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Original Research Paper

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF CARVEDILOL BY SOLID DISPERSION TECHNIQUE USING ROTA-EVAPORATION AND LYOPHILIZATION METHODS

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ABSTRACT

Despite significant advancements in the science of drug delivery, solubilization of poorly aqueous soluble drugs still remains a challenging task for formulation. The purpose of the study was to improve the physicochemical properties of poorly aqueous soluble drug carvedilol (CAR) like solubility, dissolution properties and stability of poorly soluble drug by forming dispersion with skimmed milk powder as carrier. CAR was formulated by solid dispersions using rota-evaporation method and lyophilization method in different ratios 1:1, 1:3, 1:5, and 1:7 of drug and carrier (skimmed milk powder). The formulations were evaluated for various *in vitro* parameters (Drug content, Drug release, phase solubility studies, dissolution efficiency, DSC, SEM, XRD) as well as changes in the physical state during storage under different humidity conditions. Good uniformity of drug content was observed with all formulations and lies between 96.29 % to 99.13 %. All the solid dispersions showed dissolution improvement compare to pure drug. The solubility was also increased from 23.28 µg/ml in case of carvedilol pure drug to 224.68 µg/ml and 205.31 µg/ml in case of these solid dispersions. The DE_{60} was also increased from 36.83% to 56.31% and 54.92 %. The dispersion with skimmed milk powder (1:7) by Rota evaporation Method and Lyophilization Method (1:5) showed faster dissolution rate (96.1 % and 94.88 % respectively). The tablets were formulated from the final and stable solid dispersions. These solid dispersions were selected to prepare tablets using Ac-do-sol as superdisintegrant and Avicel PH102 as diluents. Tablets were characterized for hardness, friability, disintegration time, percent drug release studies. Tablet T2 showed highest dissolution rate and best dissolution efficiency at (DE 60) minutes. The similarity factor was calculated for comparison of the dissolution profile before and after stability studies. The f2 value was found to be more than 50 (~ 94.00) thereby indicating a close similarity between both the dissolution profiles.

Keywords: Carvedilol (CAR), Skimmed milk powder (SM), Solid dispersions, Rota-evaporation Method, Lyophilisation method.

INTRODUCTION

Several techniques are commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, such as size reduction, the use of surfactants and the formation of solid dispersions. The latter are defined as dispersions of one or more active ingredients in an inert carrier in the solid state. Mechanisms involved include increased wettability, solubilisation of the drug by the carrier at the diffusion layer and reduction or absence of aggregation and agglomeration. Moreover, transformation of the crystalline drug to the amorphous state upon solid dispersion formulation increases the dissolution rate since no lattice structure has to be broken down for dissolution to take place.[1] Carvedilol (CAR), an antihypertensive agent, is used in the treatment of hypertension, congestive heart failure, cardiac arrhythmias and angina pectoris. It is a nonselective β-adrenergic blocker with selective α-adrenergic blocking. However, drug

bioavailability is very limited (25-30%), since it is practically insoluble in water and its dissolution is rate limiting for its absorption from gastro-intestinal tract.[2] Also CAR is poorly flowable and compressible drug. Carvedilol is practically insoluble in water and exhibits pH-dependant solubility. Its solubility is <1 µg/ml above pH 9.0, 23 µg/ml at pH 7, and about 100 µg/mL at pH 5 at room temperature. However, up to fourfold improvement of carvedilol bioavailability could be achieved by increasing the carvedilol solubility.[3] The solubility of carvedilol in aqueous solutions with pH ranging from 1 to 4 is limited due to its protonation, resulting in "in situ" hydrochloride salt formation, which exhibits lower solubility in media containing chlorine ions due to the common-ion effect. It's extremely low solubility at alkaline pH levels may prevent the drug from being available for absorption in the small intestine and colon, thus making it a poor candidate for an extended-release dosage form. Carvedilol undergoes significant stereoselective first-pass metabolism, resulting in low absolute bioavailability (30% or less). However, some sources suggest that this low bioavailability is the result of poor aqueous solubility.[4] The objective of the present study was enhancement of solubility of poorly soluble carvedilol with Skimmed milk powder by solid dispersion. The solid binary systems were prepared by maintaining constant drug concentration and increasing carrier concentrations using physical mixing and solvent evaporation techniques. The skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles. The principal casein fractions are α-s1, α-s2, β-casein and k-casein. β-casein is amphiphilic and acts as a detergent molecule with surfactant property. The milk also contains whey proteins with principle fractions of β-lactoglo-bulin, α-lactalbumin, bovine serum albumin and immunoglo- bulins. These molecules were found to be surface active with superior solubility than caseins. The lyophilisation procedure was chosen because it provides protection against heat denaturation of protein molecules. The objective of the present study was enhancement of solubility of poorly soluble carvedilol with skimmed milk powder by solid dispersion.[5] The dissolution characteristics of SDs were evaluated and compared with pure.

