol estimation (UV method)

A stock solution of carvedilol was prepared by dissolving 100 mg of drug in 100 mL of methanol to get 1 mg/mL solution. From this stock solution 1, 2, 4, 8, and 10 µg/mL solutions were prepared by serial dilution method with 0.1 N hydrochloric acid (HCl). The absorbance of prepared solutions was measured at 244 nm[10] against the blank (0.1 N HCl). A standard graph was plotted by with concentration on X-axis and absorbance on Y-axis.

Solubility studies of carvedilol in hydrophilic carriers

Initial solubility studies of carvedilol in selected hydrophilic carriers were performed with reference to reported method.[11] The required quantity of hydrophilic carrier solutions was prepared in water by dissolving carrier at various ratios such as 1:1, 1:2, and 1:4 (drug:hydrophilic carrier) and an excess amount of drug was added to 10 mL hydrophilic carrier solution in screw-capped bottles. Samples were shaken in an orbital shaker for 24 h at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper grade no 1 and filtered solution diluted properly with methanol. The diluted solution was analyzed for estimation of carvedilol content at 244 nm.

Preparation of solid dispersions of carvedilol

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the dissolution rate. Carvedilol solid dispersions were prepared using different hydrophilic carriers (i.e., mannitol, lactose, and PEG 4000) in different ratios, i.e., 1:1, 1:2, and 1:4 (drug:hydrophilic carrier) by solvent evaporation method. Drug and hydrophilic carrier were dissolved in a common solvent (methanol) and triturated the slurry in dry mortar until the solvent completely evaporated. The resultant solid dispersion was scraped out with a spatula and was pulverized in a mortar and pestle. The pulverized solid dispersion was passed through a sieve no. 80 to get uniform and lump-free solid dispersion. The prepared formulations were stored in a desiccator until further use.[12] The details of different ratios of solid dispersions are tabulated in Table 1.

Evaluation of solid dispersions

Fourier transform infrared (FTIR) analysis of solid dispersions

FTIR spectroscopy spectra of the carvedilol, mannitol, lactose, PEG 4000, and its solid dispersions (CMSD3, CLSD3, and CPSD4) were recorded on Perkin Elmer spectrophotometer using KBr discs. Sample preparation was done using the potassium bromide pellet method. Component of analysis was added to powdered potassium bromide in the

Table 1: Solid dispersions with different ratios of drug:hydrophilic carrier

Formulation code	Hydrophilic carrier	Drug:hydrophilic carrier
CMSD1	Mannitol	1:1
CMSD2		1:2
CMSD3		1: 4
CLSD1	Lactose	1:1
CLSD2		1:2
CLSD3		1: 4
CPSD1	PEG 4000	1:1
CPSD2		1:2
CPSD3		1: 4

PEG: Polyethylene glycol

ratio of 1:100. The mixture was compacted under pressure (10 tons/cm^2) in vacuum to form a transparent pellet (13 mm in diameter) and was subjected to immediate analysis. The instrument was operated under dry air purge, and the scans were collected at scanning speed of 2 mm/s with resolution of 4/cm over the region of 4000-400/cm.

Drug content

Solid dispersions equivalent to 10 mg of carvedilol were weighed accurately and dissolved in the 10 mL of methanol. The solution was diluted suitably and drug content was analyzed at by UV spectrophotometer at 244 nm. The drug content was calculated using the following equation:

$$\%\text{Drug content} = (M_{act}/M_t)\times 100$$

M_{act} = Actual amount of drug in solid dispersion
M_t = Theoretical amount of drug in solid dispersion

Flow properties

Bulk density and tapped density

Accurately weighed amount of solid dispersions were transferred to a 100 ml graduated cylinder to measure the apparent volumes or bulk volume (V_b). The measuring cylinder was tapped for a fixed period, and tapped volume (V_t) occupied in the cylinder was measured. The bulk density and tapped/true density were calculated in gram per milliliter by the following formula:

$$\text{Bulk density} = \text{Mass/volume} = M/V_b$$

$$\text{Tapped density} = \text{Mass/tapped volume} = M/V_t.$$

Carr's index (CI) and Hausner ratio (HR)

