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Design and Evaluation of Mucoadhesive Fast Disintegrating Sublingual Tablets Containing Poorly Soluble Drug for Enhancement of Oral Bioavailability

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ABSTRACT

The aim of this study was to prepare and evaluate sublingual fast-disintegrating mucoadhesive tablet (mFDT) containing a poorly soluble drug (carvedilol CAR) to avoid the first pass metabolism and to improve its bioavailability with reduction in dose and also dose related side effects. The tablets were prepared by direct compression method containing solid dispersion of surfactant and drug. The prepared tablets were tested for weight variation, hardness, drug content uniformity, bioadhesive strength and *in vitro* drug dissolution. The *in vitro* release of carvedilol was performed under sink conditions (phosphate buffer of pH 6.8, 37±0.5 ºC, 25 rpm) using USP-XXIV dissolution apparatus. The acceptable *in vitro* drug release profile was achieved with the formulation F2 which contains the drug and poloxamer in the ratio of 1:2 and superdisintegrant of 3%. The bioadhesive strength of formulation F2 was found to be 13.8 g. The tablets (formulation F2) containing 6.25 mg of carvedilol exhibited > 80 % of drug release within 10 min. FTIR, XRD and DSC studies showed no evidence of interactions between drug, surfactant, and excipients. The tablets apart from fulfilling all official and other specifications, exhibited higher rate of release. The mucoadhesive fast disintegrating drug delivery system of carvedilol for sublingual delivery could be successfully formulated.

Keywords*:* Solid dispersion, surfactant, poorly soluble drug, sublingual route, mucoadhesion.

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INTRODUCTION

Solid dosage forms are the popular drug delivery systems due to the advantages afforded both to the patient and the manufacturer[1]. Many patients find it difficult in swallowing tablets, capsules, and fluids, thus do not comply with prescription, which results in high incidence of non compliance. Oriented research has resulted in bringing out many safer and newer drug delivery systems. Fast-disintegrating tablets are becoming popular as novel delivery systems for drug administration as they are more convenient for children, elderly patients, patients with swallowing difficulties. The other advantages associated are their use in the absence of potable liquids, accuracy of dosage, ease of portability, alternative to liquid dosage forms, and rapid onset of action[2.]

Carvedilol is a BCS class - II drug (insoluble in water) with high lipophilic nature (log p 3.8). It has β- adrenoceptor antagonist with additional vasodilating properties and is indicated in angina and hypertension[3]. It also possesses anti-oxidant properties suggesting its use in the management of acute myocardial infarction[4]. Although CAR is completely absorbed from the gastrointestinal tract after ingestion of the oral tablets, the systemic availability is approximately 25–35% due to high hepatic first-pass metabolism[5]. Hepatic first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented when the sublingual tablets are used since the dosage form is retained only in the floor of the mouth. Formulations delivered through sublingual route of administration can result in a faster pharmacological response than oral route[6].

It is desirable to improve the solubility as well as bioavailability of carvedilol and the most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier[7]. Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization [8]. The use of surfactants (such as inulin[9], inutec SP1[10], compritol 888 ATO[11] and gelucire 44/14[12]) as carriers was shown to be effective in originating high polymorphic purity and enhanced *in vivo* bioavailability. The insertion of bioadhesive polymers into the formulation would allow an increase of the contact time of the drug with the oral mucosa in order to reduce drug dosages or applications and accordingly improve patient compliance[13].

Poloxamer 407 which is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers are known for good gelling properties[14]. This when used in the formulations was found to increase the drug residence time at the application site, which results in an enhanced bioavailability and efficacy[15]. Extremely fast tablet disintegration is required to expedite the availability of carvedilol for rapid absorption by the sublingual mucosa blood vessels. Various techniques can be used to formulate fast-disintegrating tablets[16].

This article reports the preparation of solid dispersion of carvedilol with surfactants like poloxamer 407 to improve the solubility along with mucoadhesive properties, its incorporation into fast disintegrating tablets by direct compression using super disintegrants such as sodium starch glycolate, ac-di-sol and crospovidone to aid rapid disintegration of tablets in the oral cavity with enhanced dissolution rate and hence improved patient compliance.