MATERIALS AND METHODS

Materials

Carvedilol (gift sample from Sun pharmaceutical industries Ltd, India), skimmed milk powder was purchased from Uttam's diary (Punjab, India), sodium hydroxide pellets, methanol, acetone, methanol LR, TBA, monobasic potassium phosphate, n-octanol, avicel pH 102, Ac-Di-Sol, magnesium stearate, Talc. Solid dispersions were prepared by Rota-evaporation and Lyophilization methods in four different ratios. Carvedilol and skimmed milk powder were weighed according to different weighed ratios.

Methods

Preparation of solid dispersions by rota-evaporation method

Various ratios of carvedilol (1:1, 1:3, 1:5 and 1:7) with skimmed milk were prepared**.** The selected amount of drug were taken and dissolved in a minimum amount of acetone. Different ratios of polymer were taken in pestle mortar. Drug solution was added in mortar to form a suspension. The suspension obtained was transferred in RBF and evaporated in a rotary evaporator (Heidolph Heivap Advantage ML/GB, Germany) at a rotation speed of 50 rpm at 50°C for about 15 min. Passed the dried solid dispersions through sieve no. # 60 so as to form uniform granules. The cooled granules were stored in sealed bags in desiccators for their evaluation. The prepared samples were compared for their solubility and dissolution rate studies. Composition of various solid dispersions prepared by rota-evaporation enlisted in table 1.[6]

Preparation of solid dispersions by lyophilisation technique

Solid dispersions of carvedilol using skimmed milk powder were prepared by lyophilisation method. Carvedilol (100 mg) was dissolved in TBA (20 ml) and required stoichiometric amount of skimmed milk powder was dissolved in water (5 ml), both above mentioned solutions were

mixed to obtain a homogenous carrier and drug co-solvent system. Various complexes of carvedilol with skimmed milk powder were prepared in ratios of 1:1, 1:3, 1:5, 1:7 as enlisted in table 2**.** The resulting solutions were frozen at -20°C in a deep freezer for 1 h. The resulting solution (25 ml) was taken into round bottom flask (RBF) and frozen for 2 h followed with a condenser temperature of -78.5°C. When complete freezing was achieved the RBF's were removed from freezing chamber, vacuum was applied and samples were subjected to lyophilisation for 4 h with vacuum of 0.02 mbar. A complete sublimation of solvents occurred and a dried mass (the hydrophobic drug-SM complex lyophilized powder) remained in the RBF. Dried powder was removed from the freeze- drier and placed in the desiccators until used. Composition of various solid dispersions prepared by lyophilisation technique has enlisted in table 2.[7,8]

Experimental Studies

Characterization of solid dispersions

Determination of Percentage Yield and Drug Content

Drug content of the carvedilol solid dispersions was calculated by dissolving solid dispersions equivalent to 12.5 mg of carvedilol in a suitable quantity of methanol (20 ml), filtered using 45 µm Whattman filter paper, suitably diluted with methanol and analyzed by using UV spectrophotometer against methanol as blank. Similarly, the percentage yield of each formulation was determined according to the recoverable final weight of solid dispersions and the total original weight of carvedilol and carrier.

