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ENHANCEMENT OF DISSOLUTION PROPERTIES OF CARVEDILOL BY SOLID DISPERSION TECHNIQUE USING SYLYSIA

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ABSTRACT

The objective of present study was to enhance the dissolution rate of Carvedilol (CAR) by using Solid dispersion technique. 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. Carvedilol (CAR) is a beta blocker drug. In the present investigation Solid dispersions (SD) were prepared by employing different grades of silica gel (Sylysia). They were prepared by Solvent evaporation and kneading methods in three different mass ratios 1:1, 1:2 and 1:3. Comparison of the methods was also investigated. Physicochemical characterisation of disperse systems was carried out using differential scanning calorimetry(DSC), fourier transform infrared spectroscopy(FTIR). Dissolution tests were conducted and evaluated on the basis of cumulative percentage drug release. The prepared Solid dispersions were also evaluated for precompression parameters like angle of repose, bulk & tapped density, drug content, Carr's index and Hausner's ratio. Improved dissolution was observed in 1:3 ratio disperse system of kneading method compared to solvent evaporation method. Physicochemical characterisation results suggested that CAR existed in amorphous form in all dispersion systems which show that dissolution can be enhanced.

Key words: Carvedilol, Dissolution, Kneading method, Solvent evaporation, Solid dispersions, Sylysia.

INTRODUCTION

Oral route of drug administration is the most common method of drug delivery. For oral administration the drug must possess good solubility, however most of orally administered drugs have a reduced bioavailability due to poor solubility. In British Classification System (BCS) drugs with low aqueous solubility, slow dissolution rate, high dose and high permeability are categorized as class-II drugs [1]. To overcome the low bioavailability solubility of drug can be enhanced either by particle size reduction, floating granules, cryogenic technology solid dispersions, nano suspension, micronization [2] etc.

Solid dispersion is widely used technique to improve the bioavailabilty of poorly water soluble drugs [3]. In SD systems, a drug may exist as an amorphous form in polymeric carrier and this may result in improved dissolution rates and solubility compared with crystalline material. In SD's the hydrophobic drug is dispersed in a carrier matrix which is generally hydrophilic. It enhances solubility by reducing particle aggregation, eliminating crystalanity, increasing wettability, dispersabilty and altering the surface properties [4] of drug particles.

When SD is exposed to aqueous media the carrier dissolves and drug releases as fine colloidal particles, the resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In order to prepare solid dispersions, solvent evaporation [5-9] or kneading method is commonly adopted. Each method has its advantages and disadvantages. Solid method can be used for thermolabile drugs as minimal heat is required in this process.

In the present study SD's of CAR were prepared using solvent and kneading method with different grades of Sylysia as carrier. Sylysia is an amorphous silica gel

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characterized by high purity and hygroscopity which is used in pharmaceutical, nutraceutical, food and cosmetic industry. It is available in different grades, the nature of carriers used to prepare SD's typically influence the type of method employed. Carvedilol (CAR) is a beta blocker drug. and is freely soluble in methanol, but it is practically insoluble in water which makes it a suitable candidate for solid dispersion formulation [10,11] in order to characterize the physicochemical properties of solid dispersions, the formulation were tested using DSC, FTIR…

MATERIALS & METHODS

Carvedilol(CAR) is a gift sample from Heterolabs, Hyd., India. Sylysia was produced from Fuji chemicals, Japan. All other materials and reagents were of analytical grade.

Preparation of Solid Dispersions

They were prepared with three different mass ratios 1:1, 1:2 and 1:3 by Solvent evaporation and kneading methods.

Solvent evaporation method

Solvent evaporation method of drug (CAR):carriers were prepared at three different mass ratios(1:1, 1:2 and 1:3).CAR was dissolved in methanol to get clear drug solution. After that carrier (passed through sieve no.#80)was then added to clear drug solution and stirring. The solvent (methanol) was removed by evaporation technique (or) dried properly using heating mantle at 45ºc for 60min. The mass obatained was further dried at 50ºc for 24hrs in an hot air oven. The product was crushed, pulverized and passed through a sieve number #80. The prepared/obtained product was then filled in glass bottles, sealed and stored in a desicator until further use.

Kneading method

In kneading method the drug (Carvedilol) and surface active carriers SYL770 FCP, SYL 550 FCP, SYL 440 FCP in the ratio of i.e., 1:1, 1:2 and 1:3 were weighed accurately and triturated in a mortar and pestle by adding drop by drop of methanol for size reduction of the particles. This method was continued for nearly 45 min and made into dough like mass. The Kneaded dispersion was dried at 50°C for 24hrs in an Hot air oven. The product was crushed, pulverized and passed through a sieve number # 80. The prepared/obtained product was then filled in glass bottles, sealed and stored in a desicator until further use. The data for composition of solid dispersions was given in the Table 1.