MATERIALS AND METHODS

Materials

Carvedilol, mannitol, magnesium stearate and talc were obtained as a gift sample from Aurobindo Pharma Pvt, Ltd., Hyderabad. Poloxamer 407 was obtained as gift sample from Orchid Health Care Pvt., Ltd. Chennai. Crospovidone, Sodium starch glycolate and Croscarmellose sodium were procured from Dr. Reddy's lab, Hyderabad, India. All other chemicals and reagents used were of laboratory or analytical grade.

Methods

Estimation of carvedilol

Carvedilol contents were estimated by UV Spectrophotometric method by measuring the absorbance at 240 nm. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 0.5-6 µg/ml (r = 0.9998), when a standard drug solution was repeatedly assayed (n=6)[17].

Preparation of physical mixture (PM)

Carvedilol and surfactant in the ratio of 1:1 were sifted through a 80-mesh (425 µm) screen, mixed together with trituration in a glass mortar, and stored in a desiccated environment until further evaluation.

Preparation of solid dispersions

Solid dispersions (SDs) of carvedilol in Poloxamer 407 were prepared by kneading (KN) method. The required quantities of drug and carrier (Poloxamer 407) were dissolved in the solvent (methanol) to get a clear solution in a dry mortar. The mixture was kneaded for 30 min

by continuous trituration. Small volume of the solvent was added to maintain the mixture as thick slurry during kneading process. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 45°C for 1 hour in a hot air oven. The dried product was powdered and passed through mesh no. 80 in each case. Solid dispersions in Poloxamer 407 were prepared at four different ratios of drug: carrier namely 1:0.5, 1:1, 1:2 and 1:3.

Physical characterization and saturation solubility study

The excess amount of the pure drug and formulations PM and SDs were added to conical flasks containing 10 ml of different buffer solutions and subjected to shaking on a rotary shaker for 48 hours at 37°C. Then the flasks were removed and filtered. Suitable aliquots were withdrawn from the filtered solution and analyzed by UV-Visible spectrophotometer (Model SL-150, Elico Pvt. Ltd., India) at a wavelength of 240 nm for the drug content after appropriate dilution with buffer and the solubilities of solid dispersions were compared with pure drug solubility[18].

Practical Yield

Percentage practical yield was calculated to select appropriate method of production of solid dispersions[19]. The prepared SDs were collected and weighed to determine practical yield (PY) from the following equation 1.

$$PY\ (\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug+carrier)}} \times 100 \qquad \text{equation 1}$$

Drug content

Solid dispersions and mixtures of carvedilol were tested for drug content uniformity. Accurately weighed amount of sample was dissolved in 10 ml of methanol and stirred on magnetic stirrer for 10 min. The solution was filtered through membrane filter (0.45 µm), diluted suitably and assayed for drug content (DC) spectrophotometrically and % drug content was calculated using the following equation 2.

$$DC\ (\%) = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100 \qquad \text{equation 2}$$

Preparation of carvedilol fast disintegrating tablets

Fast disintegrating tablets containing 6.25 mg of carvedilol were prepared by direct compression method and the various formulae used in the studies are shown in table 1. Solid dispersions equivalent to 6.25 mg of drug and colloidal silicone dioxide were mixed in a polyethylene cover. Mannitol, super disintegrants (like croscarmellose sodium, crospovidone, sodium starch glycolate) and talc were then added to the above material in geometrical dilution method.

Magnesium Stearate was added just before compression to the above mixture and mixed well. The final blend was evaluated for various parameters like angle of repose, bulk density, compressibility index and Hausner's ratio. After evaluation, the final blend was compressed into the tablets with single station punching machine (Cadmach TB-024) using 7 mm flat punches-die set. The prepared tablets were subjected to evaluation of tablet properties.

Table 1: Composition of mucoadhesive fast disintegrating sublingual tablets

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersion (SD-III) (mg)	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Croscarmellose sodium	2.25	4.5	6.75						
Cros povidone (mg)	-	-	-	2.25	4.5	6.75	-	-	-
Sodium starch glycolate (mg)	-	-	-	-	-	-	2.25	4.5	6.75
Mannitol (mg)	127.5	125.3	123.0	127.5	125.3	123.0	127.5	125.3	123.0
Aerosil (mg)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium stearate (mg)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Total weight (mg)	150	150	150	150	150	150	150	150	150

MICROMERITICAL PROPERTIES OF POWDER BLEND:

Powder blend was evaluated for its flow and compressibility parameters[20].