$$\% \text{ Yield} = \left(\frac{a}{b+c}\right) \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

In equation 1 a is the weight of the solid dispersion, b is the weight of carvedilol taken for solid dispersion preparation, and c is the weight of skimmed milk powder taken for solid dispersion preparation.[9]

Solubility of solid dispersions

Solid dispersions equivalent to 12.5 mg were added to 20 ml of phosphate buffer pH 6.8 in screw capped vials. The vials were capped properly and shaken at 37 °C in a temperature controlled water bath for 48 h. Resultant samples were centrifuged and filtered, suitably diluted with phosphate buffer pH 6.8 and analyzed by UV spectrophotometer at 285.5 nm.

In vitro dissolution studies

Dissolution studies were conducted by using USP XXIV paddle method (apparatus 2) official in USP. The stirring rate was 100 rpm. Phosphate buffer pH 6.8 was used as dissolution medium (900 ml) and was maintained at 37±0.5°C.[7] A 5 ml aliquot of sample was withdrawn at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min. The samples were filtered using Whatman filter paper. The collected samples were suitably diluted and analyzed for carvedilol content by UV spectrophotometric method at 285.5 nm. The volume withdrawn at each time interval was replaced with equal volume of fresh dissolution media. Dissolution studies were performed in triplicate and mean values were taken. A model independent approach, dissolution efficiency (DE) was employed to evaluate the dissolution rate of carvedilol from solid dispersion. DE is defined as the area under the dissolution curve up to the time t, (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100 % dissolution in the same time. DE_{60} was calculated from the dissolution data from equation 2 and used for comparison.

$$DE\ \% = \frac{\int_0^t y.dt}{y100.dt} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots 2$$

Infrared spectroscopy

The infrared spectra (IR) of the samples was performed on fourier transformed infrared spectrophotometer (Perkin Elmer 400 spectrum USA). The pellets of the drug and KBr were prepared on KBr press. The spectra were scanned over wave number range of 4000 to 400 cm^{-1} at ambient temperature.

X-Ray Diffraction (XRD)

The X-ray diffraction patterns were recorded using XPERT-PRO diffractometer with Cu Kα filter generated at 45kV voltage and 40mA current over a diffraction angle of 2θ.

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (4000 Perkin Elmer, USA) was used to determine the degree of drug crystallinity in solid dispersions. About 2-4 mg of sample in open aluminium standard pan was heated at a scanning rate of 20°C/min from a temperature -50°C to 220°C under nitrogen gas flow.

Scanning Electron Microscopy (SEM)

The morphology of carvedilol, skimmed milk powder and solid dispersions were determined using a scanning electron microscope (SEM) (Jeol model JSM-6610, JAPAN) operated at an accelerating voltage of 3 kV. Samples were prepared by mounting powder on to a brass stub using graphite glue and coated with gold under vacuum before use.

Preparation of Tablets

Formulation of blends

The selected solid dispersions of carvedilol CAR 4, CAR 7 and excipients such as superdisintegrant (Ac-Di-Sol) and Avicel PH 102 as diluents were co-grounded in a pestle mortar and passed through sieve no. 60. Finally talc and magnesium stearate were added and mixed for 5 min.

Characterization of Blend

Bulk density

The bulk density (ρ_b) of the blend was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the (equation 3).

$$\rho_b = M / V_b \quad \text{.....3}$$

Tapped density

The tapped density was determined by tapping the measuring cylinder containing a known mass of blend 100 times using density apparatus. V_t i.e. the minimum volume occupied in the cylinder and the weight (M) of the blend was determined. The tapped density (ρ_t) was calculated by the given formula (equation 4)

$$\rho_t = M / V_t \quad \text{..... 4}$$

Compressibility index

The simplest way for measurement of flow of the powder is its compressibility, an indication of the ease with which a material can be induced to flow. It is expressed as compressibility index (I) which can be calculated as follows (equation 5)

