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Formulation and evaluation of mouth dissolving tablets containing carvedilol solid dispersion

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ABSTRACT

The solubility behavior of drug is one of most challenging aspect in formulation development. The purpose of the study was to improve the physicochemical properties of carvedilol like solubility, dissolution properties and stability of poorly soluble drug by forming solid dispersion. Two methods solvent evaporation and fussion methods were employed for the formation of the solid dispersions. Solid dispersions of carvedilol were prepared using combination of two carriers i.e. nicotinamide, polyvinylpyrrolidone (PVP) K30 for the selection of an optimized solid dispersion. The results from the differential scanning calorimetry (DSC), X-ray diffraction patterns (XRD) and scanning electron microscopy (SEM) showed that solid dispersion exist in the amorphous form, hence showed marked increase in the saturation solubility and dissolution rate of carvedilol than that of pure drug. Based on the physical characters and in-vitro drug release pattern, ratio 1:5:3 w/w/w (Drug: nicotinamide: PVP K30) solid dispersion prepared by fusion method, was selected as ideal batch for incorporation in mouth dissolving tablet. The mouth dissolving tablets of carvedilol were prepared by direct compression method. The prepared MDT was evaluated for hardness, friability, weight variation, wetting time, disintegration time and drug content analysis. All these properties were found to be ideal. The in vitro release of carvedilol from its solid dispersion incorporated MDTs was significantly improved when compared to it marketed product.

Key word: Solid dispersion, Mouth dissolving tablets, Carvedilol, Solubility

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INTRODUCTION

Most of the new chemical entities (NCEs) are poorly water soluble drugs [1] not well-absorbed after oral administration, which can detract them from their inherent efficacy [3, 4, 5]. Moreover, most promising NCEs, despite their high permeability are generally not well absorbed due to low solubility [6, 7]. Frequently dissolution is the rate-controlling factor in the bioabsorption of these drugs, as it is often the slowest of the various stages involved in the release of the drug from its dosage form and passage into systemic circulation. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [6, 8]. Solid dispersion is one of the most successful strategies to improve drug release, thus increasing their bioavailability and reducing side effects [9, 10]. The carvedilol is the drug candidate chosen for the study. Carvedilol is white crystalline powder, chemically (±)1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy) ethyl] amino]-2-propanol with a molecular weight of 406.5 g/mol and molecular formula $C_{24}H_{26}N_2O_4$. Carvedilol is an alpha as well as beta adrenoreceptor-blocking agent used in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrhythmia and hypertension. It is soluble in ethanol and practically insoluble in water (6-8 µg/ml). carvedilol, an inherently long-acting beta-blocker, was classified according to the Biopharmaceutical Classification System as a drug with low solubility and it is presented as an immediate-release dosage form in the World Health Organization essential drug list. Thus solid dispersion technique was used to enhance drug dissolution. The mouth dissolving tablets of prepared solid dispersion were prepared to make the drug available in a soluble

form in the mouth, which facilitate its absorption from the buccal cavity. The drug disperses and dissolves in the saliva which passes into the stomach. In such cases the bioavailability of the drug increases. Many elderly patients have difficulty in swallowing tablets, capsules and powders. To alleviate this problem, these mouth dissolving tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease.

MATERIALS AND METHODS

Carvedilol was obtained as a gift sample from Maxtar Bio-Genics (Baddi). Polyvinyl pyrrolidone K30, Sodium carboxymethyl cellulose and Sodium starch glycolate were of analytical reagent (AR) grade, and purchased from Central Drug House (P) Ltd, (New Delhi). Nicotinamide and microcrystalline cellulose were purchased from Loba Chemie (P) Ltd, (Mumbai). All other chemicals and solvents used were of analytical reagent grade.

Preparation of solid dispersion by solvent evaporation method

The solid dispersions were prepared with combination of drug: nicotinamide: PVP K30 in 1:5:1, 1:5:3, 1:5:5 w/w/w ratios by mean of solvent evaporation method using ethanol as solvent as given in Table 1. This solution was continuously stirred using a magnetic stirrer until the solvent was evaporated and then dried overnight at 50^0C. The samples thus obtained were pulverized using mortar pestle and sieved through a 60 mesh screen.

Preparation of solid dispersion by fusion method

Carvedilol, PVP K30 and nicotinamide were accurately weighed according to the weight ratio of the formulation listed in Table 1. The mixture was melted at 110 ±5 ^{o}C on hot plate. When mixture was completely dissolved the melt was poured on a stainless steel plate and closed at ambient temperature. It was then stored in vaccum overnight before being pulverized. The resulting powder was sieved to 60 mesh and stored in desiccator for further use.

Preparation of physical mixtures

The physical mixture of carvedilol, nicotinamide and PVP K30 were prepared by geometrical mixing method. The physical mixture of carvedilol with PVP K30 (CPP) and nicotinamide (CNP) in 1:7 w/w, 1:10 w/w ratio were prepared by blending them with triturating for 10 min followed by sieving through 60 mesh screen.

Table 1: Composition of carvedilol solid dispersion prepared by solvent evaporation method and fusion method using combination of carriers

S. No.	Formu	Drug:nicotinamide:PVP K30 (w/w/w)	Method of preparation
1	F1	1:5:1	Fusion
2	F2	1:5:3	Fusion
3	F3	1:5:5	Fusion
4	F4	1:1:5	Solvent evaporation
5	F5	1:3:5	Solvent evaporation
6	F6	1:5:5	Solvent evaporation

Characterization of solid dispersions

Saturation solubility in 0.1N HCl

The saturation solubility study of pure drug (carvedilol), physical mixtures and its solid dispersions were carried out by adding an excess amount of carvedilol alone, physical mixtures and solid dispersions into separate 20 ml glass tubes containing each 10 ml of 0.1 N HCl. The tubes were sealed and agitated at 120 rpm in thermostated shaking water bath at 25 ± 0.5^{o}C for 24 hours. After 24 hours the samples were filtered through a 0.45 µm millipore filter and samples obtained were suitably diluted. Each diluted samples were than analyzed spectrophotometrically at 284 nm.

In vitro drug dissolution studies of carvedilol, physical mixtures and solid dispersion

The *in vitro* drug release for all the solid dispersion, physical mixtures and carvedilol batches were measured in USP II dissolution apparatus (Paddle type). The dissolution media used was 900 ml of 0.1 N HCl. In each dissolution vessel quantities of solid dispersions equivalent to 12.5 mg of carvedilol were placed. The test was performed at 37 ± 0.5 °C with rotation speed of 50 rpm. 10 ml aliquots of dissolution medium were withdrawn at predetermined time point of 5, 10, 15, 30, 45, 60, 90, and 120 minutes and replaced with 10 ml of fresh dissolution medium kept at 37 ± 0.5 °C. The samples withdrawn were filtered through 0.45 µm millipore filters and assayed spectrophometrically for the drug at 284 nm.