Estimation of Carvedilol

10 mg of Carvedilol was accurately weighed and transferred into 10 mL volumetric flask, dissolved in few ml of methanol and the final volume was made upto 10 mL with methanol to get a stock solution of concentration 1mg/ml. From stock solution further dilutions were made to get the solution ranging from 1 µg/mL to 5 µg/mL. The absorbance of these solutions was measured at 341 nm in UV-Visible Spectrophotometer (Elico SL 150). The absorbance was plotted against concentration of CAR. The method obeyed Beer's law in the concentration of 1-5 µg/mL. The data was given in the Table 2 and shown in (Fig 1) was added.

Solubility determination

Solubility studies were performed according to the method described by Higuchi and Connors [12]. An excess of Carvedilol was added to 5mL of each fluid in a 25 mL stoppered conical flasks and the mixture were shaken for 48 hrs at room temperature (25±1°C) on a rotory flask shaker. After 48 hrs of shaking 1 mL aliquots were withdrawn and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for drug measuring absorbance at 341 nm. Shaking was continued until three constructive estimations were same. The solubility experiments were run in triplicate. The results are given in Table 3 and shown in (Fig 2) was added.

In-vitro dissolution studies of CAR Solid Dispersion

The quantity of Solid Dispersion equivalent to 200 mg of CAR was placed in dissolution medium. The dissolution study of dispersion was conducted using dissolution testing apparatus II (paddle method) in 900 ml of 0.1N HCl solution at 37±0.5°C and at speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain volume after each sampling and analyzed Spectrophotometrically at 341 nm against suitable blank using UV-visible Spectrophotometer (Elico SL150) and given in (Table 4) and shown in (Fig 3), first order and Hixson crowell plots were shown in (Fig 4,5)

Differential Scanning Calorimetry (DSC)

Approximately 2 mg of CAR Solid Dispersion samples were taken in aluminum pan, sealed with aluminum cap and kept under nitrogen purging [13] (atmosphere). The samples were scanned from 30.0-300.0°C with the scanning rate of 10.00°C rise/min using differential scanning calorimeter (DSC). It is given in (Table 5) and shown in (Fig 6,7).

Fourier Transform Infrared spectroscopy (FT-IR)

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra [14]. The solid dispersions were evaluated for physical properties like angle of repose, bulk & tapped density,carr's index, hausner ratio and data was given in (Table 7-9). ATR analysis is less complicated than using KBr pellets, it is fast and a very small amount of the sample is needed. It is given in (Table 6) and shown in (Fig 8-15).

EVALUATION

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane.

The angle of repose was determined by funnel method suggested by Newman. Angle of repose is determined by following formula:

$$\theta = Tan^{-1}\frac{h}{r}$$

Where,

θ = angle of repose,

h = height of the cone

Bulk density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/mL and is given by

$$D_t = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

Tapped density (D_t)

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

$$D_t = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

Carr's Index (I)

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

$$I = (D_t - D_b/D_t \times 100$$

Where, D_t is the tapped density of the powder

D_b is the bulk density of the powder.

Compressibility Index and Hausner's ratio (H)

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of the bulk density, size, shape, surface area, moisture content and cohesiveness of the materials. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

$$\text{Compressibility Index} = (1\text{-}V/V_0) \times 100$$

Where,

V = volume of powder blend before tap

V_0 = volume of powder blend after 100 tappings.

Hausner's ratio (H) is a number that is correlated to the flowability of a powder. The Hausner's ratio is related to the Carr's Index by the formula

$$H = 100/(100\text{-}C)$$

Hausner's ratio also expressed as,

$H = D_t / D_b$ (or) **Hausner's ratio = tapped density/ bulk density**

RESULTS AND DISCUSSION

In-vitro dissolution studies

The tablets were evaluated for *in-vitro* dissolution studies in 0.1N HCl Solution. The average dissolution study data of all the formulations were shown.

Among all the formulations, Solid dispersions prepared with SYL 550 (KM 1:3) showed about 99.60±0.27% i.e. highest drug release in 60 min and SD's containing SYL 770 (KM 1:3) showed faster drug release of about 75.51±1.10% in 20 min. Pure drug showed drug release about 59.81±0.74% in 60 min but lesser amount of the drug release compared with SD's prepared with SYL 550 FCP (KM 1:3) and SYL 770(KM 1:3).

The DSC thermo grams were recorded using a differential scanning calorimeter. Approximately 2-5 mg of each sample was heated in a pierced aluminum pan from 25°C to 300°C at a heating rate of 10°C/min under a stream of nitrogen [15, 16]. The DSC thermo grams of Pure CAR, Solid Dispersions prepared using SYL 550 shown. The DSC thermo gram of CAR exhibits endothermic peak at 122.0°C corresponding to its melting point and is confirmed by literature data. Solid Dispersion of CAR and SYL 550 showed endothermic peak at 118.8°C which shows a weak interaction in the Solid Dispersion.