$$I = \rho_t - \rho_b / \rho_t \times 100 \quad \text{..... 5}$$

Where, ρ_t = tapped density

ρ_b = bulk density

Angle of repose

It was determined by the funnel method in which the blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius (r) and the height of the heap formed was measured and angle of repose (θ) was calculated using the formula (equation 6)

$$\tan\theta = h/r \; ; \; \theta = \tan^{-1}(h/r) \quad \text{..... 6}$$

Hausner's ratio

Hausner ratio (Hr) is an indirect index of ease of powder flow. It is calculated by the following formula (equation 7)

$$Hr = \rho_t / \rho_b \quad \text{..... 7}$$

Where, ρ_t is tapped density and

ρ_b is bulk density

Low Hausner's ratio i.e < 1.25 indicates better flow properties

Preparation of Tablets

The tablets of selected solid dispersion CAR 4 AND CAR 7 weighing 200 mg were prepared by direct compression method by using 8 mm concave die punch set with single punch machine. Each tablet contained solid dispersions equivalent to 10 mg of carvedilol. The formula for tablet is as follows in table 3.

Characterization of tablets

After compression of powder the tablets were evaluated for organoleptic properties such as colour, odour, taste, thickness, hardness, friability, content uniformity, disintegration time and *in vitro* dissolution studies.

General Appearance

The general appearance of a tablet, its visual identification and over all elegance is essential for consumer acceptance. This includes tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws etc.

Tablet Thickness

Thickness of the tablet is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer (Mityato, Japan).

Weight Variation

In this case twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation of each tablet was determined. The weight variation test would be satisfactory method of determining the drug content uniformity.

Friability

Friability of the tablets was determined using Roche friabilator. In this the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Pre-weighed sample of tablets are placed in the friabilator and were subjected to 100 revolutions. The friability (% F) was determined by the formula (equation 8)

$$\% F = (1\text{-}W_{\circ}/W) \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots 8$$

Where, %F is percentage friability
$W_{\circ}$ is initial weight of the tablets before test
W is the final weight of the tablets after test

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

Content Uniformity

Ten tablets were randomly selected, weighed and powdered in a glass mortar pestle. The weight of the powder equivalent to 10 mg of carvedilol was weighed and dissolved in 20 ml of methanol in volumetric flask. 10 ml of this solution was taken and volume was made upto 100 ml with methanol and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml methanol in separate volumetric flask. The content uniformity in each formulation was determined spectrophotometrically at 286 nm.

In Vitro Disintegration Test

In vitro disintegration time was determined using disintegration test apparatus. In this case, one tablet was placed in each of six tubes of apparatus and a disc was added to each tube i.e. 3 inches long, opens at the top, and held against a 10 mesh screen at the bottom end of the basket rack assembly. The basket rack assembly was positioned in a 1 litre of phosphate buffer pH 6.8. The time taken for the tablet to disintegrate completely and pass through the screen was measured.

In Vitro Dissolution Test

In vitro dissolution studies of tablets were performed in phosphate buffer pH 6.8 using rotating paddle method. A tablet was added to 900 ml of phosphate buffer pH 6.8 at 100 rpm at 37 $^{\circ}$C ± 0.5 $^{\circ}$C. 5 ml of aliquots were withdrawn at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min and immediately filtered through Whatmann filter paper no. 41. At each sampling, an equal volume of fresh medium was added. The concentration of carvedilol was measured spectrophotometrically at 285.5 nm. The dissolution efficiency (% DE_{60}) of the tablets was determined in order to compare with the marketed tablet.