Differential scanning calorimetry

The thermal behavior of carvedilol, nicotinamide, PVP K30 and solid dispersions was investigated using a Diamond DSC (Perkin Elmer, USA). Accurately weighed samples (10 mg) were heated in hermetically sealed standard aluminum pans. The thermograms were obtained over the temperature range of 100-200 °C with heating rate of 10 °C min^{-1} under the nitrogen atmosphere maintained at a flow rate of 20 ml/min.

X-ray diffraction studies

The X-ray diffraction (XRD) studies were carried out to determine the physical state of the drug in the solid dispersions and physical mixtures. The X-ray diffraction (XRD) pattern of carvedilol, nicotinamide, PVP K30, physical mixtures and solid dispersions were recorded on a scanning powder X-ray diffractometer using an X' Pert PRO instrument, equipped with an X' Pert PRO Data Collector software. The radiation used was generated by a Cu Kα source fitted with a Ni filter at 0.154 nm wavelengths at 40 mA and 45 kV. Samples were scanned for 2θ values over a range from 5 - 45°, at a scan rate of 10°/min. The X ray diffractograms of powdered samples of carvedilol, nicotinamide, PVP K30, physical mixtures and solid dispersions were compared.

FTIR spectroscopy

FTIR spectra of the carvedilol, physical mixture and solid dispersions were taken using Rkin-Elmer FT-IR spectrometer. Potassium bromide pellet method was employed and back-ground spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 500-4000 cm^{-1} at spectral resolution of 2 cm^{-1} and ratio against background interferogram.

Scanning electron microscopy (SEM)

The samples were coated with a thin gold-palladium layer using a sputter coater unit and the surface topography was analyzed with a scanning electron microscope operated at an acceleration voltage of 15 kV.

Preparation of mouth dissolving tablets

The mouth dissolving tablets of carvedilol were prepared by direct compression method according to the proportions given in Table 2. The raw material were passed through screen (40 mesh) prior to mixing. The powdered sample of ratio 1:5:3 w/w/w (Drug: nicotinamide: PVP K30) solid dispersion prepared by fusion method, containing amount equivalent to 12.5 mg of carvedilol was mixed with other excipients. Finally talc and magnesium stearate were added and mixed for 10 minutes. The prepared final powder blend was compressed using single punch tablet compression machine. The tablet weight was adjusted to 230 mg.

Table 2: Composition of carvedilol mouth dissolving tablets

S. No.	Ingredients	FD1	FD2	FD3	FD4	FD5	FD6	FD7	FD8
1	Carvedilol	12.5	12.5	12.5	12.5	-	-	-	-
2	*SD eq. of carvedilol	-	-	-	-	12.5	12.5	12.5	12.5
3	Sodium starch glycolate	-	-	4.6	9.2	-	-	4.6	9.2
4	Croscarmelose sodium	2.3	4.6	-	-	2.3	4.6	-	-
5	Xylitol	46	46	46	46	46	46	46	46
6	MCC	46	46	46	46	46	46	46	46
7	Talc	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
8	Mg. stearate	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6
9	Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10	Total weight of tablet	230	230	230	230	230	230	230	230

**SD eq. Refers to amount (mg) of solid dispersion equivalent to. All the quantities are in mg*

Evaluation of flow properties of final powder blend of different batches

Angle of Repose

The angle of repose is measure of extent of interparticle forces or index of flow. The angle of repose was determined by fixed funnel method in which the funnel was secured with its tip at a given height above a graph paper placed on a horizontal flat surface. The powdered blends were poured carefully through the funnel until apex of conical pile just touches the tip of funnel. The radius of the base of the cone was measured. The angle of repose was measured using the following equation.

$$\text{Angle of repose "Q"} = \text{Tan}^{-1}\left[\frac{H}{R}\right]$$

Where**,** H = Distance between tip of funnel and the base, R = Radius of the base of the cone.

Bulk Density and Tapped density

The bulk density of final powdered blend was determined by pouring 10 gram of final blend of a given batch into a 250 ml graduated glass cylinder which was kept at an angle of 45 degree to horizontal while pouring. The cylinder was straightened up and the volume occupied by the material was noted down. The bulk density was calculated by dividing the weight by the occupied volume. After noting the bulk density the glass cylinder containing final blend was tapped initially 500 times followed by 750 times and lastly 1250 times if needed and final tapped volume was determined (USP 30 NF 25). The tapped density was calculated by dividing the weight by the final tapped volume.

$$\text{Bulk density} = \frac{M}{V_1}$$

$$\text{Tapped density} = \frac{M}{V_2}$$

Where M = mass of test sample, V_1 = unsettled apparent volume and V_2 = final tapped volume.

Compressibility index and Hausner ratio

The Carr compressibility index and Hausner ratio of the powdered blend were computed on the basis of tapped density and bulk densities.

$$\text{Carr compressibility index} = \frac{(\text{Tapped density} - \text{bulk density}) \text{ X } 100}{\text{Tapped density}}$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of carvedilol mouth dissolving tablets

The prepared mouth dissolving tablets were evaluated for various official specifications.

Hardness

The crushing strength of the tablets (hardness) was measured using a Monsanto hardness tester. The force required to crush the tablet was measured in Kg / cm^2. The test was done in triplicate for each batch.

Friability

The friability of a sample of 10 tablets was measured using a Roche Friabilator. Ten preweighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated using formula:

$$\% \text{ Friability} = \frac{(W_i - W_f) \times 100}{W_i}$$

Where W_i = initial weight of tablets
W_f = final weight of tablets

Weight variation

20 tablets of each batch were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight.

Wetting time

The wetting time of the tablets was evaluated by the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. A preweighed tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time.

In vitro dispersion time

The tablet was added to 10 ml of water and time required for complete dispersion was measured. Three tablets from each formulation batches were randomly selected and *in vitro* dispersion time was performed.

Drug content analysis

Twenty tablets were accurately weighed and finally powdered. The quantity of powder equivalent to 12.5 mg of carvedilol was taken and dissolved in 100 of methanol. The samples were filtered through a 0.45µm millipore filter

and samples obtained were suitably diluted. Each diluted samples were than analyzed spectrophotometrically at 284 nm.

