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Research Article

Formulation and Evaluation of Carvedilol Solid Dispersions for Dissolution Rate Enhancement

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ABSTRACT

Solid dispersions in water soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability of a range of hydrophobic drugs. The poor solubility of Carvedilol leads to poor dissolution and hence variation in bioavailability. The purpose of present investigation was to increase the solubility and dissolution rate of Carvedilol for enhancement of oral bioavailability. In the present investigation solid dispersions using various carriers like Mannitol, Lactose, Urea and PEG4000 in different ratios were prepared by Solvent evaporation method. The prepared solid dispersions were characterized for drug content, solubility and dissolution rate. The dissolution rate was substantially improved for carvedilol from its solid dispersions compared with pure drug. Dissolution of drug increased with an increase in carrier content. The dissolution rate was increased 3 folds with solid dispersions containing 1:4 ratio of drug : PEG4000.

Keywords: Carvedilol; Mannitol; Lactose; Urea; PEG4000; Solid dispersions.

INTRODUCTION

Carvedilol (CAR), an antihypertensive agent, is 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]. Carvedilol is poorly flowable and compressible drug[3]. Being categorized as class II compound as per the BCS classification system, it posses very poor bioavailability and shows significant first pass metabolism[4,5]. Moreover, it is desirable to improve the solubility as well as bioavailability of carvedilol. There were several ways in which bioavailability of the drug can be enhanced all of which aimed at increasing the surface area of the drugs which includes. Micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation, complexation with cyclodextrins[6].

The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier. 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 melting (fusion), solvent, or melting solvent method. Solid dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material[7]. 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. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution

process and drug solubility and wettability may be increased by surrounding hydrophilic carriers[8].

In this study an attempt was made to prepare Carvedilol solid dispersions by using water soluble carriers like mannitol, lactose, urea and PEG 4000 in proportions viz. 1:1, 1:2 and 1:4 (drug: carrier) by solvent evaporation method.

MATERIALS AND METHODS

MATERIALS

Carvedilol was obtained as a gift sample from Aurobindo pharma Ltd., (Hyderabad, India). Mannitol and PEG4000 were procured from Merck specialities Pvt.ltd, Mumbai. Urea was procured from Reachem laboratory chemicals Pvt. Ltd, Chennai. Lactose was procured from Molychem, Mumbai. All other reagents used were of analytical grade.

Method of estimation of Carvedilol

Stock solution was prepared by dissolving 100 mg of accurately weighed carvedilol in 100 ml of methanol to get 1 mg/ml solution. Further 10 ml of this solution was pipetted into 100 ml volumetric flask and made up to 100 ml with 0.1 N HCl to get 100 µg/ml solution. Further 10 ml of this solution was pipetted into 100 ml volumetric flask and made up to 100 ml with 0.1N HCl to get 10 µg/ml solution. From this 1, 2, 4 and 8 ml solutions were pipetted into a series of 10 ml volumetric flask and were made up to 10ml with 0.1N HCl to get 1, 2, 4 and 8 µg/ml solutions of carvedilol respectively. The absorbances of resulting solutions were measured at 244 nm[9] against the blank. A graph was plotted by taking concentration on X-axis and absorbance on Y-axis.

Preliminary solubility studies of Carvedilol

Solubility measurements of Carvedilol were performed according to a published method[10]. An excess amount of Carvedilol was added to 10ml of aqueous solution of water soluble carriers like urea, mannitol, lactose and PEG-4000 in the various ratios such as 1:1, 1:2 and 1:4 in screw capped bottles. Samples were shaken in an orbital shaker for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper grade no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Carvedilol in UV 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 bioavailability. Carvedilol solid dispersions were prepared by using carriers (i.e. mannitol, lactose urea and PEG 4000) in proportions viz. 1:1, 1:2 and 1:4 (drug: carrier) by solvent evaporation method. The drug and carrier was dissolved in methanol and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a sieve no 80. Then the prepared formulations were stored in a desiccator until further use[11].