Carr's index and Hausner ratio are calculated using following formulae:[13,14]

$$\text{Carr's index} = [(\text{Tapped density} - \text{Bulk density})/\text{Tapped density}]\times 100$$

$$\text{Hausner ratio} = \text{Tapped density/bulk density}$$

Angle of repose

The angle of repose was measured by fixed funnel method.[15]

In vitro drug release study

The dissolution rate of carvedilol as such and from its solid dispersions prepared was studied in 0.1 N HCl (900 ml) employing USP 8-station dissolution rate test apparatus (M/s LabIndiaDisso 8000) with a paddle stirrer at 50 rpm. Carvedilol or its solid dispersions equivalent of 10 mg of carvedilol was used in each test. A temperature of 37°C ± 1°C was maintained in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for carvedilol at 244 nm. All the dissolution experiments were conducted in triplicate (n = 3).

Dissolution efficiency (DE) studies

The DE of the batches was calculated by the method mentioned by Khan.[16] It is defined as the area under the dissolution curve up to a certain time, t, (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time. DE_{20} values were calculated from dissolution data and used to evaluate the dissolution rate.

RESULTS AND DISCUSSION

Carvedilol was estimated by UV spectrophotometric method by measuring the absorbance at 244 nm. The UV method was validated for linearity, accuracy, precision, and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/mL (r = 0.999). Based on the initial solubility studies data, pure drug is highly insoluble in water, and solubility was found to be 15.52 mcg/ml. The solubility of carvedilol in different hydrophilic carrier at different rations was analyzed, and results are shown in Table 2. The solubility of carvedilol was found to be 30.10, 48.65 and 78.96 mcg/mL with mannitol, lactose, and PEG 4000 at 1:4 weight ratios, respectively. A 1.94, 3.13, and 5.08 folds increase in solubility was observed with 1:4 weight ratios of drug and mannitol, lactose, and PEG 4000, respectively. The finalized ratios are 1:1, 1:2, and 1:4 in each case of hydrophilic carriers. Solid dispersions of carvedilol in different hydrophilic carriers were prepared by solvent evaporation method employing various weight ratios of drug:hydrophilic carrier.

Table 2: Solubility studies results

S. No	Drug:hydrophilic carrier	Solubility in mcg/mL
1	Pure drug	15.52
2	Carvedilol+Mannitol (1:1)	24.60
3	Carvedilol+Mannitol (1:2)	26.09
4	Carvedilol+Mannitol (1:4)	30.10
5	Carvedilol+Lactose (1:1)	35.60
6	Carvedilol+Lactose (1:2)	45.60
7	Carvedilol+Lactose (1:4)	48.65
8	Carvedilol+PEG 4000 (1:1)	69.32
9	Carvedilol+PEG 4000 (1:2)	76.35
10	Carvedilol+PEG 4000 (1:4)	78.96

PEG: Polyethylene glycol

FTIR spectroscopy

The compatibility of carvedilol with selected hydrophilic carriers in the study was evaluated by FTIR spectra. FTIR spectrum of pure drug and solid dispersions is shown in Figures 2 and 3, respectively. IR spectrum of carvedilol was characterized by strong absorption peaks at 3345, 2923, 1099, and 979/cm assigned to N-H, C-H, C-O, and O-H stretch, respectively. From the spectral study, it was observed that there was no significant change in the IR absorption peaks of pure drug and solid dispersions. Hence, there was no drug–excipient interaction between the pure drug and hydrophilic carriers used in the study.