In vitro dissolution study of tablets

The *in-vitro* dissolution study of tablets was carried out using USP II dissolution apparatus (Paddle method). The in-vitro dissolution media used was 0.1 N HCl. The mouth dissolving tablet of formulation batch was dropped into 900 ml of dissolution media maintained at a temperature of 37±0.5°C and stirred at a specified rpm i.e. 50 rpm. 10 ml aliquots of dissolution medium were withdrawn at time interval of 5, 10, 15, 30, 45, 60 minutes which was replaced with 10 ml of fresh dissolution medium kept at 37± 0.5°C. The samples withdrawn were filtered through 0.45 µm millipore filters, diluted and assayed at 284nm using a UV-visible double beam spectrophotometer.

RESULTS AND DISCUSSION

Characterization of solid dispersions

Saturation solubility study

The saturation solubility of the pure drug, physical mixtures and solid dispersions prepared by different carriers and different methods as shown in Table 3 and Figure. 1. Carvedilol is almost insoluble in 0.1 N HCl with saturation solubility of 0.063 mg/ml. The physical mixtures of carvedilol with nicotinamide and PVP K30 leads to increase in solubility whereas a significant increase in solubility in 0.1 N HCl was obtained for the solid dispersions prepared with different carriers and methods.

Table 3: Solubility data of carvedilol and physical mixtures in 0.1 N HCl

Formulation	Solubility (mg/ml)
Carvedilol	0.063±0.035
CNP	0.153±0.037
CPP	0.168±0.029

Data are represented as mean ±S.D (n=3)

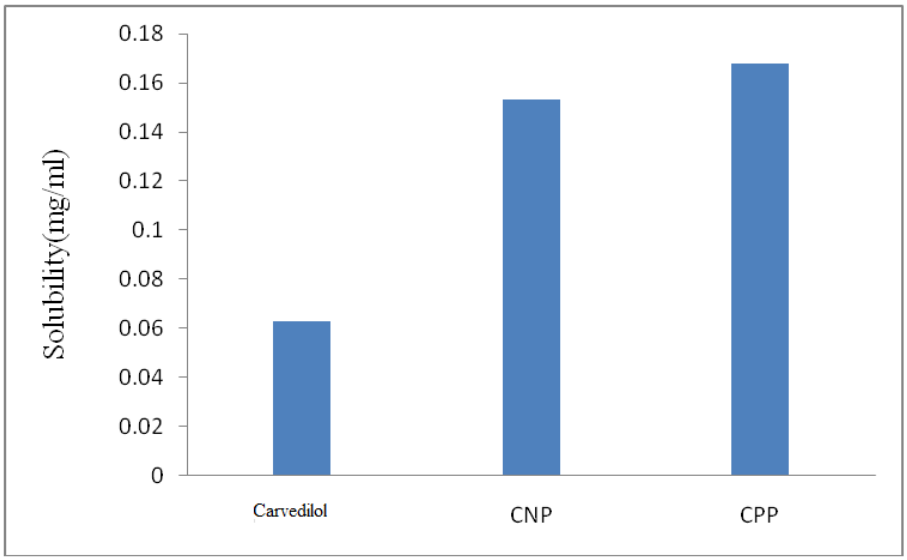

Figure. 1: Solubility graph of carvedilol and physical mixtures

In vitro Dissolution study of carvedilol, physical mixtures and solid dispersions

In the dissolution study, the carvedilol alone yielded the slowest initial dissolution rate when compared with the physical mixtures as shown in Table 4 and Figure. 2. The dissolution rates of solid dispersion were greater than those from physical mixtures and carvedilol alone as shown in Figure. 2 and 3.

Further combinations of carriers were used to prepare the solid dispersions. Based upon the result, F2 batch with drug: nicotinamide: PVP K30 in ratio of 1:5:3 w/w/w prepared by fusion method showed maximum dissolution rate as shown in Figure. 3. This batch (F2) was converted into a cost effective tablet formulation with improved dissolution.

Table 4: Dissolution profile of carvedilol and physical mixtures

Time(min)	% Cumulative release		
	Carvedilol	CNP	CPP
0	0.0	0.0	0.0
10	24.95±0.345	34.25±0.070	36.33±0.212
15	27.94±1.411	39.1±0.431	42.32±0.566
30	29.87±0.566	41.79±0.423	45.85±0.778
45	33.48±0.423	43.56±0.211	48.69±0.424
60	36.30±1.130	46.27±0.211	49.31±1.272
90	39.81±0.566	48.29±0.354	52.13±0.849
120	41.25±0.211	50.57±0.283	54.45±0.495

Data are represented as mean ±S.D (n=3)

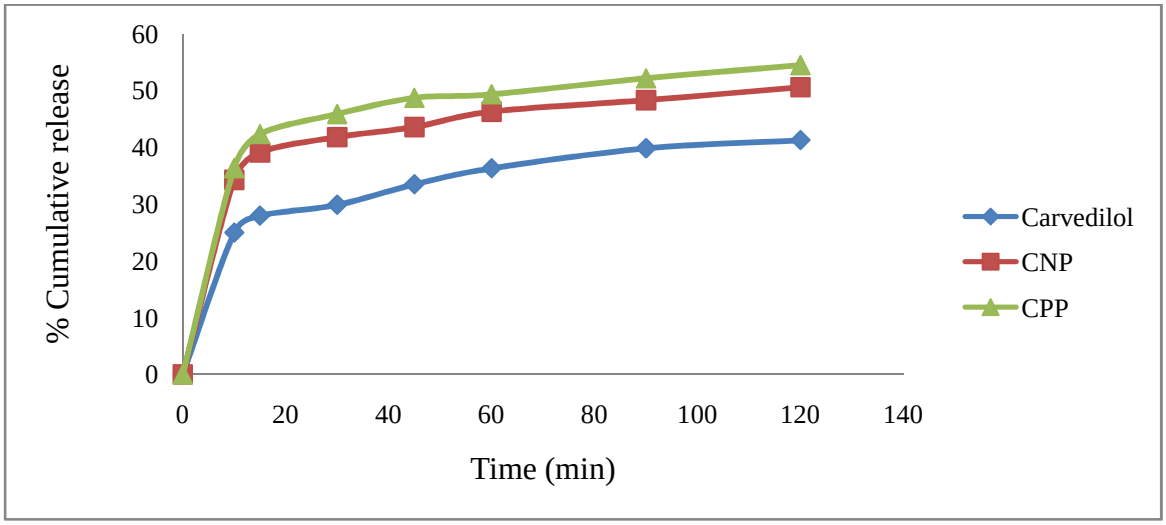

Figure. 2: Plot of *in vitro* drug release of carvedilol and its physical mixtures with carriers