Evaluation of solid dispersion

Solid dispersions obtained from the above method were screened for their solubility. The solid dispersion showing good solubility were further studied for drug content, micromeritic properties, in vitro release studies[12].

Solubility studies of Carvedilol solid dispersion

Solubility measurements of Carvedilol were performed according to a published method[13]. Solid dispersions equivalent to 100 mg of carvedilol was shaken with 10ml distilled water in stoppered conical flask in an orbital shaker for 24 hours at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with 0.1N HCl. The diluted solution was analyzed for the Carvedilol in UV 244 nm.

Drug content

Solid dispersions equivalent to 10 mg of Carvedilol were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 244 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows:

% Drug content = (M_{act}/M_t) X 100

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

Determination of 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 of time and tapped volume (Vt) occupied in the cylinder was measured. The bulk density and tapped/true density were calculated in gram per milliliter by the following formula:

Bulk Density= Mass/Volume= M/Vb

Tapped Density= Mass/Tapped volume =M/Vt.

Carr's index and Hausner ratio

Carr's index and hausner ratio are calculated by using following formulae[14,15]

Carr's index = [(Tapped density – Bulk density)/Tapped density] X 100

Hausner Ratio = Tapped density / bulk density
Angle of repose

A funnel was fixed in a stand in such a way that the top of the funnel was at a height of 6 cm from the surface. The Solid dispersions were passed from the funnel so that they formed a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation[16]

$$\Theta = \tan^{-1} (h/r)$$

h = Height of the heap
r = Radius of the heap

In vitro release studies

In vitro dissolution studies[17] were performed for prepared solid dispersion. The following conditions were maintained for the dissolution process:
Instrument: LABINDIA DS-8000 Dissolution test apparatus.
Apparatus: Paddle type.
Temperature: 37±0.5°C
RPM: 50
Dissolution medium: 0.1N Hcl.
Volume of medium: 900 ml.
Sampling intervals: 5, 10, 15, 20, 30, 45, 60, 90 minutes.
Sample volume: 5 ml withdrawn and replaced with 5 ml of 0.1N HCl.

Dissolution efficiency studies

The dissolution efficiency (DE) of the batches was calculated by the method mentioned by Khan[18]. 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. DE20 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 method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 1-8 µg/ml (r = 0.999).

In case of solid dispersions initially preliminary solubility analysis (Figure 1) were carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility found to be 19.3 mcg/ml (Table 1).

From this Mannitol, Lactose, Urea and PEG 4000 in the ratio of 1:1, 1:2, 1:4 are selected for the preparation of the solid dispersion. Complete composition of twelve formulations is shown in Table 2. Solid dispersions were prepared by solvent evaporation method with their respective carriers. All the SDs prepared was found to be fine and free flowing powders. After preparation of solid dispersion solubility analysis were carried out (Table 3) and compared with pure drug. The formulation with PEG 4000 in the ratio of 1:4 (drug to carrier) which had increased the solubility almost 5 fold compared to that of pure drug. (Figure **2**).

Micromeritics and morphology studies

Flowability of Carvedilol (Pure drug) and its solid dispersions was assessed by determination of Carrís index (CI), Hausnerís ratio (HR) and angle of repose. Micormeritic behaviors of the untreated carvedilol powder and all prepared solid dispersions are listed in Table 4. Table 4 shows that the flowability represented in terms of Carrís index, Hausnerís ratio and angle of repose was much improved compared to those of original powders (untreated carvedilol). In case of pure Carvedilol, powder could not pass through the funnel during the angle of repose experiment. The poor flow of carvedilol could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. These results are significantly different from those of untreated carvedilol. Actual drug content of all twelve formulations are shown in (Table 4). The drug content of the prepared SDs was found to be in the range of 95.8 - 99.49%.