Angle of repose:

Flow properties of the powder were measured by measuring the angle of repose, using the equation 3 and the results are shown in Table 3.

$$\theta = \tan^{-1}(h/r) \qquad \text{equation 3}$$

Where h is the height of the heap and r is the radius of the heap

Compressibility index:

The ease with which a material can be induced to flow, Compressibility index (C), is calculated using the following equation 4 and the results are shown in Table 3.

$$C = (\rho_t - \rho_b) / \rho_t \times 100 \qquad \text{equation 4}$$

Where ρ_t - Tapped density, ρ_b - Untapped bulk density

Hausner's ratio:

Hausner's ratio is an index of ease of powder flow; it is calculated by following equation 5 and the results are shown in Table 3.

$$\text{Hausner's ratio} = \rho_t \backslash \rho_b \qquad \text{equation 5}$$

Where ρ_t - Tapped density, ρ_b -Untapped bulk density

EVALUATION OF MUCOADHESIVE FAST DISINTEGRATING TABLETS

Weight Variation

Twenty tablets from a batch size of 100 were randomly selected from each formulation and

weighed using a Shimadzu digital balance. The mean ± standard deviation (s.d.) was recorded and the results are shown in Table 4.

Thickness Variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer (Digimatic micrometer, Mitutoyo, Japan). The mean ± s.d. values were calculated and the results are shown in Table 4.

Hardness

Tablets require a certain amount of strength resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and s.d. values were calculated and the results are shown in Table 4.

Friability

The friability of mFDT was measured utilizing a USP-type Roche friabilator (Pharmalab, Ahmedabad, India). A sample of whole tablets corresponding to 6.5 g was placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated according to following equation 3 and the results are shown in Table 4.

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \qquad \text{equation 6}$$

Drug content uniformity

Ten tablets from each formulation were taken, crushed and mixed. 6.25 mg of carvedilol equivalent of mixture was extracted thoroughly with 100 mL of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 240 nm. This procedure was repeated thrice and the mean was chosen. The results are shown in Table 4.

Wetting Time

Five circular tissue papers were placed in a petri dish of 10 cm diameter. A tablet was carefully placed on the surface of the tissue paper in the petri dish at 25°C. 10 mL of water containing 1% brilliant blue FCF (Blue 1), a water-soluble dye, was added to the petri dish. The dye solution would enable to identify complete wetting of the tablet surface. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time[21]. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch and the results are shown in Table 5.

Water Absorption Ratio

The weight of the tablet prior to placement in the petri dish was noted (w_b) utilizing a Shimadzu digital balance. The wetted tablet was removed and reweighed (w_a). Water absorption ratio (R) was determined according to the following equation 7 and the results are shown in Table 5.

$$R = \frac{w_a - w_b}{w_b} \times 100 \qquad \text{equation 7}$$

Where w_b and w_a were tablet weights before and after water absorption, respectively.

***In vitro* disintegration time**

In vitro disintegration time (DT) of the mFDTs was determined following the procedure described by Gohel *et al*[22]. 10 mL of water at 25°C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates (n=6) and mean ± s.d. values were recorded and the results are shown in Table 5.

Measurement of mucoadhesive strength

Ex vivo mucoadhesive strength of carvedilol sublingual tablets was measured by using modified physical balance using the method described by Kashappa Goud *et al*[23]. Porcine sublingual mucosa was used as the model substrate and phosphate buffer pH 6.8 was used as the moistening fluid. Freshly excised porcine sublingual mucosa was obtained from the local slaughterhouse and used within three hours of slaughter. The tablet was laid onto the model membrane under constant weight of 50 gm for a total constant period of 5 min. Bioadhesive strength was measured in terms of weight in grams of water required to detach the tablet from the porcine buccal mucosa. The addition of water was stopped when tablet was detached from porcine sublingual mucosa. The weight of water required to detach the tablet from sublingual mucosa was noted as *ex vivo* mucoadhesive strength. Mucoadhesive strength was performed in triplicate and the results are shown in Table 5.

COMPATIBILITY STUDIES

Fourier transform infrared spectroscopy

Fourier transform infrared spectra were obtained using Shimadzu FTIR-8400S spectrometer, Japan. Samples of carvedilol, physical mixture, solid dispersion and formulation were ground and mixed thoroughly with potassium bromide at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 T for 5 min in a hydraulic press. The scanning range was 40 to 4000 $cm^{-1}$and the resolution was 4 cm^{-1}.