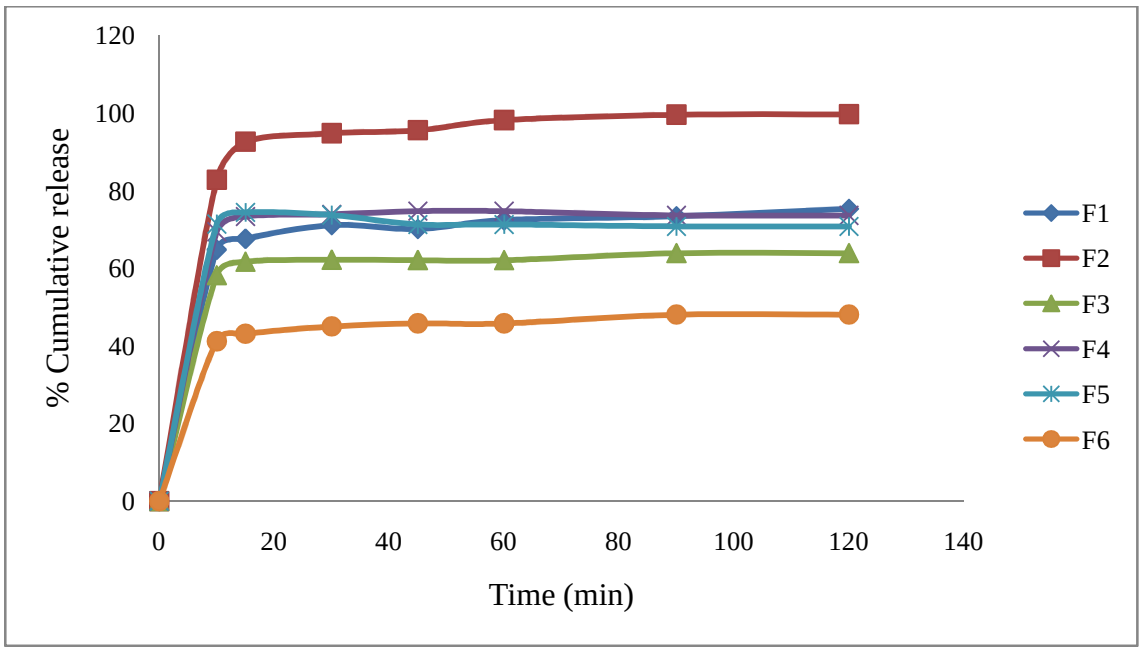

Figure. 3: Plot of *in vitro* drug release of carvedilol from solid dispersion prepared by using nicotinamide and PVP K30 as combined carriers by fusion method and solvent evaporation method

Differential scanning calorimetry

The DSC thermogram obtained from carvedilol, nicotinamide, PVP K30 and the solid dispersion with nicotinamide and PVP K30 are shown in Figure. 4. The DSC thermogram of carvedilol alone showed a sharp endothermic peak at 114 °C, which is in agreement with the theoretical melting point of the crystalline form of carvedilol. For nicotinamide DSC thermogram show a sharp peak at 127 ^{0}C corresponding to its melting point as shown in Figure.

4. In case of solid dispersion the characteristics endothermic peak, corresponding to drug melting was broadened with reduction of height of peak and shifted toward a higher temperature with reduced intensity. It may be attributed to change in physical state of carvedilol from crystalline to amorphous form due to solid dispersion.

Table 5: Dissolution profile of solid dispersion prepared by using nicotinamide and PVP K30 as combined carriers by fusion method and solvent evaporation method

Time(min)	% Cumulative release					
	F1	F2	F3	F4	F5	F6
0	0.0	0.0	0.0	0.0	0.0	0.0
10	64.8±0.984	82.8±0.259	58.2±0.654	69.4±0.485	71.4±0.341	41.2±0.982
15	67.6±0.323	92.6±0.965	61.7±0.581	73.3±0.347	74.4±0.653	43.1 ±.748
30	71.1±0.456	94.8±0.728	62.2±1.376	73.9±0.684	73.7 ±1.43	45.1±0.154
45	70.1±0.765	95.6±0.593	62.1±0.573	74.7±0.576	71.3±0.357	45.8±0.874
60	72.4±0.211	98..2±0.593	62.1±0.573	74.7±0.576	71.3±0.357	45.8±0.874
90	73.4±0.458	99.6 ±0.110	63.9±0.891	73.6±0.935	70.8±0.492	48.6±0.387
120	75.3±1.287	99.7 ±0.714	63.9±0.891	73.6±0.935	70.8±0.492	48.6±0.387

Data are represented as mean ±S.D (n=3)

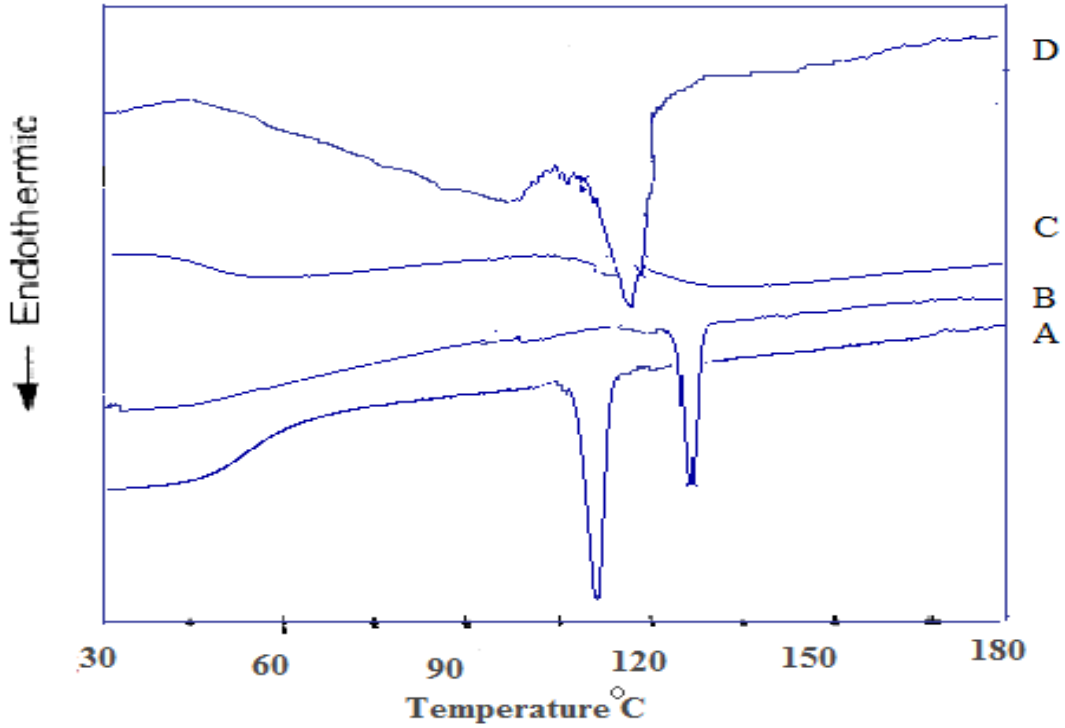

Figure. 4: The DSC thermogram of (A) Carvedilol, (B) Nicotinamide, (C) PVP K30 (D) Solid dispersion (Drug: nicotinamide: PVP K-30 in 1:5:3)