Dissolution rate studies

The dissolution curves of untreated carvedilol and its solid dispersions in 0.1 M HCl (pH 1.2) are shown in Figure 3, 4, 5, 6. The release rate profiles were expressed as the cumulative percentage drug released *vs.* time. Table 5 shows percentage of drug dissolved in 90 min. Dissolution efficiency values at 20 min (DE20) for carvedilol and its solid dispersions were shown in Table 4. *In vitro* release studies reveal that there is marked increase in dissolution rate of carvedilol from all the solid dispersions when compared to pure drug itself. From the *in vitro* drug release profile, it can be seen that formulation SDP4 containing PEG 4000 (1:4 ratio of drug : PEG) shows higher dissolution rate compared with other formulations i.e., 101.3% drug release in 20 min. the increase in dissolution rate is in the order of SDP4 > SDP2 > SDU4 > SDP1 > SDU2 > SDU1 > SDL4 > SDL2 > SDL1 > SDM4 > SDM2 > SDM1>PD.

CONCLUSION

Solid dispersions prepared from hydrophilic polymers like mannitol, lactose, urea, PEG4000 using the solvent evaporation technique were effective in improving drug dissolution. These solid dispersions were analyzed for solubility and *in*

vitro dissolution profile. Dissolution of drug increased with an increase in carrier content. Solid dispersions prepared with PEG 4000 had shown enhanced solubility with improved dissolution rate.

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Table 1: Preliminary solubility studies of Carvedilol

S.No	Carrier (Drug:Carrier)	Solubility mcg/ml
1	Pure drug	19.3
2	Carvedilol+Mannitol	24.57
3	Carvedilol+Mannitol	26.41
4	Carvedilol+Mannitol	29.53
5	Carvedilol+Lactose	35.51
6	Carvedilol+Lactose	42.23
7	Carvedilol+Lactose	46.89
8	Carvedilol+Urea	52.33
9	Carvedilol+Urea	58.55
10	Carvedilol+Urea	62.71
11	Carvedilol+PEG 4000	68.55
12	Carvedilol+PEG 4000	72.59
13	Carvedilol+PEG 4000	77.88

Table 2: Formulation plan of Carvedilol solid dispersions

S.No	Formulation	Composition	Drug : Polymer
1	SDM1	Carvedilol+Mannitol	1:1
2	SDM2	Carvedilol+Mannitol	1:2
3	SDM4	Carvedilol+Mannitol	1:4
4	SDL1	Carvedilol+Lactose	1:1
5	SDL2	Carvedilol+Lactose	1:2
6	SDL4	Carvedilol+Lactose	1:4
7	SDU1	Carvedilol+Urea	1:1
8	SDU2	Carvedilol+Urea	1:2
9	SDU4	Carvedilol+Urea	1:4
10	SDP1	Carvedilol+PEG 4000	1:1
11	SDP2	Carvedilol+PEG 4000	1:2
12	SDP4	Carvedilol+PEG 4000	1:4

Table 3: Solubility studies of Carvedilol Solid dispersions

S.No	Carrier (Drug:Carrier)	Solubility mcg/ml
1	Carvedilol+Mannitol(1:1)	27.52
2	Carvedilol+Mannitol(1:2)	28.71
3	Carvedilol+Mannitol(1:4)	32.67
4	Carvedilol+Lactose(1:1)	48.019
5	Carvedilol+Lactose(1:2)	53.36
6	Carvedilol+Lactose(1:4)	59.2
7	Carvedilol+Urea(1:1)	68.41
8	Carvedilol+Urea(1:2)	69.5
9	Carvedilol+Urea(1:4)	75.54
10	Carvedilol+PEG 4000(1:1)	79.6
11	Carvedilol+PEG 4000(1:2)	87.02
12	Carvedilol+PEG 4000(1:4)	93.96

Table 4: Drug content, micromeritic properties, solubility and dissolution efficiency of Carvedilol and its solid dispersions