Stability Studies

Carvedilol tablets were kept in ambered coloured bottles and the stability studies of CAR tablets were checked as per ICH guidelines at 40 ± 2°C and 75 ± 5% RH up to 3 months. During the study period the formulations were withdrawn at predetermined time intervals of 0, 15, 30, 45, 60, 75, and 90 days for change in physical characterization, drug content and *in vitro* dissolution studies. FDA has placed more emphasis on a dissolution profile comparison in the area of post- approval changes. Among several methods investigated for dissolution

profile comparison, f_2 (similarity factor) is the simplest. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using similarity factor (f_2). The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of square errors and is a measurement of the similarity in the percent (%) dissolution between the curves. Generally similarity factor in the range of 50-100 is acceptable according to US FDA and it was determined by the formula (equation 9).[10]

$$f_2 = 50 \log \{[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5} * 100 \quad .....9$$

Where, n is the no. of time points, Rt is the dissolution value of the reference batch (prechange) at time t and Tt is the dissolution value of the test batch (postchange) at time t.

RESULTS AND DISCUSSION

Percentage Yield

The % yield was calculated to know about % yield or efficiency of any method which helps in selection of appropriate method of production. The decrease in % yield which is attributed to difficulty of sieving (table 4 and figure 1).

Drug Content

The drug content of the prepared solid dispersions was found to be in the range of 96.29-99.13 % indicating the application of present methods for the preparation of solid dispersions with high content uniformity (table 4).

Solubility Studies

Solubility of drug increased with the increase in the ratio of polymer. But in case of CAR 7 molar ratio of 1:7 solid dispersion the solubility of drug decreased due to less drug-polymer entrapment (table 5 and figure 2).

Dissolution Studies

The *in vitro* release profile of carvedilol and all solid dispersions CAR 1, CAR 2, CAR 3, CAR 4, CAR 5, CAR 6, CAR 7 and CAR 8 are shown in table 6 and table 7. Figure 3 and figure 4 showed the comparison of cumulative percent drug released versus time. In all the cases, cumulative percent released was much greater than pure carvedilol. The dissolution rates were enhanced with increasing concentration of polymer. Higher dissolution rates were shown by the solid dispersions of drug with skimmed milk powder as compared to the pure drug.

Pure carvedilol yielded the slowest percent release due to its hydrophobic property causing the powder to float on the surface of the dissolution media and prevented its surface to make contact with the medium for initial time intervals. Hence the enhancement of the carvedilol dissolution rate by solid dispersion technique compared with that of the pure drug could presumably be explained by the following factors: 1) surfactant properties of the carrier 2) low viscosity of the carrier 3) a decrease in crystallinity and size of the drug crystals in the solid dispersions 4) increased solubility of the drug.

When the mixture comes in contact with the media, the polymer particles might have hydrated rapidly into polymer solution solubilises the adjacent drug particles and subsequently releases the drug into the medium.

Dissolution Efficiency

Dissolution efficiency of pure carvedilol, solid dispersions prepared with skimmed milk powder by different methods at 60 min were calculated which is shown in table 8 and comparison of % DE_{60} of different formulations is shown in figure 5.

FTIR Studies: FTIR (Fourier Transform Infrared Spectroscopy)

The IR spectra of SDs were compared with the standard spectrum of carvedilol. FTIR spectrum of carvedilol, skimmed milk powder and their solid dispersions are shown in figure 6, figure 7, figure 8, figure 9, and figure 10. From the FTIR study it was found that some of the peaks of the drugs were shifted broadened, some present with reduced intensity and some vanished. This was referred to formation of a complex between the drug and carrier. Complexation was leading to formation of an amorphous form of drug with skimmed milk powder by solid dispersion leading to improve the dissolution rate of drug.

X-RD (X-Ray Diffraction) Studies

X-RD pattern of CAR (figure 11) showed several sharp high intensity peaks at diffraction angle 2θ of 5.9666, 17.546, 17.7051 and 18.5126, which suggested CAR as crystalline material. Table 5.7 shows XRD data of CAR and physical mixture. XRD pattern of skimmed milk powder (figure 12) showed its amorphous nature. XRD pattern of physical mixture (figure 13) showed several characteristic sharp peaks of CAR at diffraction angles of 2θ of 5.9884, 17.1862, 17.7061 and 18.6132. Significant peaks of both carvedilol and skimmed milk powder were present in physical mixture and slight significant shift in the peaks was observed, which suggested very less to no chemical interaction between drug and polymer.