Powder X-ray diffraction study

The PXRD graph of carvedilol, nicotinamide, PVP K30, and solid dispersions of F2 batch obtained by fusion method were shown in Figure. 5. The PXRD spectra of carvedilol show numerous distinct peaks for crystallinity at 2θ value of 6, 11.5, 13, 15, 17, 18.5, 24, 26 and 29^{o} indicating that carvedilol present in the highly crystalline form. The major X-ray diffraction peaks of carvedilol solid dispersion were suppressed or absent, indicating the decrease in the crystallinity of the carvedilol. These results of PXRD were strongly supported by the above DSC observations.

Fourier transform infrared spectroscopy

The infrared spectra of pure carvedilol, physical mixtures and solid dispersion (F2) as shown in Figure. 6. Carvedilol showed characteristic peaks at 3344.23 cm–^{1} (O-H stretching), 2923.35 cm^{-1} (Amine stretching), 1593.42 cm^{-1} (N-H bending vibrations) and 1249.79 (O-H bending and C-O stretching) cm^{-1} and 1020.27 cm^{-1}(alkyl aryl ether bending vibration) and the solid dispersion showed the similar characteristic absorption band with out any significant change in the wave number of drug indicating no chemical interaction between drug and carriers.

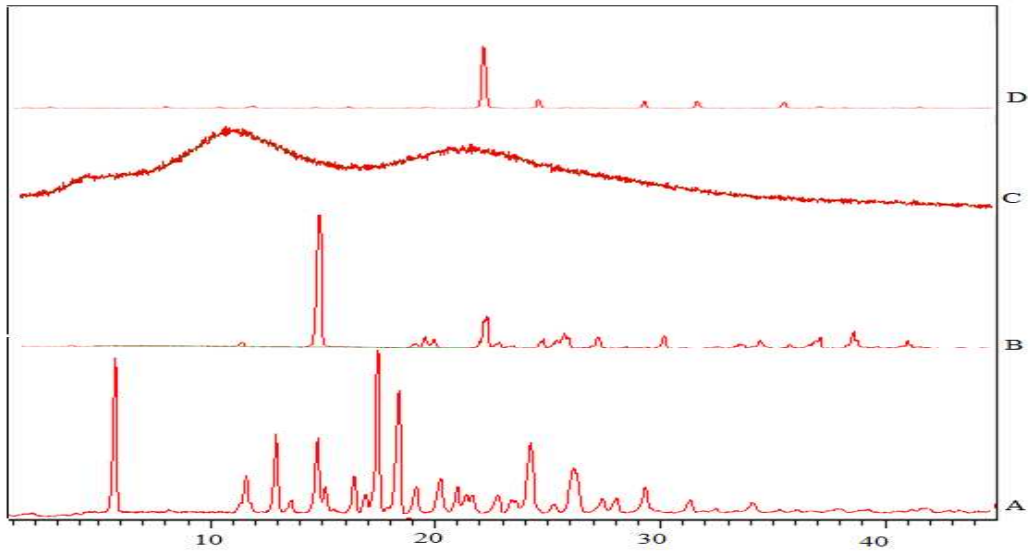

Figure. 5: PXRD of (A) Carvedilol (B) Nicotinamide (C) PVP K30 (D) Solid dispersion (F2)

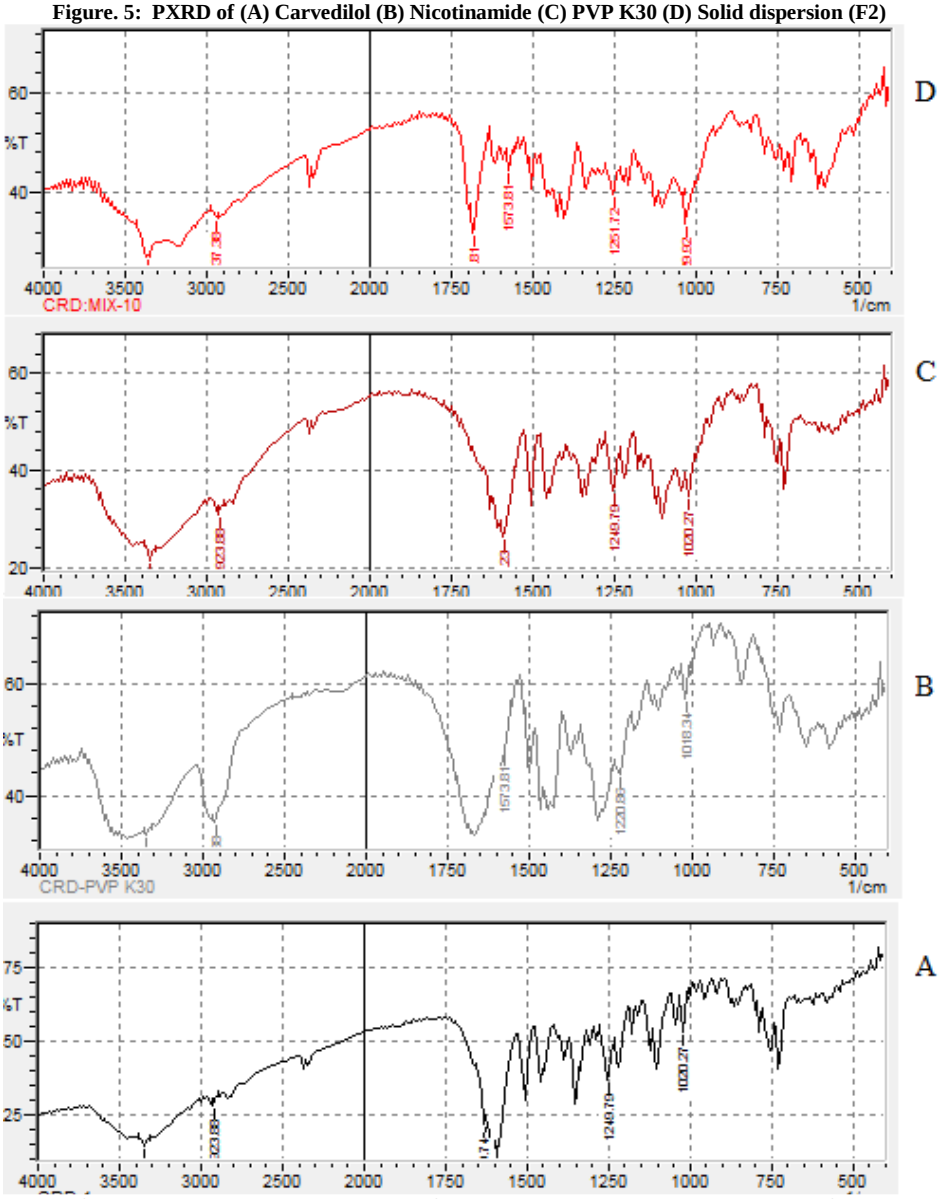

Figure. 6: FTIR spectra of (A) Carvedilol (B) Physical mixture of drug and PVP K30 (C) Physical mixture of carvedilol and nicotinamide (D) Solid dispersion (F2)