Table 1. Composition of Solid Dispersions

1

Methods	Mass Ratio	Solvent	Trituration/ Kneaded Time	Temp.Time	Sieve No:
Solvent Evaporation method (SE)	1:1, 1:2, 1:3	Methanol	……..	HAO at 50°C For 24 hrs	#80
Kneading method (KM)	1:1, 1:2, 1:3	Methanol	45 (min)	HAO at 50°C For 24 hrs	#80

Table 2. Calibration curve data for the estimation of Carvedilol

SI No.	Concentration (µg/mL)	Absorbance (at 341 nm)
1	1	0.195
2	2	0.273

3	3	0.388
4	4	0.466
5	5	0.599

Values are mean, SD ± n=3

Table 3. Solubility analysis data of CAR in various Buffers

S. No	Solution	Concentration (mg/mL)
1	Distilled water	0.021
2	Ph 1.2 Buffer	0.35
3	Ph 6.8 Buffer	0.07
4	Ph 7.4 Buffer	0.024

Table 4. Comparison of *in-vitro* dissolution profile of Carvedilol in Pure form and its Solid Dispersions with SYL 770 FCP, SYL 550 FCP, SYL 440 FCP KNEADING METHOD (KM), [KM-I (1:3), KM-II (1:3), KM-II (1:3) and (PD)

Time (min)	Mean % CAR released (x ± SD n=3) (KM 1:3)			
	KM I	KM II	KM III	PD
0	0	0	0	0
5	58.46±1.26	57.38±1.70	50.34±2.33	30.04±4.26
10	66.31±1.19	69.83±1.39	55.21±3.22	33.56±3.75
15	72.54±1.27	76.87±2.13	58.73±3.37	35.45±2.82
20	75.51±1.35	83.36±1.72	66.04±2.78	38.16±3.27
30	79.30±1.76	89.05±1.81	72.81±1.88	50.34±2.58
45	84.45±1.48	93.92±1.92	73.89±3.71	53.81±2.29
60	87.15±2.33	99.60±0.32	76.06±3.87	59.81±1.10

Table 5. Data for Differential Scanning calorimeter (DSC)

DSC	PURE DRUG (CAR)	CAR:SYL 550 (KM 1:3)
PEAK	122.4°C	118.2°C

Table 6. Compatibility studies for Solid Dispersions by FT-IR

Frequency	Functional group	Pure carvedilol	CAR+SYL(770)	CAR+SYL(550)	CAR+SYL(440)
3100-3000	Aromatic CH stretch	3028.27	3010.79	3011.30	3011.48
1600-1585	Aromatic C=C stretch	1586.42	1587.72	1589.00	1589.39
1600-1585	Aromati C-C stretch	1606.30	1598.33	1504.67	1588.69
1250-1020	Alicyclic C-N stretch	1039.79	1212.70	1212.71	1091.52
3500-3220	Alicycic N-H stretch	3338.41	3480.10	3460.84	3398.77
1150-1085	Ether C-O stretch	1155.00	1089.85	1086.36	1091.32
3550-3220	Alcoholic O-H stretch	3642.48	3460.10	3300.66	3340.84
3350-3310	Aliphatic N-H stretch	3028.27	3741.10	3011.30	3367.20
3000-2840	Aliphatic C-H stretch	2875.00	2945.57	2948.12	2969.71
1124-1087	Alcoholic C-O stretch	1039.72	1089.65	1212.71	1091.22

Table 7. Physical Evaluation of Solid Dispersions CAR with SYL 770 FCP

Parameters	Solvent Evaporation (SE)			Kneading Method (KM)		
	SE 1:1	SE 1:2	SE 1:3	KM 1:1	KM 1:2	KM 1:3
Angle of Repose (degrees)	22.66 ±0.16	21.45 ±0.33	24.33±0.46	26.02 ±0.02	26.28 ±0.31	23.22±0.38
Bulk density (g/cc)	0.78 ±0.32	0.77 ±0.24	0.79±0.26	0.93 ±0.44	0.92 ±0.67	0.87±0.49
Tapped density(g/cc)	0.96 ±0.21	0.95 ±0.54	0.92±0.47	1.01 ±0.05	0.99 ±0.21	0.92±0.58
Carr's Index (%)	18.64	15.25	11.26	9.72	8.65	16.27
Hausner's ratio	1.336	1.346	1.075	1.098	1.085	1.318
Flow comment	Good	Good	Excellent	Excellent	Excellent	Good
Drug content (%)	95.21±.058	95.36±0.71	98.26±0.21	98.84±0.55	99.05±0.45	96.38±0.69

Table 8. Physical Evaluation of Solid Dispersions CAR with SYL 550 FCP

Parameters	SE -II1:1	SE -II1:2	SE-II1:3	KM-II1:1	KM-II1:2	KM-II1:3
Angle of Repose (degrees)	22.66± .16	21.45± 0.33	25.93± 0.06	26.02 ±0.02	26.28± 0.31	21.33± 0.34
Bulk density(g/cc)	0.78 ±0.32	0.77 ±0.24	0.91 ± 0.42	0.93 ±0.44	0.92 ±0.67	0.86±0.36
Tappeddensity(g/cc)	0.96 ± 0.21	0.95 ± 0.54	0.98± 0.51	1.01 ± 0.05	0.99 ± 0.21	0.98± 0.55
Carr'sIndex (%)	18.64	15.25	9.55	9.72	8.65	10.05
Hausner's ratio	1.336	1.346	1.096	1.098	1.085	1.066
Flow comment	Good	Good	Excellent	Excellent	Excellent	Excellent
Drug content (%)	95.21±.058	95.36±.71	98.78±0.65	98.84±0.55	99.05±0.45	98.66±0.66