A total drug amorphization were observed in the XRD diffractogram of CAR-SM rota evaporated solid dispersion in drug/ polymer ratio 1:7 (CAR 4) and lyophilized solid dispersion in drug/ polymer ratio 1:5 (CAR 7) only two broad peaks at diffraction angle 2θ of 16.54°, 19.34° and 16.54°, 27.67° respectively corresponding to the diffraction pattern of drug were recorded while other peaks of carvedilol crystals were completely disappeared thus suggesting that CAR 4 and CAR 7 inhibited the crystallization of carvedilol through the formation of complex. XRD of solid dispersions are shown in fig 14 and figure 15.

SEM (Scanning Electron Microscopy)

SEM images of pure carvedilol, skimmed milk powder, physical mixture and solid dispersions are shown in figure 16, figure 17, figure 18, figure 19, figure 20 and figure 21. The pure carvedilol shown in figure 16, figure 17 at different magnifications showed blunt crystals. The parent carvedilol crystals were in the form of rod shaped crystals, which is in confirmation with the earlier report. This rod shaped form of carvedilol leads to very poor flow and compression difficulties. The prepared solid dispersion agglomerates were spherical to larger extent and remaining was irregular in shape with smooth surface, which enabled them flow very easily. In case of solid dispersions figure 18, figure 19, figure 20 and figure 21. It was difficult to distinguish the presence of carvedilol crystals appeared to be incorporated into particles of the skimmed milk powder.

DSC (Differential Scanning Calorimetry)

The characteristic endothermic peak, corresponding to drug melting point disappeared in solid dispersions. This might be due to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Absence of peak for the drug indicates that the drug is distributed homogenously in an amorphous state within the solid dispersions without any interaction. No characteristic melting peak of CAR i.e. 119.17 °C was found in DSC curves of CAR 4 as shown in figure 25 and CAR 7 as shown in figure 26 solid dispersions. The peaks in the solid dispersions (CAR4 and CAR 7) appeared at 95.42°C, 149.59°C and 95.42°C, 136.36°C respectively. Thus clearly indicated that drug was in an amorphous state which confirmed the results obtained from XRD.

Formulation and Characterization of Tablets

The tablets were made of the final and stable formulation CAR 4 and CAR 7. Total two formulations were formulated and designated as T1and T2. The characterization of mixed blend was performed for the flow property of powder which includes bulk density, tapped density, hausner's ratio, compressibility index, angle of repose as shown in table 9 for quality control parameters like hardness, thickness, friability, disintegration time, *in vitro* dissolution studies and drug content are shown in table 10. Drug content in the selected solid dispersions as shown in table 11. Dissolution efficiency of all the tablets were calculated at 60 min and data is shown in table 12. Flowability of CAR and its tablet blend was determined. HR and angle of repose was much improved compared to those of original powder (untreated carvedilol). In case of pure CAR powder couldnot pass through the funnel during the angle of repose experiment. The poor flow of CAR could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. It is obvious from CI value that the flow of untreated CAR is extremely poor due to high