Sample	Drug content (%)	Carr's index	Hausner ratio	Angle of repose(°)	Aqueous solubility(mcg/ml)	Dissolution efficiency
Pure drug	100	38.37	1.62	45	19.3	16.68
SDM1	96.4	16.77	1.201	30.32	27.52	17.95
SDM2	97.6	16.62	1.199	29.72	28.71	20.90
SDM4	95.8	16.52	1.197	29.51	32.67	27.13
SDL1	99.49	16.19	1.193	29.68	48.019	22.51
SDL2	98.8	14.33	1.167	29.24	53.36	25.67
SDL4	97.8	13.98	1.162	28.59	59.2	26.76
SDU1	99.5	15.22	1.179	30.03	68.41	27.96
SDU2	97.4	14.20	1.165	29.56	69.5	28.25
SDU4	96.5	14.15	1.164	27.47	75.54	58.97
SDP1	98.8	14.29	1.166	26.56	79.6	42.31
SDP2	98.7	14.10	1.164	24.54	87.02	59.30
SDP4	97	13.83	1.16	22.68	93.96	92.01

Table 5: Cumulative % drug release of carvedilol solid dispersions

Time (min)	PD	SDM1	SDM2	SDM4	SDL1	SDL2	SDL4	SDU1	SDU2	SDU4	SDP1	SDP2	SDP4
5	9.7	27.62	37.34	51.33	36.45	51.68	62.47	69.15	74.05	80.55	76.99	84.74	88.40
10	18.6	38.11	45.56	65.25	53.31	65.51	71.28	75.15	76.42	86.26	80.00	87.71	92.27
15	24.8	45.19	55.26	71.40	62.96	70.07	72.38	79.48	80.50	88.61	84.36	88.28	96.35
20	28.1	52.12	65.28	75.00	71.78	76.87	80.62	83.48	84.06	90.07	87.23	91.44	101.3
30	30.3	60.42	71.34	79.24	73.24	78.71	82.31	84.92	88.44	95.47	90.30	97.29	-----
45	35.5	67.62	75.21	80.48	78.63	81.37	86.06	89.66	91.33	99.55	92.30	100.49	------
60	37.3	70.66	77.40	81.63	82.44	85.29	88.66	92.64	96.28	------	99.04	------	------
90	42.2	77.46	82.54	83.94	86.01	88.51	91.46	94.92	98.58	-----	-------	------	------