Table 9. Physical Evaluation of Solid Dispersions CAR with SYL 440 FCP

Parameters	Solvent Evaporation (SE)			Kneading method(KM)		
	SE 1:1	SE 1:2	SE 1:3	KM 1:1	KM 1:2	KM 1:3
Angle of Repose (degrees)	20.74 ±0.12	20.86±0.48	24.22±0.36	26.22±0.92	25.50±0.42	25.18±0.66
Bulk density (g/cc)	0.72 ±0.84	0.74 ±0.24	0.80±0.72	0.83 ±0.56	0.85 ±0.24	0.84±0.36
Tapped density (g/cc)	0.92 ±0.10	0.92 ±0.52	0.95±0.22	0.95 ±0.21	0.96 ±0.05	0.97±0.07
Carr's Index (%)	18.54	18.09	9.69	9.42	9.45	9.72
Hausner's ratio	1.156	1.21	1.06	1.042	1.021	1.018
Flow comment	Good	Good	Excellent	Excellent	Excellent	Excellent
Drug content (%)	92.45±0.55	94.01±0.76	98.03±0.075	97.74±0.26	98.34±0.056	98.29±0.078

Fig 1. Calibration curve of Carvedilol

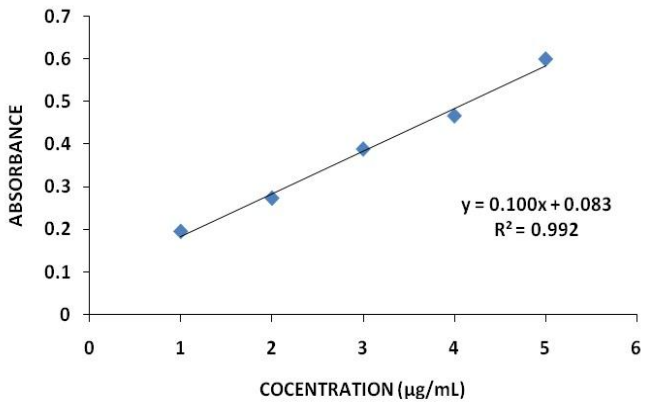


Fig 2. Solubility analysis plot of CAR in various buffer Solutions

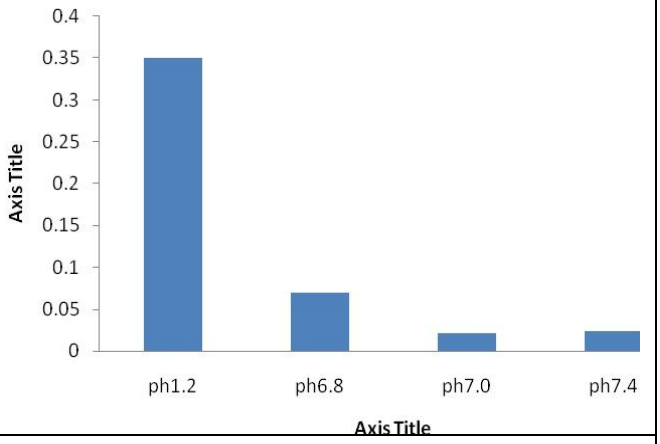


Fig 3. Comparative *in-vitro* dissolution profiles of Carvedilol Solid Dispersions (KM), [KM-I (1:3), KM-II (1:3), KM-III (1:3)] and Pure drug (PD)

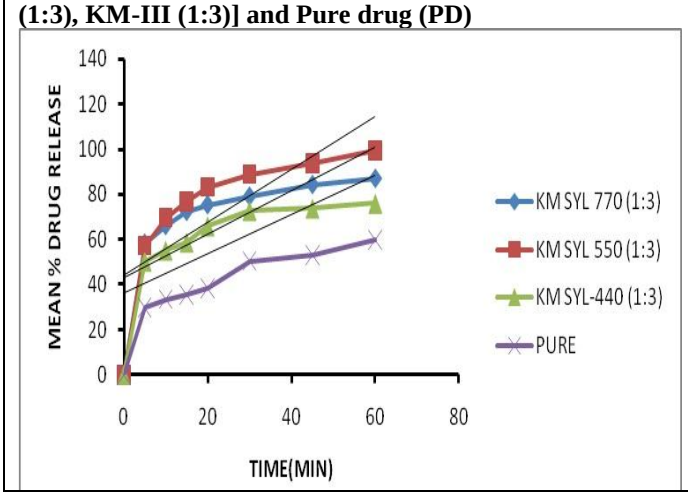


Fig 4. First order plot of Carvedilol Solid Dispersions (KM), [KM-I (1:3), KM-II (1:3), KM-III (1:3)] and Pure drug (PD)