cohesivity and adhesivity. Because of poor flowability and compatibility of untreated CAR powder. The micrometric properties of CAR can be improved forming tablet blends using magnesium stearate (antiadherent) and talc (glidant, lubricant). All tablet blends showed lower CI than untreated CAR, which is an identical improvement in flow behaviour of the particles could be due to an increase in true density of CAR powders as shown in table 9. The difference in the bulk density of CAR samples may be related to their markedly different crystal habbits, leading to different contact points and frictional, cohesive forces between the crystals. These are in good agreement morphology of CAR 4 and CAR 7 tablet blends. Dissolution was carried out on the tablets and marketed preparation. The in vitro release data in table 12 indicated that the maximum drug release was found in T2. Dissolution profile of carvedilol from marketed tablet and best formulations (T1 and T2) are shown in figure. 27. *In vitro* release studies reveal that there is marked increase in dissolution efficiency of carvedilol from all the solid dispersions when compared to marketed tablet. From the *in vitro* drug release profile, it can be seen that formulation CAR 4 containing SM (1:7 ratio of drug : SM) and CAR 7 containing SM (1:5 ratio of drug : SM) showed higher dissolution efficiency compared with marketed tablet i.e., 54.25 % and 58.61% respectively in 60 min. The results *in vitro* drug release of CAR solid dispersion tablets (T1 and T2) indicated that no dissolution was achieved for marketed tablet with only 57.66 % dissolved after 60 min. Results in table 13 showed that the dissolution of marketed tablet was slowest as compared to solid dispersion tablets (T1 and T2) which showed significant enhancement in CAR dissolution because as the soluble carrier dissolves the insoluble drug gets exposed to dissolution media in the form of very fine particles which dissolves quickly. The disintegrant Ac-Di-Sol shows the faster disintegration and thus enhances the dissolution rate of tablets. The evident improvement obtained with rota evaporated products was a consequence of the closer contact between the components and the better dispersion of the drug into the hydrophilic carrier obtained through rota evaporated technique.

Stability Studies

The T2 formulation showed no significant variation in all the parameters under the test period at different conditions i.e. (40 ± 2°C and 75 ± 5 % RH). The results are shown in table 14 and *in vitro* release studies has enlisted in table 14. There was no significant variation in the *in vitro* drug release profile over a period of three months as shown in figure 28. The similarity factor was calculated for comparison of the dissolution profile before and after stability studies. The f_2 value was found to be more than 50 (~ 94.00) which indicated a close similarity between both the dissolution profiles (T2 and S2) dissolution profile of T2 and S2 tablets were shown in table 15.

Hence, the results of the stability studies confirmed that the developed formulation is very stable.[11]

CONCLUSION

The objective of the present study was to improve the solubility and dissolution behaviour of the poorly water soluble drug Carvedilol by solid dispersion technique using skimmed milk powder as carrier. Results from the present study suggest that the low oral bioavailability of CAR could be well circumvented by lyophilisation monophase solution technology and rota evaporation technique. Complexation with SM significantly improved the dissolution rate of CAR through a number of factors such as drug amorphization and increased drug high degree of porosity. The present results showed that the solid dispersion and the solvent evaporation (rota evaporation method and lyophilisation method) seem to possess great potential to significantly enhance the solubility and dissolution rate of poorly soluble drugs. Results showed that in rota evaporation technique carvedilol was absorbed after equilibrium in acetone solution. Thus this method was suitable to produce dispersions with best distribution of drug within the carrier in thin

layer and as a consequent best possible drug release. TBA was found to be an excellent freeze-drying medium. It is miscible with water in any proportion. It possesses a very high vapour pressure (41.25 mmHg at 25°C), a high melting point (24°C) and has a low toxicity. Moreover, adding TBA to water results in formation of larger needle- shaped ice crystals with a higher surface area and porosity than round ice crystals that can facilitate sublimation. All these factors contribute TBA as an ideal freeze- drying medium that could be removed rapidly and completely by freeze- drying. Among all the prepared formulations, the rota evaporates i.e. CAR 4 solid dispersion prepared by SM and lyophilized dispersion i.e. CAR 7 prepared by SM showed marked increase in the solubility as well as dissolution when compared to pure drug and marketed formulation. Physical characterization of prepared solid dispersions have also been performed by DSC, FTIR, XRD and SEM to find the evidence of interaction and XRD analysis showed that there was a considerable decrease in the crystallinity of the drug which increased the surface area thereby increasing the dissolution and enhancement in the drug release. Freeze dried solid dispersions in 1:7 ratios (CAR-SM) and rota evaporated solid dispersions 1:8 ratios (CAR-SM) were proven to be advantageous in context of enhancing carvedilol dissolution characteristics in basic medium. SEM photograph of solid dispersions (CAR-SM) clearly revealed a change in the morphology of the drug particles. The formation of amorphous aggregates was observed in CAR 4 and CAR 7 solid dispersions. The selected solid dispersion with the best ratio from each method were formulated into tablets using Avicel PH102 (diluents), Ac-Di-Sol (superdisintegrant), talc and magnesium stearate as excipients. *In vitro* results demonstrated that rotaevaporated and lyophilized solid dispersion tablets (T1 and T2) containing carvedilol can result in rapid dissolution of carvedilol at intestinal pH.