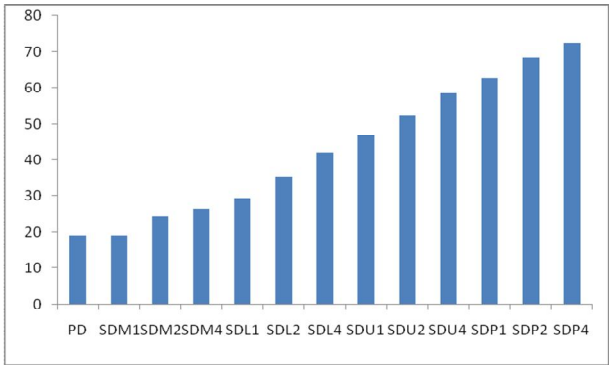

Fig. 1: Preliminary solubility studies of Carvedilol

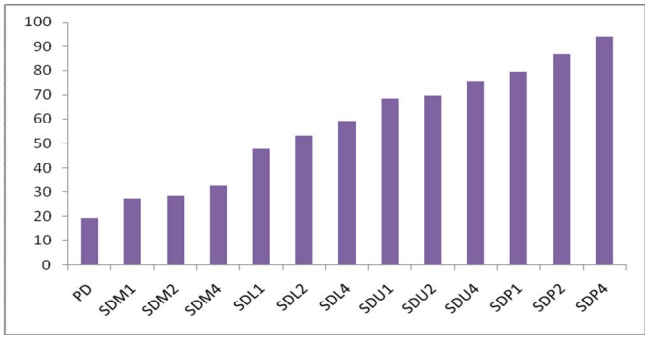

Fig. 2: Solubility studies of Carvedilol Solid dispersions

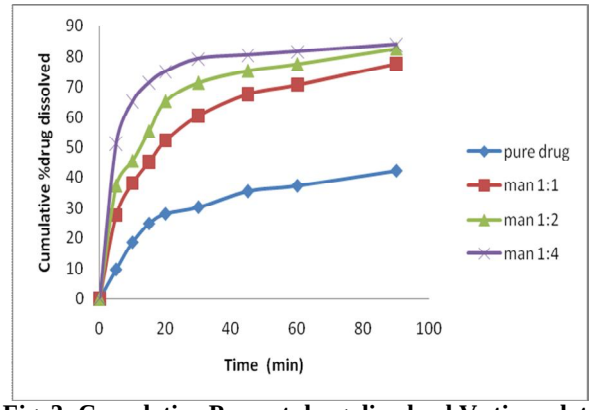

Fig. 3: Cumulative Percent drug dissolved Vs time plots of Carvedilol solid dispersions containing Mannitol

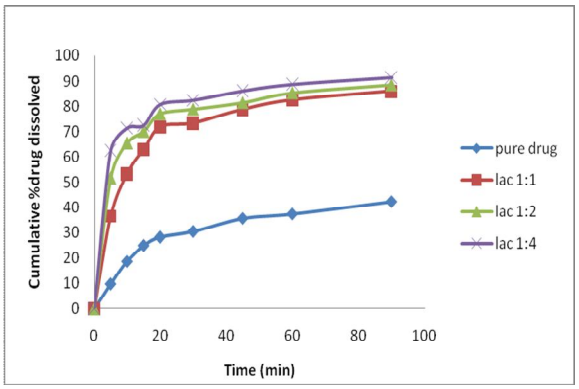

Fig. 4: Cumulative Percent drug dissolved Vs time plots of Carvedilol solid dispersions containing Lactose

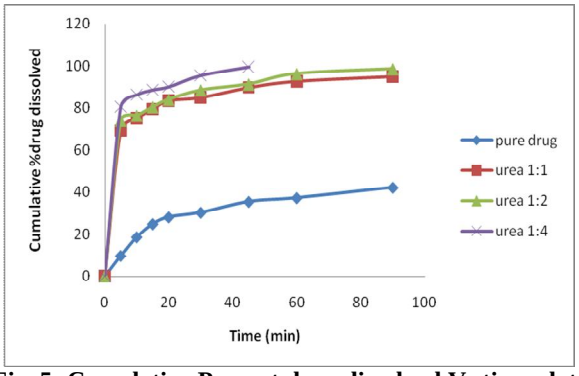

Fig. 5: Cumulative Percent drug dissolved Vs time plots of Carvedilol solid dispersions containing Urea

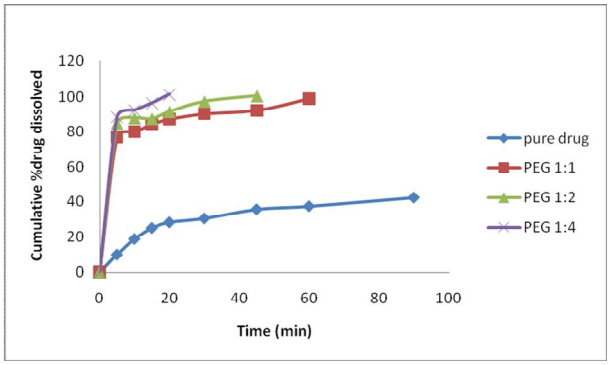

Fig. 6: Cumulative Percent drug dissolved Vs time plots of Carvedilol solid dispersions containing PEG4000

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