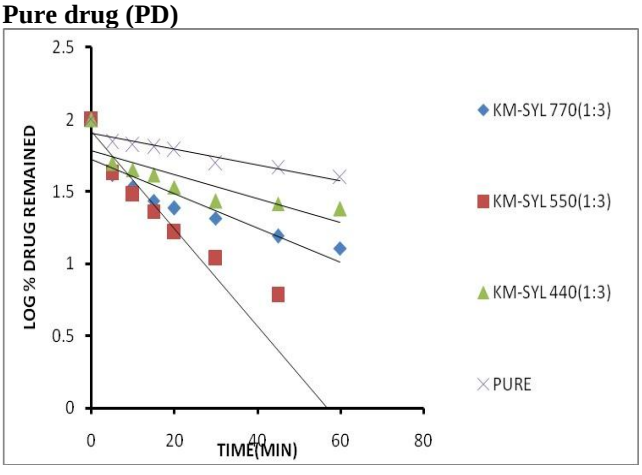


Fig 5. Hixson-Crowell's dissolution plots of Carvedilol Solid Dispersions (KM), [KM-I (1:3), KM-II (1:3), KM-III (1:3)] and Pure drug (PD)

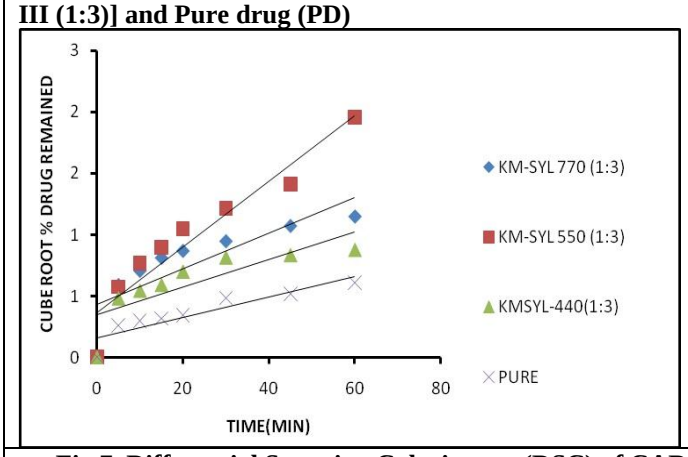


Fig 6. Differential Scanning Calorimetry (DSC) of pure CAR

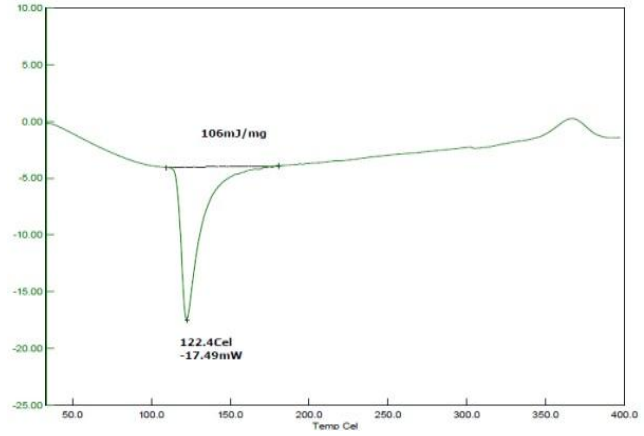


Fig 7. Differential Scanning Calorimetry (DSC) of CAR: SYL 550(1:3) Solid dispersion prepared by Kneading method

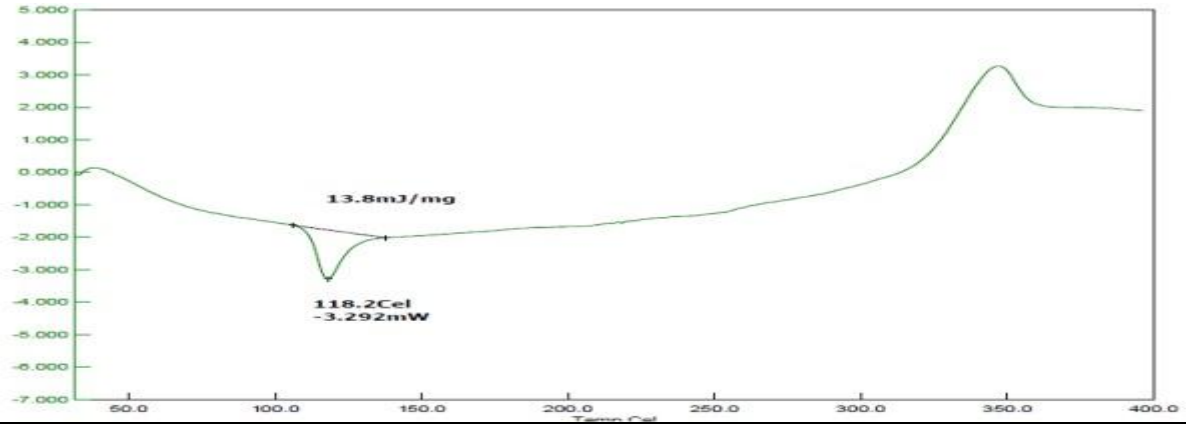


Fig 8. FT-IR spectra of Pure CAR (E1)