Powder X-ray diffraction (PXRD)

PXRD patterns were recorded using Philips PW 1729 X- ray generator, USA fitted with a copper target, a voltage of 40 kV, and a current of 30 mA. The scanning rate was 1°/min over a 2 θ range of 1-50°. PXRD patterns were traced for carvedilol, physical mixture, solid dispersion and formulation. The samples were slightly ground and packed into the aluminum sample container.

Differential scanning calorimetry (DSC)

DSC analysis of the samples was carried out on a Perkin-Elmer DSC7, USA. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 5 and 300 °C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2.

***In Vitro* Release Studies**

Release studies of carvedilol from different formulations were performed according to USP XVIII apparatus II, paddle method utilizing a dissolution system (Disso 2000, Lab India, India). Paddle speed was maintained at 25 rpm and 300 mL of phosphate buffer of pH 6.8 was used as the dissolution medium. Samples (3 mL) were collected at predetermined time intervals (0,0.5,1,3,5, 10, 20, 40, and 60 min) and replaced with equal volume of fresh medium, filtered through a 0.22 µm filter and analyzed with a UV—Visible spectrophotometer (λ = 240 nm). Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved. The release studies were performed in replicates of six.

Statistical Analysis

To compare between different formulations, in all of the studies statistical analysis was done utilizing one-way analysis of variance (ANOVA). A statistically significant difference was considered when $p < 0.05$.

RESULTS AND DISCUSSION

Carvedilol is practically insoluble in water as the intrinsic solubility of carvedilol in pure water at room temperature is found to be 8.4µg/ml. Results of maximum solubility of pure drug, physical mixture and solid dispersions in different buffer media like 0.1N HCl, Glycine buffer (GB), Purified water (PW) and phosphate buffer (PB) of pH 6.8, pH 7.2 and pH 7.4 were depicted in figure 1. SD-III (1:2) showed highest saturation solubility compared to solid dispersions. This may be due to the inherent differences between the carriers in terms of hydration, dissolution and possible complexation of drug with carriers.

Solid dispersions of carvedilol were prepared by using carrier like poloxamer 407. All the SDs prepared were found to be fine, flowing powders. Percent practical yield for all formulations of

solid dispersions were found to be between 93.06-97.22%. The drug content of the prepared SDs was found to be in the range of 95-98%. The dissolution efficiency data obtained for all formulations were in the range of 43-96.5%. Maximum % drug content was found in the SD-III (1:2) and results are tabulated in table 2.

Table 2: Practical yield, Drug content and *in vitro* dissolution data for pure drug and solid dispersions (Mean±s.d, n=3)

S.No.	Solid dispersions (Drug : carrier)	Practical Yield (%)	Drug Content (%)	Dissolution Efficiency (DE_{30})
1	Pure drug	-	99±0.9	19.88±1.24
2	Physical Mixture (1:1)	97.22±1.5	96±1.4	31.01±1.30
3	SD-I (1:0.5)	94.47±1.3	96±1.3	43.27±2.01
4	SD-II (1:1)	96.17±0.9	97±1.3	60.41±1.68
5	SD-III (1:2)	96.81±1.1	98±1.1	96.89±1.95
6	SD-IV (1:3)	93.34±1.1	97±1.4	85.09±1.05

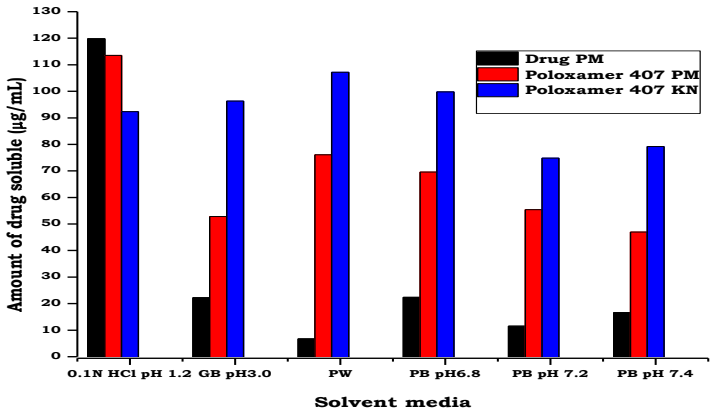

Figure 1: Solubility studies of carvedilol solid dispersions in different buffer media

Fast disintegrating tablets of carvedilol were prepared by direct compression method employing solid dispersion (SD-III) along with superdisintegrants in different ratio. A total of three formulations were designed. The flow properties of the powder mixture were significant for the uniformity of mass of the tablets. The flow of the powder mixture was analyzed before compression to tablets. The values of pre-compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Low Hausner`s ratio (≤1.25), compressibility index (≤20.16) and angle of repose (≤36.89) values indicated a fairly good flowability of powder mixture and the results are depicted in table 3.