Scanning electron microscopy

The scanning electron microphotographs of carvedilol, and solid dispersion prepared with nicotinamide and PVP K30 are shown in Figure. 7. The micro photographs of carvedilol consisted of mixture of some large crystals with micro particles. Solid dispersion on the other hand looked like an irregular shaped matrices. Therefore it is possible that the reduced particle size, increased surface area and the close contact the hydrophilic carriers and the drug may be responsible for enhanced dissolution of solid dispersion.

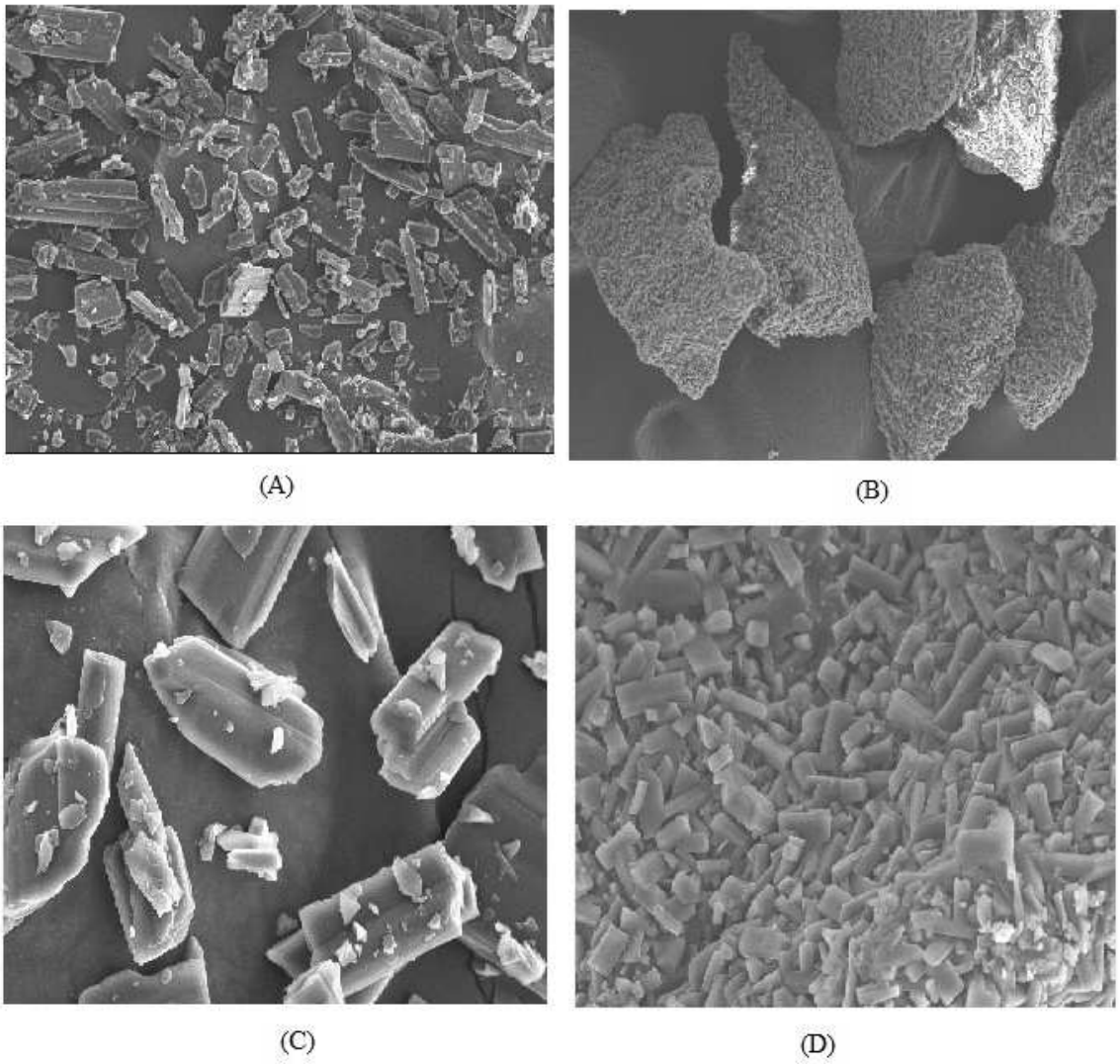

Figure. 7: Scanning electron microscope photographs: (A) Carvedilol (Magnification at ×200) (B) Solid dispersion (F2) (Magnification at ×200) (C) Carvedilol drug (Magnification at ×1000) (D) Solid dispersion (F2) (Magnification at ×1000

Table 6: Pre compression parameters of final powder blend

Formulation code	Angle of repose (degree)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio	Compressibility Index (%)
FD1	23.61±0.042	0.587±0.125	0.677±0.182	1.153	13.293
FD2	24.58±0.124	0.554±0.098	0.634±0.154	1.144	12.618
FD3	24.37±0.172	0.529±0.157	0.609±0.133	1.151	13.136
FD4	24.29±0.059	0.565±0.169	0.647±0.083	1.145	12.673
FD5	23.78±0.158	0.638±0.089	0.746±0.014	1.169	14.477
FD6	22.55±0.071	0.675±0.157	0.804±0.149	1.191	16.044
FD7	24.98±0.082	0.703±0.142	0.837±0.045	1.190	16.009
FD8	23.91±0.143	0.684±0.148	0.815±0.057	1.191	16.073

Data are represented as mean ±S.D (n=3)

Evaluation of final powder blend and mouth dissolving tablets

Pre compression parameters of final powder blend

The values of pre compression parameters evaluated were within prescribed limits and indicated good free flowing properties. The results are shown in Table 6.