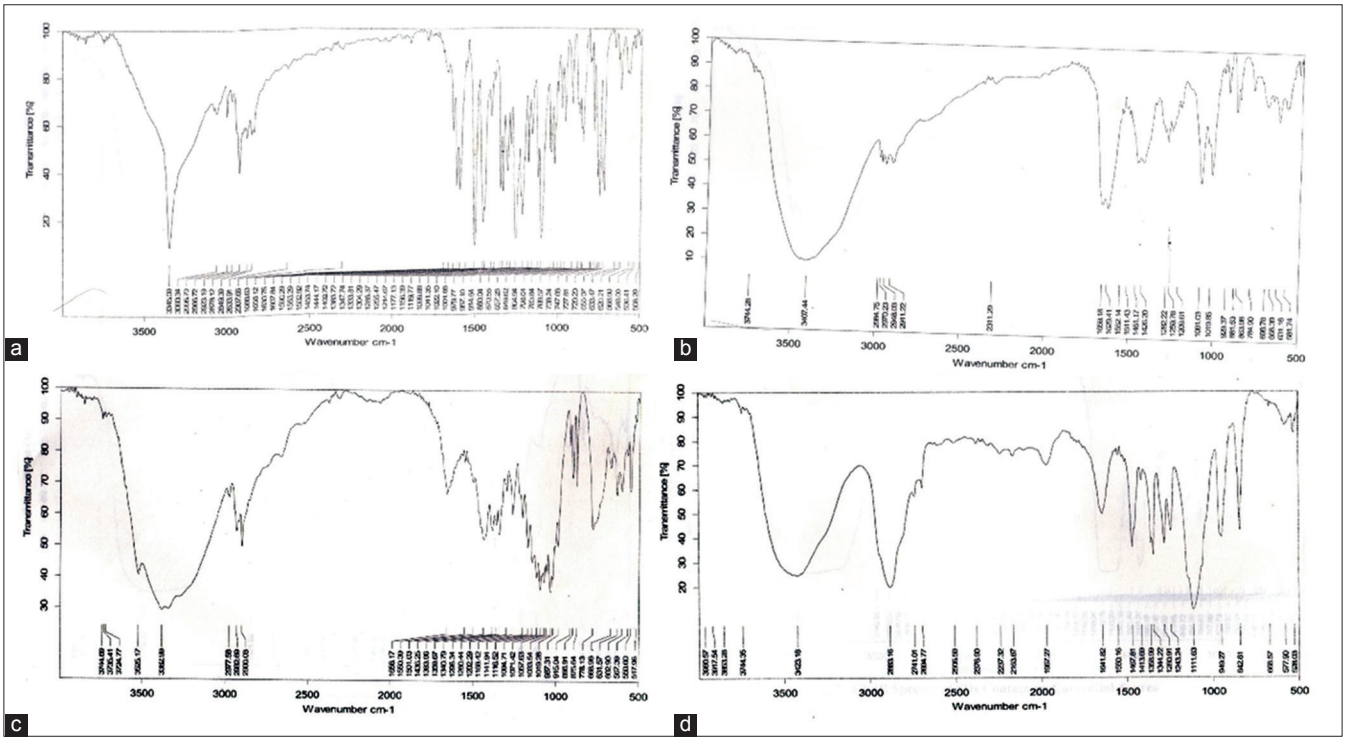

Figure 2: Fourier transform infrared spectrum of carvedilol and hydrophilic carriers used. (a) Carvedilol. (b) Mannitol. (c) Lactose. (d) Polyethylene glycol 4000