As the tablet powder blend was free flowing, tablets produced were of uniform weight with acceptable weight variation in the range from 148 mg to 150 mg due to uniform die fill. Hardness (4.2- 4.7 kg/cm^2) and friability loss (0.4 - 0.87 %) indicated that tablets had a fair

mechanical resistance. Drug content was found to be high (≥97.6 %) in all the tablet formulations. Uniform distribution of the active agent was assessed by UV, the content of carvedilol was found within the 98.1% of the theoretical value. Post-compression parameters of mucoadhesive sublingual FDTs were presented in table 4.

Table 3: Micromeritical properties of powder blend

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Angle of Repose (^{0})	Hausner's Ratio	Compressibility Index (%)
F1	0.498	0.598	26.31	1.17	15.81
F2	0.510	0.597	26.91	1.18	15.38
F3	0.512	0.600	27.14	1.17	14.87
F4	0.505	0.591	27.62	1.18	14.64
F5	0.508	0.595	28.07	1.17	14.72
F6	0.508	0.597	28.27	1.17	14.92
F7	0.514	0.595	29.39	1.16	13.85
F8	0.515	0.598	29.74	1.16	13.91
F9	0.515	0.602	29.22	1.16	14.43

Table 4: Evaluation of mucoadhesive fast disintegrating sublingual tablets (Mean±s.d)

Formulation	Avg. weight (mg ± SD, n=20)	Hardness (Kg/cm^2 ± SD, n=10)	Thickness (mm) (n=10)	Friability (%)	Drug Content Uniformity (%)
F1	149.8 ± 0.93	4.43 ± 0.29	3.28 ± 0.01	0.510	99.8±1.11
F2	149.7 ± 0.97	4.42 ±0.33	3.27 ± 0.04	0.470	99.6±0.99
F3	149.7 ± 0.95	4.45 ± 0.23	3.29 ± 0.01	0.470	99.0±1.25
F4	149.8 ± 0.82	4.43 ± 0.24	3.28 ± 0.02	0.480	100.2±1.02
F5	149.6 ± 0.69	4.45 ± 0.16	3.28 ± 0.04	0.510	100.4±1.34
F6	149.8 ± 0.94	4.43 ± 0.30	3.29 ± 0.01	0.511	100.3±1.54
F7	149.8 ± 0.93	4.52 ±0.34	3.28 ± 0.02	0.521	99.9±1.62
F8	149.8 ± 0.91	4.55 ± 0.24	3.27 ± 0.02	0.511	99.7±1.54

Table 5: Evaluation of mucoadhesive fast disintegrating sublingual tablets (Mean±s.d, n=10)

Formulation	Mucoadhesive strength (g)	Wetting time (sec.)	Water absorption ratio	Disintegration time (sec., n=10)
F1	13.24±1.23	25.0±1.03	75.0±3.58	32.0
F2	13.85±0.94	20.0±0.85	88.7±2.98	24.0
F3	14.45±1.25	19.0±1.42	96.3±4.12	22.0
F4	13.72±1.03	29.0±1.24	67.4±4.25	48.0
F5	12.93±1.58	26.0±1.25	85.8±3.68	35.0
F6	13.41±0.23	25.0±1.02	94.8±3.76	29.0
F7	13.54±0.23	32.0±1.58	64.7±4.15	55.0
F8	14.01±0.23	30.0±1.64	82.8±4.28	41.0
F9	13.57±0.23	31.0±1.45	93.3±3.97	34.0

The most important parameter that needs to be optimized in the development of mucoadhesive fast disintegrating tablets is the mucoadhesive strength and disintegration time of tablets. The disintegration time of the tablets were significantly increased with the concentration of the super disintegrant until optimal level, however it decreased with further increase in the disintegrant

concentration, which may be due to its rapid capillary activity and hydration with little tendency to gel formation. Wetting time is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water and were found to be in the range of 16 – 28 seconds and results were depicted in table 5.