Post compression parameters

The results of all the post compression parameters are shown in Table 7 and 8. In all the formulations, hardness and friability test was found with in pharmacopoeia limit indicating good mechanical strength. Drug content was found to be high and uniform in all formulations. The tablets were subjected for evaluation of *in vitro* dispersion time. The formulations prepared with solid dispersion were showed dispersion time between the ranges of 36 – 49 sec. In all the formulations the *in vitro* dispersion time decreased with increase in the concentration of sodium starch glycolate and croscarmellose sodium. As the dissolution process of the tablet depend upon the wetting time followed by *in vitro* dispersion time of tablet. Wetting time of the prepared tablets is shown in Figure. 8. The measurement of wetting time is conformation test for the evaluation of such tablets. It was observed as the concentration of croscarmellose sodium increased the time taken for wetting was reduced.

Table 7: Results of post compression parameters of mouth dissolving tablets

Formulation code	Hardness(kg/cm^2) mean±S.D)	Friability (%) mean ± S.D (n=6)	Dispersion time(seconds) mean ± S.D (n=6)
FD1	3.8±0.10	0.648±0.12	47±1.25
FD2	3.6±0.19	0.519±0.14	43±1.98
FD3	4.0±0.17	0.634±0.08	44±0.87
FD4	3.8±0.19	0.515±0.18	37±0.73
FD5	3.6±0.07	0.636±0.16	46±1.98
FD6	3.8±0.14	0.602±0.18	36±0.67
FD7	4.0±0.17	0.694±0.20	43±0.53
FD8	3.9±0.11	0.546±0.15	41±0.84

Table 8: Results of post compression parameters of mouth dissolving tablets

Formulation code	Weight variation mean ± S.D (n=20)	Drug content %	Wetting time (seconds) mean ± S.D (n=3)
FD1	234±0.91	99.43	37±1.31
FD2	231±1.78	98.78	39±1.05
FD3	233±1.58	98.73	36±1.55
FD4	234±1.84	99.08	33±1.39
FD5	232±1.47	99.71	39±1.76
FD6	236±1.19	98.37	30±0.49
FD7	232±1.39	98.38	37±1.49
FD8	234±1.24	98.53	34±1.59

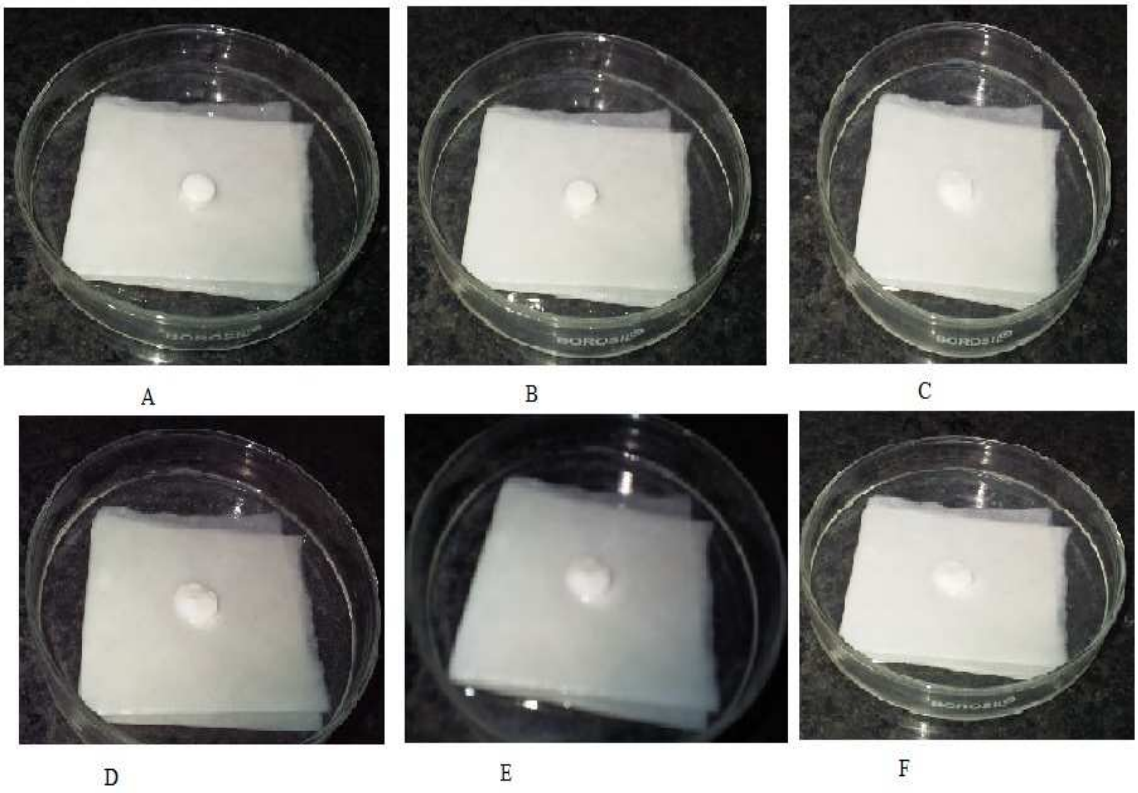

Figure. 8: Images showing wetting time of MDTs (A) 5 sec, (B) 10 sec, (C) 15 sec, (D) 20 sec, (E) 25 sec and (F) 35 sec

***In vitro* dissolution studies**

All the prepared batches of tablets were characterized by a uniform thickness, weight and diameter. Based on the result of *in vitro* dissolution studies the dissolution of carvedilol has improved considerably for mouth dissolving tablets prepared from solid dispersion (FD5-FD8) as compared to mouth dissolving tablets in which carvedilol is used as such (FD1-FD4) as shown in Table 9-10, Figure. 9-10 . F6 formulation gave better dissolution as compared to all the other batches by exhibiting almost 100% drug release in 15 min. Based on the dissolution results of the all prepared batches FD6 was selected as best formulation batch for rapid release of drug.