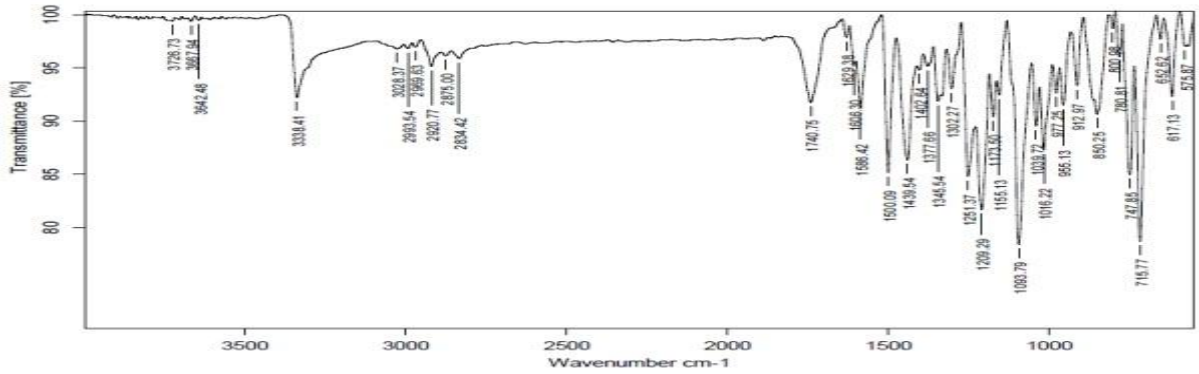


Fig 9. FT-IR spectra of physical mixture of CAR with SYL-770 FCP (E2)

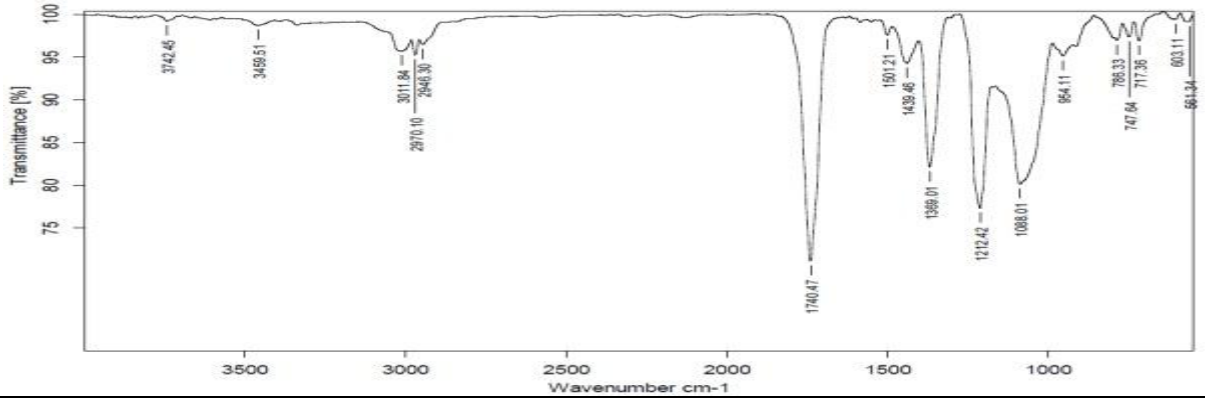


Fig 10. FT-IR spectra of kneading method mixture of CAR with SYL 770 (E3)