In order to further study whether Carvedilol undergoes a polymorphic change during preparation of mucoadhesive FDTs and to test for possible intermolecular interactions between carvedilol and excipients, FTIR was used. The FTIR spectra of pure Carvedilol, carvedilol with Poloxamer and formulation are depicted in figure 2**.** All the principal IR peaks of carvedilol were present in formulation. This clearly indicates that there is no interaction between carvedilol and excipients.

The X-ray diffractograms of pure carvedilol, physical mixture, solid dispersions and formulation were shown in figure 3. Numerous diffraction peaks of carvedilol were observed at 2 θ of 12.8°, 15.62°, 17.46°, 18.56°, 20.1°, 24.3° and 26.2° indicating the presence of crystalline nature of carvedilol. The physical mixture also showed some crystallinity. On the other hand, 1:2 solid dispersion and formulation did not show any crystallinity of carvedilol.

The DSC curve of carvedilol showed a sharp endothermic peak (T_{peak} = 115 °C) corresponding to its melting point, indicating its crystalline nature. The thermal behavior of the poloxamer is that expected for hygroscopic, amorphous substances, with a large endothermic effect in the 90-140 °C range due to polymer dehydration. Thermal behavior of carvedilol and corresponding drug carrier system are depicted in figure 4.

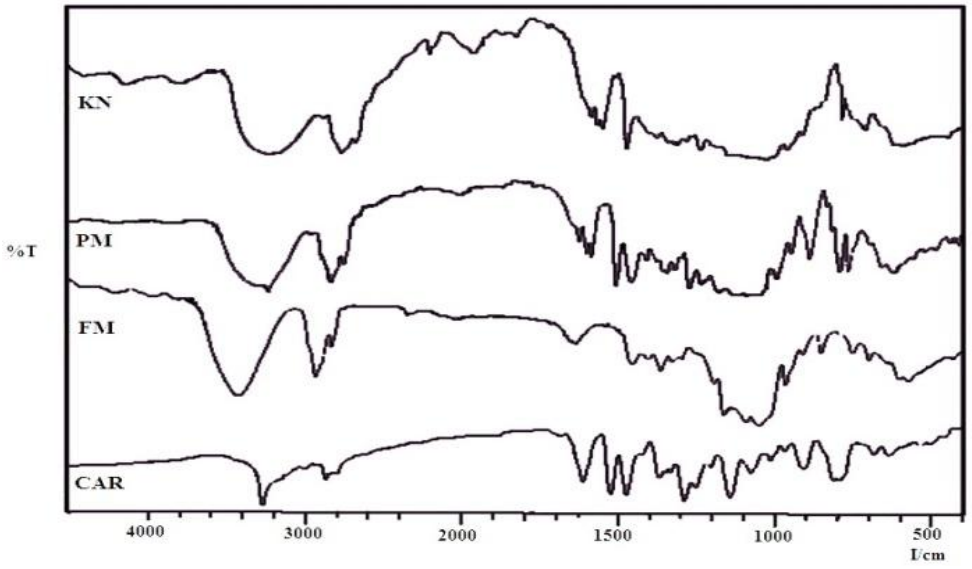

Figure 2: **FTIR Spectra of Carvedilol (CAR), Physical mixture (PM), SD-III (KN) and F2 Formulation (FM)**

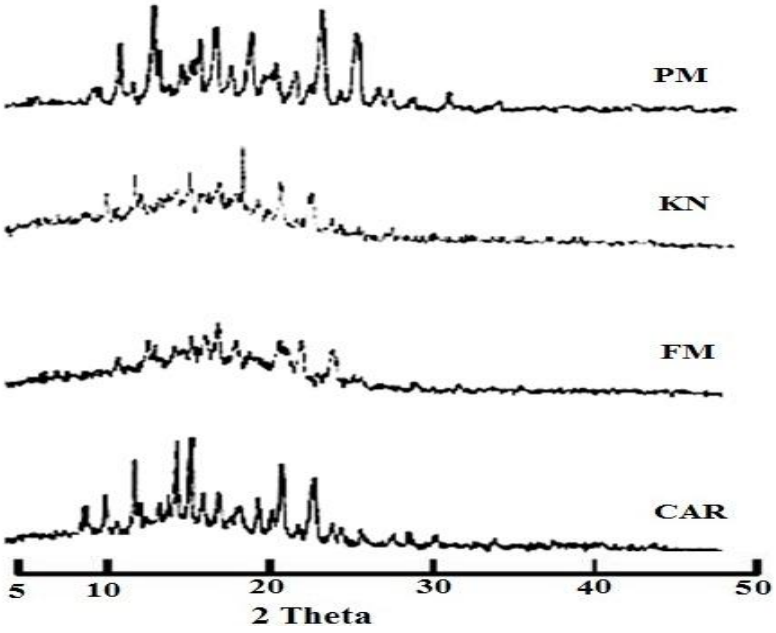

Figure 3: X-ray diffractograms of Carvedilol (CAR), Physical mixture (PM), SD-III (KN) and F2 Formulation (FM)