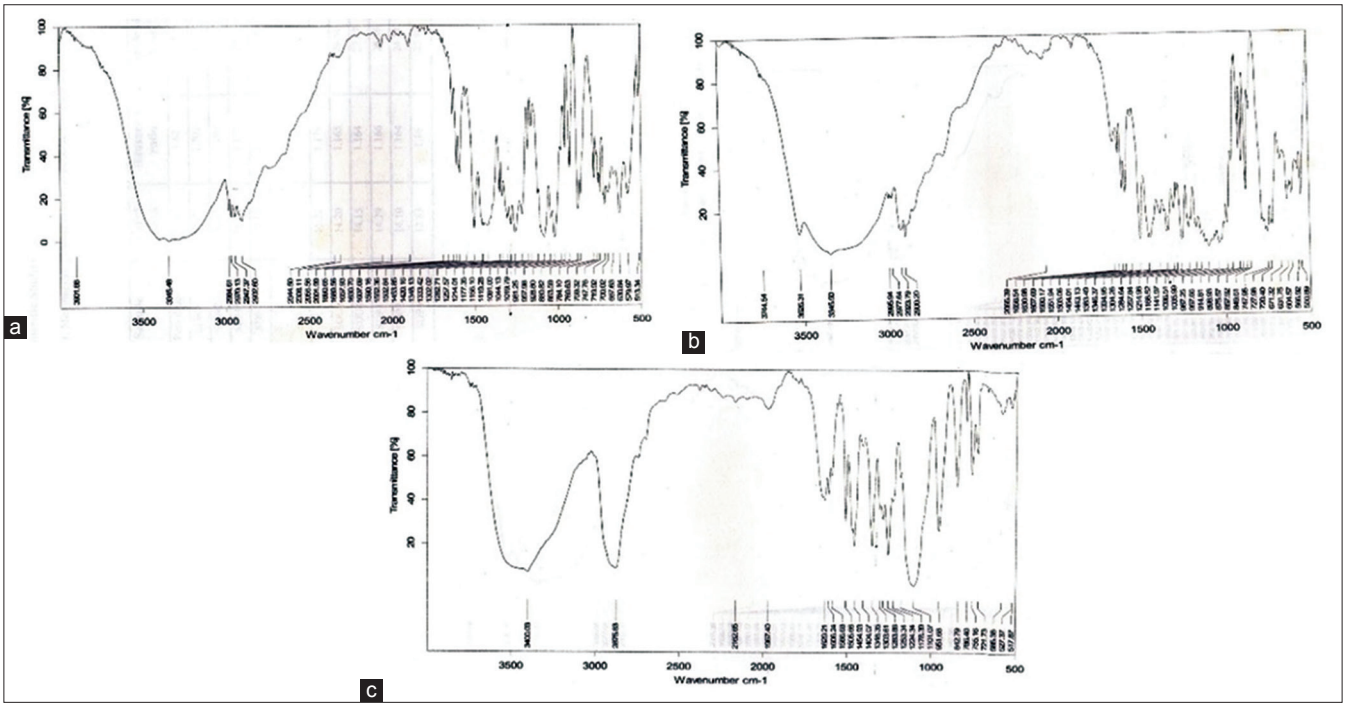

Figure 3: Fourier transform infrared spectrum of solid dispersions prepared with hydrophilic carriers. (a) Carvedilol:mannitol (1:4). (f) Carvedilol: lactose (1:4). (c) Carvedilol:polyethylene glycol 4000 (1:4)

Micromeritics and morphology studies

Flow properties of carvedilol (pure drug) and its solid dispersions were assessed by determination of CI, HR, and angle of repose. Micromeritic characteristics of the pure carvedilol and prepared solid dispersions are listed in Table 3. Based on the results obtained, flowability represented in terms of CI, HR, and angle of repose was much improved compared to the pure drug. In case of pure drug, powder could not pass through the funnel during the angle of repose experiment. The poor flow of pure drug could be due to the irregular shape and cohesiveness of the powder. Prepared solid dispersions flow was significantly increased when compared to pure drug. All the solid dispersions prepared were found to be fine and free-flowing powders with an angle of repose in the range 20-30°. Low CV (<1.0%) in the percent drug content indicated uniformity of drug content in each batch of solid dispersions prepared.

In vitro drug release study

The dissolution rate of carvedilol alone and from its solid dispersions was studied in 0.1 N HCl (pH 1.2). All the solid dispersions prepared gave rapid and higher dissolution of carvedilol when compared to pure drug. The dissolution curves of zero order and first order plots are shown in Figures 4 and 5, respectively. The dissolution parameters of carvedilol and its solid dispersions are given in Table 4.