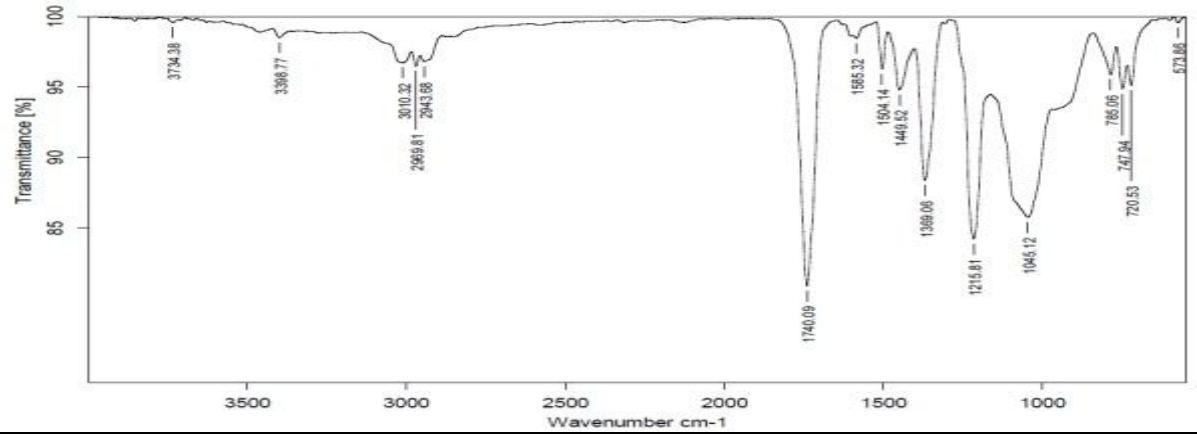


Fig 11. FT-IR spectra of physical mixture of CAR with SYL-550 FCP (E4)

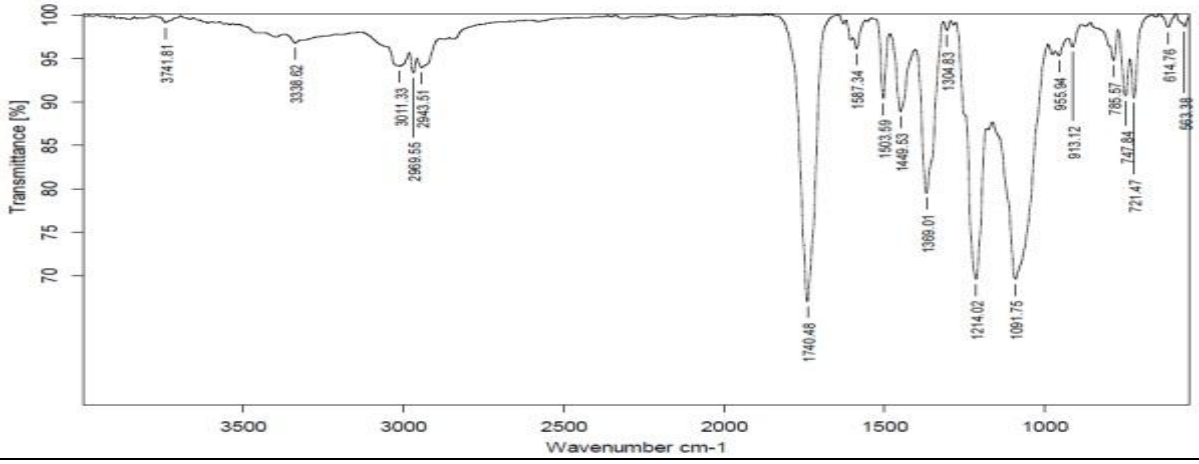


Fig 12. FT-IR spectra of kneading method mixture of CAR with SYL 550 FCP

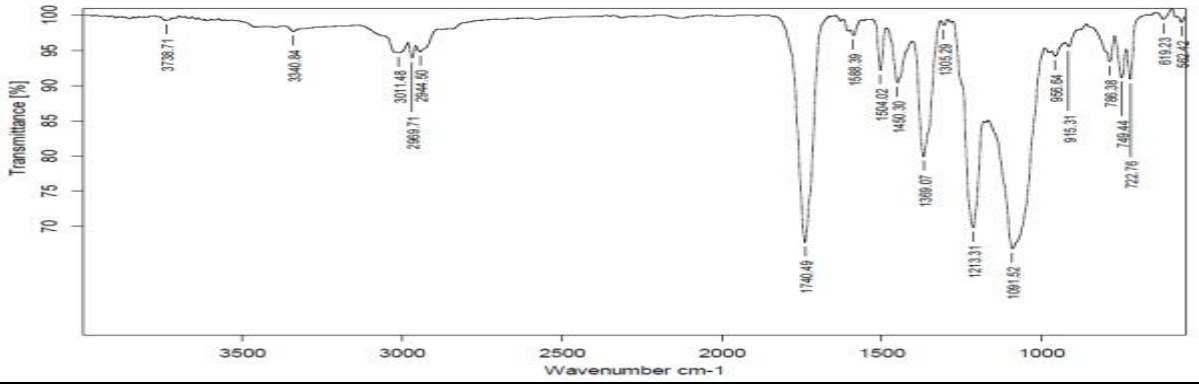


Fig 13. FT-IR spectra of physical mixture of CAR with SYL-440 FCP (E6)