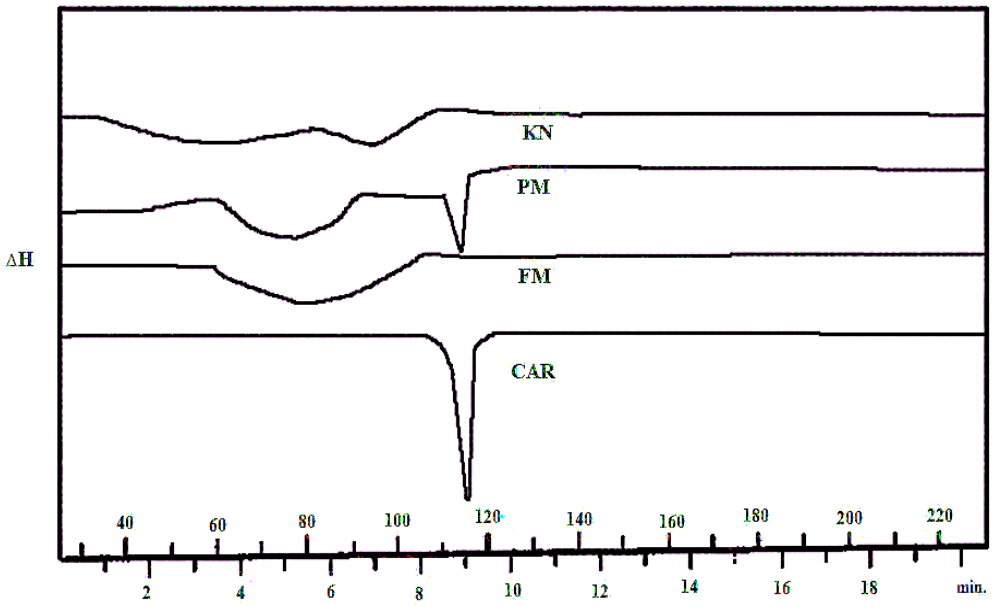

Figure 4: DSC curves of Carvedilol (CAR), Physical mixture (PM), SD-III (KN) and F2 Formulation (FM)

It showed that dissolution of tablets was proportionate with superdisintegrant concentration. Also the results indicated that the dissolution profiles of tablet containing super disintegrants are in agreement with disintegration time. The release profiles of tablets containing 1.5-4.5% w/w of superdisintegrants were observed. As the concentration of superdisintegrants increased the release of the drug was also increased. The selected formulations F2 have released 90.0% in 20

min. The investigated superdisintegrants can be ranked based on overall in-vitro release profile of carvedilol FDT tablet as cross carmellose sodium > crospovidone > sodium starch glycolate. The maximum increase in the dissolution rate was observed with the SD-III (F2) among the other formulations which was shown in figure 5. Many factors contributed to faster release rate such as decrease in particle size, decrease in agglomeration of particles, increased wettability and decrease in crystallinity of the drug. The results of dissolution profile of FDT were in accordance with that of disintegration data and results shown in table 6, figure 5 and 6.