Solid dispersions of carvedilol showed superior dissolution properties when compared to pure drug. Both dissolution rate

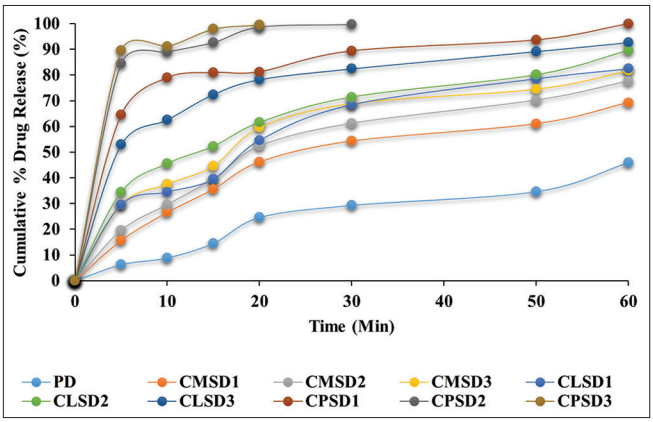

Figure 4: Zero order plots of carvedilol and its solid dispersions

Table 3: Drug content and micromeritic characteristics of carvedilol and its solid dispersions

Formulation code	Drug content (%)	Carr's index	Hausner ratio	Angle of repose (°)
Carvedilol	100.1	39.56	1.69	48.9
CMSD1	96.5	17.23	1.190	29.12
CMSD2	97.9	16.56	1.185	28.96
CMSD3	96.5	14.98	1.197	24.02
CLSD1	99.50	1369	1.165	26.35
CLSD2	97.8	13.65	1.156	27.96
CLSD3	99.5	12.95	1.165	21.26
CPSD1	96.2	14.36	1.145	29.63
CPSD2	98.6	14.39	1.158	30.27
CPSD3	99.3	14.98	1.145	25.69

Table 4: Dissolution parameters of carvedilol and its solid dispersions

Formulation code	Dissolution efficiency (DE_{20})	Number of folds increase	Release rate constant K_1 (min^{-1})	Number of folds increase
Carvedilol	8.96	-	0.0095	-
CMSD1	18.69	2.09	0.0182	1.91
CMSD2	24.69	2.76	0.02348	2.47
CMSD3	36.94	4.13	0.02568	2.70
CLSD1	23.69	2.65	0.02810	2.95
CLSD2	29.65	3.31	0.03279	3.45
CLSD3	41.26	4.60	0.03682	3.87
CPSD1	45.62	5.09	0.04684	4.93
CPSD2	68.39	7.63	0.18714	19.7
CPSD3	95.67	10.70	0.23488	24.7

(K1) and DE_{20} values were much higher in the case of solid dispersions when compared to pure drug. The dissolution data were analyzed as per the zero order and first order kinetics in each case. The R^2 values were higher in the first order model than in the zero order model indicating that the dissolution of carvedilol as such and from its solid dispersions followed first order kinetics. The corresponding dissolution rate (K_1) values of various products were estimated. The 2.70, 3.87, and 24.70 folds increase in the dissolution rate (K1) was observed with formulations CMSD3, CLSD3, and CPSD3 when compared to the pure drug, respectively. The dissolution rate (K_1) number folds increased is graphically shown in Figure 6. The DE_{20} was also increased from 8.96% in the case of carvedilol pure drug to 36.94%, 41.26%, and 95.67 % in the case of CMSD3, CLSD3, and CPSD3, respectively. The DE_{20} of pure drug and its solid dispersion comparison is graphically shown in Figure 7. Thus, solid dispersions of carvedilol prepared employing mannitol, lactose, and PEG 4000 as carrier showed marked enhancement in the DE_{20} of carvedilol. The 4.13, 4.60, and 10.70 folds increase in the DE_{20} of carvedilol was observed with solid dispersions CMSD3, CLSD3, and CPSD3, respectively.