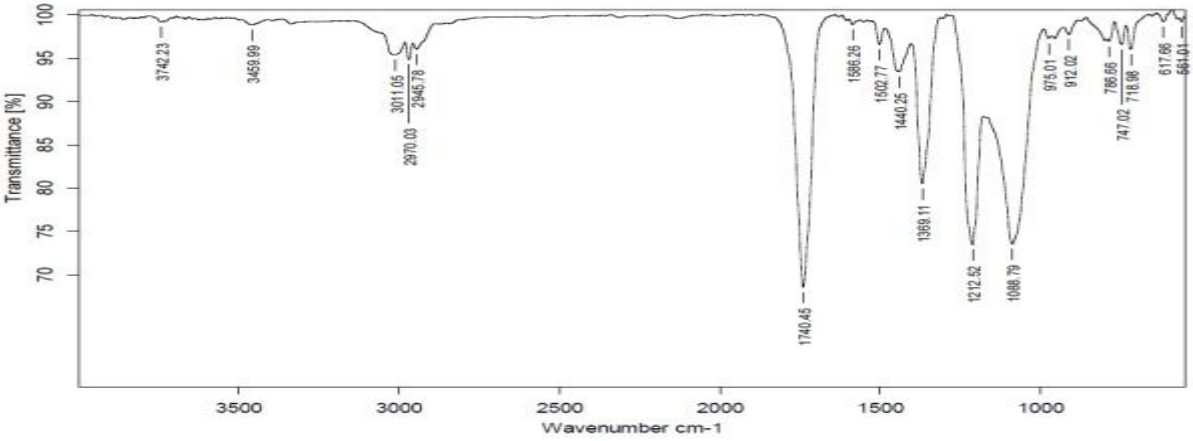


Fig 14. FT-IR spectra of kneading method mixture of CAR with SYL 440 FCP

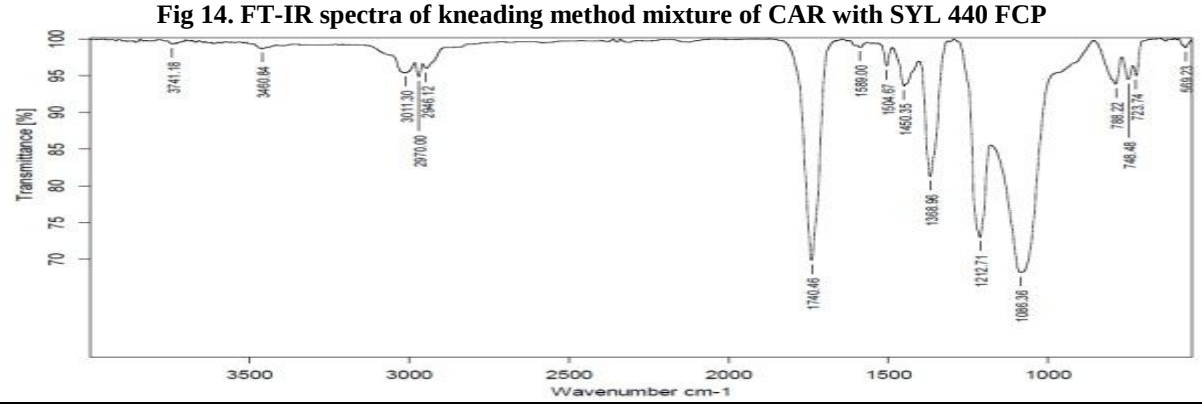
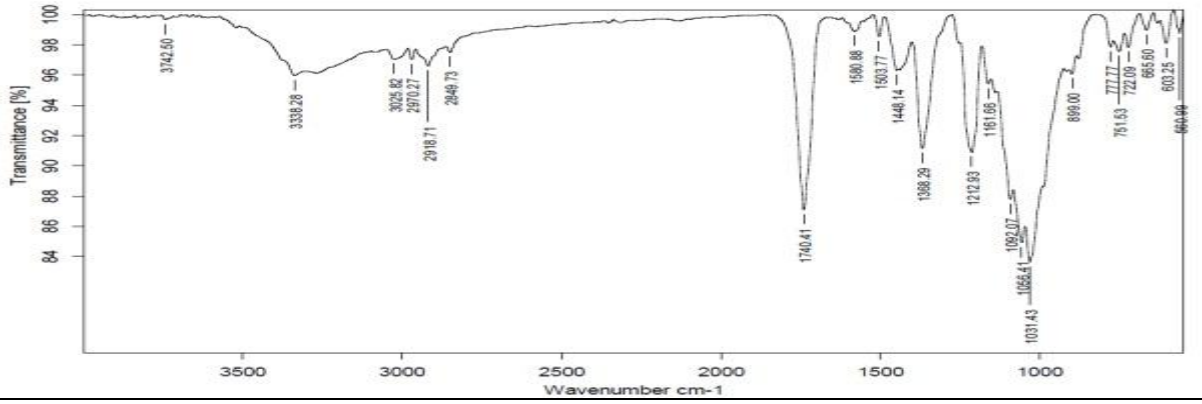


Fig 15. FT-IR spectra of tablet formulation of CAR with SYL 550 FCP



CONCLUSION

From the above results it can be concluded that solid dispersions improved the dissolution rate of poorly soluble drug Carvedilol(CAR). 1:3 ratio kneaded systems showed better drug release compared to dispersions of solvent evaporation method. The DSC thermograms of solid dispersions showed a shift in endothermic peak compared to pure drug which indicates complete amorphization of drug polymer.

From the FTIR data it has been observed that there is no reaction between drug and the carrier when compared to pure drug.

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