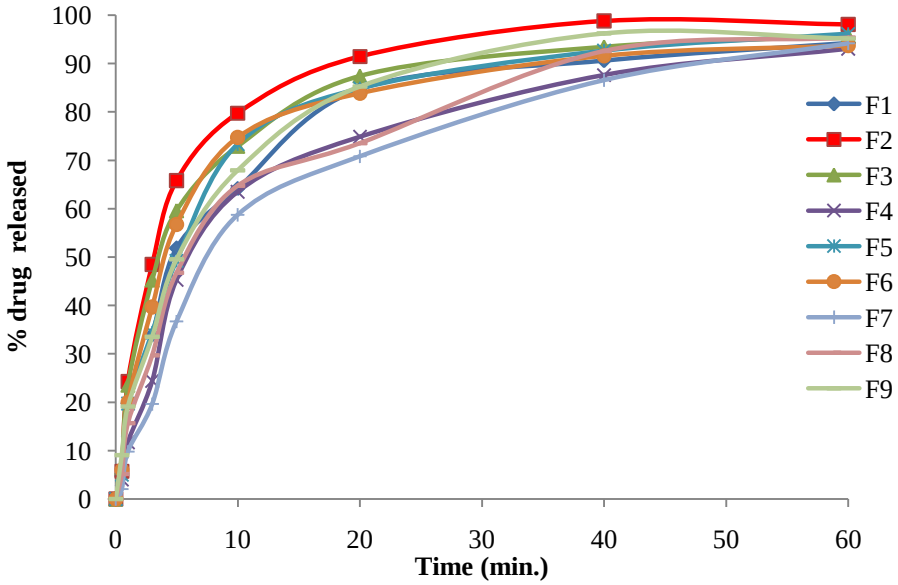

Figure 5: *In vitro* dissolution profile of different formulations

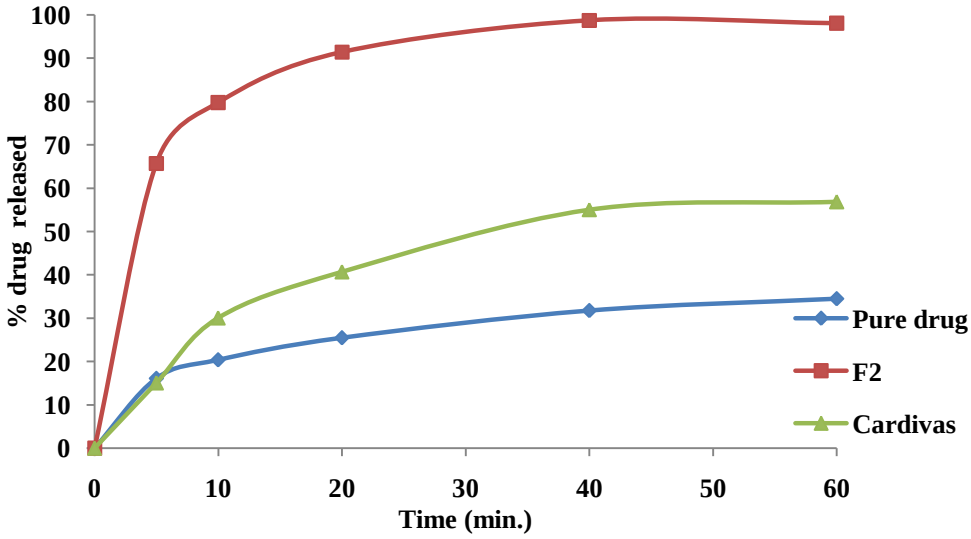

Figure 6: *In vitro* dissolution profile comparison with pure drug, F2 formulation and marketed formulation

Table 6: *In vitro* dissolution profile of different formulations

Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	4.76	5.78	6.51	4.06	5.06	6.04	2.04	5.14	9.04
1	19.8	24.25	23.54	11.7	19.7	20	9.81	15.7	19.1
3	33.9	48.49	45.28	24.4	34.4	39.7	19.7	29.7	33.5
5	51.9	65.8	59.59	45.3	49.3	56.7	36.7	46.7	49.6
10	64.2	79.8	72.92	63.5	73.4	74.7	58.7	64.7	68
20	84.7	91.5	87.48	74.9	84.9	83.9	70.9	73.6	85.3
40	90.6	98.8	93.5	87.7	92.7	91.6	86.6	92.6	96.3
60	94.3	98.1	95.7	93.1	96.2	93.7	94.2	95.4	95.2

CONCLUSION

This study was undertaken with an aim to formulate and characterize fast disintegrating tablets of carvedilol using solid dispersion with carrier such as Poloxamer 407 by direct compression method. FTIR, DSC study revealed that there is no drug-excipients interaction between Carvedilol and excipients. The decrease in crystallinity in formulation indicated the enhancement of solubility. It was observed that the formulation-F2 containing croscarmellose sodium was showing disintegration time of 24 seconds, wetting time of 20 sec with mucoadhesion of 14 g and highest dissolution rate 80% in 10 min and 98 % in 1 hr. This formulation when compared to other formulations indicated that the prepared fast disintegrating tablet formulation was suitable for sublingual route of administration with enough bioadhesion to retain the tablet in the floor of the mouth thereby causing enhancement of oral bioavailability.

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