Table 9: *In vitro* dissolution study of mouth dissolving tablets in 0.1 N HCl

Time		% Cumulative release			
	FD1	**FD2**	**FD3**	**FD4**	**Marketed product**
0	0	0	0	0	0
5	16.1±0.176	17.8±0.341	15.8±0.719	16.4±1.088	56.8±0.543
10	19.6±0.369	21.4±0.309	17.7±0.403	19.3±0.922	61.4±0.392
15	21.7±0.269	23.7±0.773	20.9±0.584	22.8±0.729	74.3±0.248
30	23.3±0.725	24.4±0.942	22.7±0.235	23.3±0.749	81.9±0.030
45	27.4±0.223	30.9±2.118	25.4±0.593	28.2±0.371	83.7±0.432
60	31.8±1.054	33.1±0.231	27.7±0.851	31.3±1.089	86.4±0.844

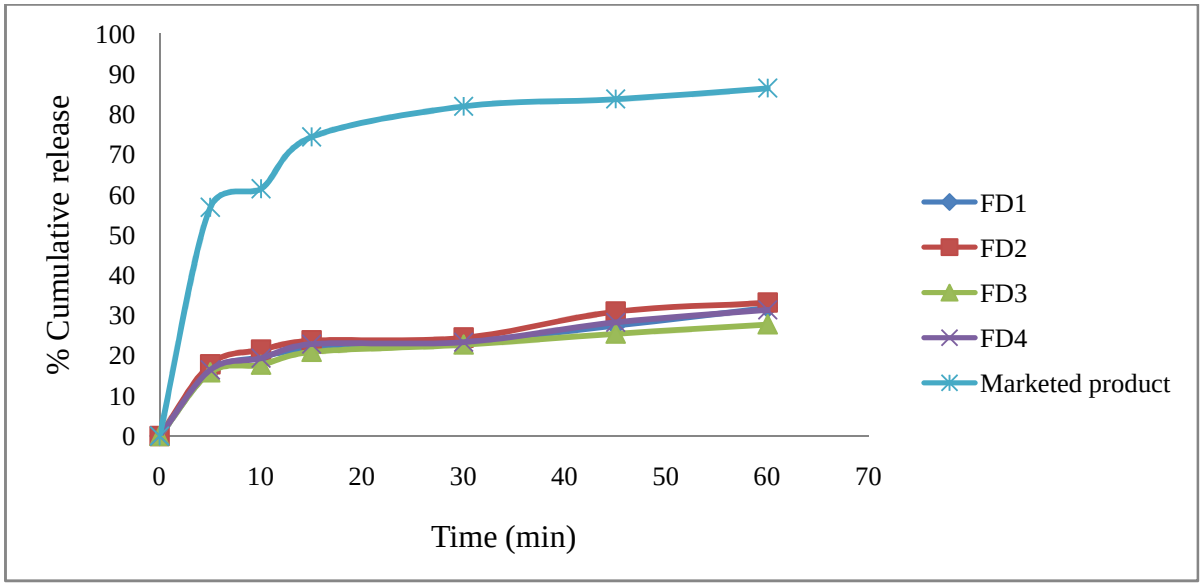

Figure. 9: Plot of *in vitro* drug release of carvedilol from formulation FD1-FD4 and marketed product

Table 10: *In vitro* dissolution study of mouth dissolving tablets in 0.1 N HCl

Time		% Cumulative release			
	FD5	**FD6**	**FD7**	**FD8**	**Marketed product**
0	0	0	0	0	0
5	67.4±0.893	70.5±0.854	61.4±0.454	66.4±0.458	56.8±0.543
10	72.3±1.294	85.7±0.489	67.3±0.788	71.7±1.439	61.4±0.392
15	80.5±1.486	97.7±1.204	76.5±0.384	80.9±1.936	74.3±0.248
30	84.6±1.039	98.1±0.059	81.6±0.482	84.4±0.984	81.9±0.030
45	88.1±0.348	101.8±0.471	84.1±0.592	87.7±0.838	83.7±0.432
60	91.4±0.429	99.8±0.468	86.4±0.837	91.6±0.584	86.4±0.844

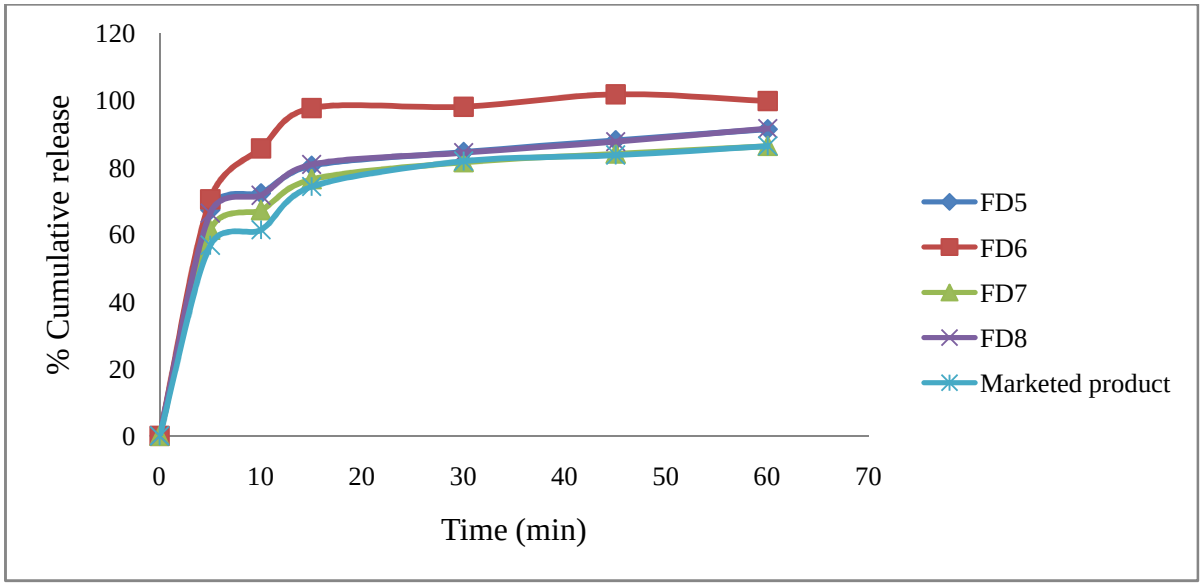

Figure. 10: Plot of *in vitro* drug release of carvedilol from formulation FD5-FD8 and marketed product

CONCLUSION

The present investigation was done to select an optimum solid dispersion and to formulate different batches of mouth dissolving tablets containing optimum solid dispersion which was compared with batches of MDTs formulated using Carvedilol alone. The characterization of powdered blend of all the batches was done for determination of pre-compression parameters. The values of pre- compression parameters like bulk density, tapped density, Hausner ratio, Compressibility index and angle of repose of all the batches were evaluated which were within prescribed limits and indicated a good flow property. The result for characterization of blend indicates good flow properties. After compression of powder blend, the tablets were evaluated for various post compression parameters i.e. friability, wetting time, hardness and disintegration time, weight variation and percentage drug content.

The effect of concentration and type of superdisintegrants on *in vitro* drug release used in formulation of MDTs was also investigated. The *in vitro* drug release results of mouth dissolving tablets showed that batch formulated containing 2% superdisintegrant i.e. crosscarmellose (Batch FD6) showed maximum *in vitro* drug release with almost 100% in 15 minutes. The accelerated stability study with FD6 batch revealed no significant difference of FD6 batch samples for physical description, assay and *in vitro* drug release at the end of three months kept at 40°C and 75% RH with that of the initial samples

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