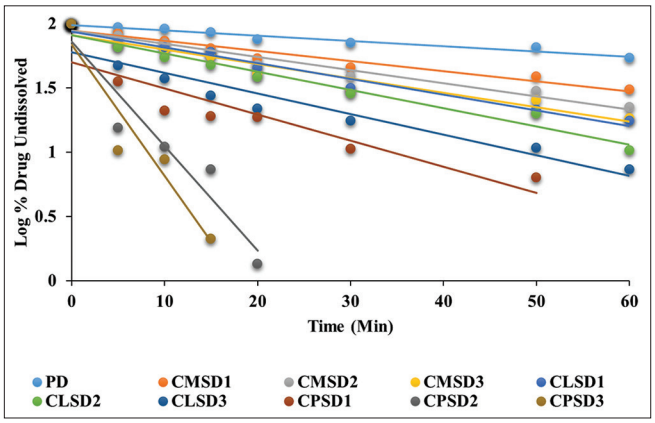

Figure 5: First order plots of carvedilol and its solid dispersions

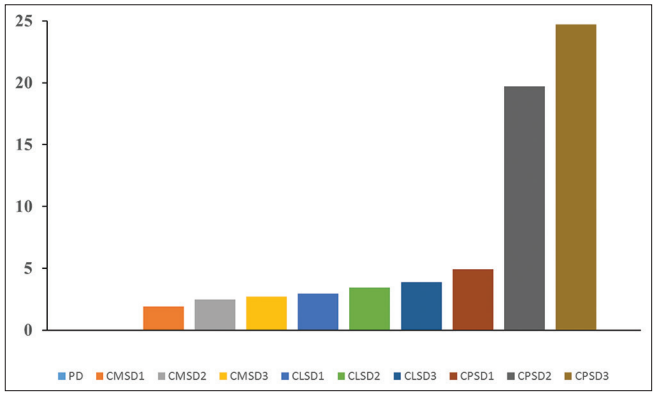

Figure 6: Dissolution rate (K_1) increase in folds chart of carvedilol and its solid dispersions

CONCLUSION

The solubility of pure drug was significantly increased in the presence of different hydrophilic carriers. Solid dispersions prepared by solvent evaporation method employing with different hydrophilic polymers such as mannitol, lactose, and PEG 4000 in various weight ratios enhanced the solubility of pure drug and gave higher dissolution. These solid dispersions were analyzed for *in vitro* dissolution profile. Solid dispersions showed a significant increase in dissolution rate (K_1) and DE_{20} in the presence of hydrophilic carriers. The increased dissolution rate was observed with increase in hydrophilic carrier concentration. From the selected hydrophilic carrier, PEG 4000 has shown significant impact on the aqueous solubility and dissolution rate of carvedilol when compared to the reaming two hydrophilic carriers.

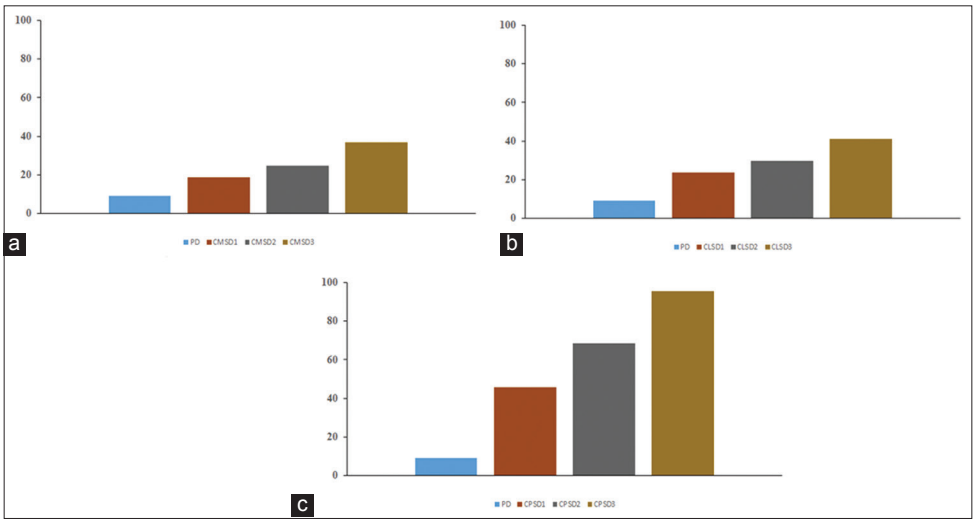

Figure 7: Dissolution efficiency (DE_{20}) comparison charts of carvedilol and its solid dispersions. (a) Pure drug and solid dispersions with mannitol. (b) Pure drug and solid dispersions with lactose. (c) Pure drug and solid dispersions with polyethylene glycol 4000

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