The developed tablets (T1 and T2) may be an alternative to conventional oral tablets of carvedilol which usually suffers from a slow dissolution and poor solubility and low oral bioavailability. The physical stability of the final formulations proved to be unchanged after the storage upto 3 months at accelerated stability condition (40 ± 2° C and 75 ± 5 % RH).

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Table 1: Compositions of S.D containing CAR and SM with rota-evaporation method

S. No.	Formulation code	Drug : Carrier ratio
1	CAR1	1:1
2	CAR 2	1:3
3	CAR 3	1:5
4	CAR 4	1:7

Table 2: Composition of S.D containing CAR and SM with lyophilization method

S. No.	Formulation code	Drug : Carrier ratio
1	CAR 5	1:1
2	CAR 6	1:3
3	CAR 7	1:5
4	CAR 8	1:7

Table 3: Composition of optimized solid dispersion tablets

Ingredients	Weight (mg)	Weight (mg)
SD 1:5 (T1)	60	-
SD 1:7 (T2)	-	80
Ac-Di-Sol	8	8
Avicel pH 102	120	100
Talc	6	6
Magnesium stearate	6	6

Table 4: Percent yield and percent drug content of S.D with rota-evaporation method and lyophilization method

Formulation code	% Yield	% Drug Content
CAR 1	83.2%	97.12±0.385
CAR 2	82.6%	98.18±0.669
CAR 3	79.03%	96.29±0.266
CAR 4	80.38%	99.13±0.259
CAR 5	84.2%	97.12±0.385
CAR 6	83.6%	98.18±0.669
CAR 7	78.03%	96.29±0.266
CAR 8	79.01%	98.15±0.259

All results were calculated as mean ± SD, n=3

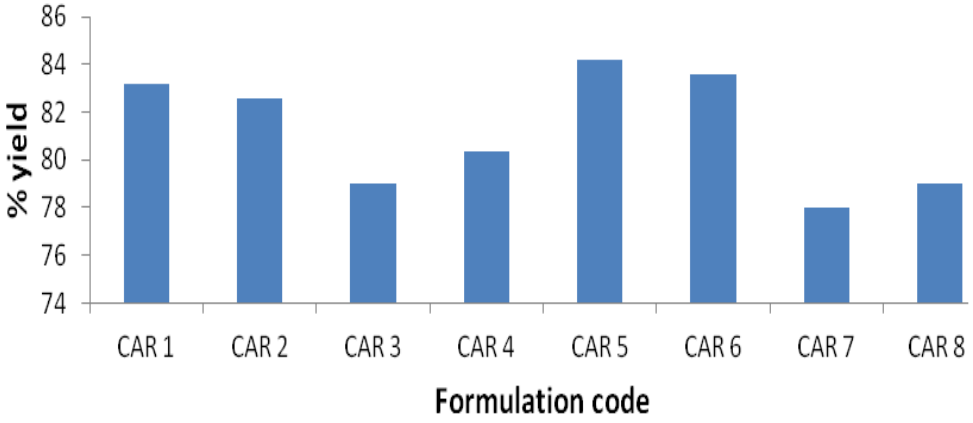

Figure 1: Percentage yield of different solid dispersions of carvedilol.

Table 5: Solubility of S.D with rota-evaporation method and lyophilization method

Formulation code	Solubility (µg/ml)
CAR 1	43.43±0.010
CAR 2	117.5±0.021
CAR 3	150.62±0.019
CAR 4	224.68±0.017
CAR 5	66.56±0.010
CAR 6	186.75±0.021
CAR 7	205.31±0.019
CAR 8	65.98±0.017

All results were calculated as mean ± SD, n=3

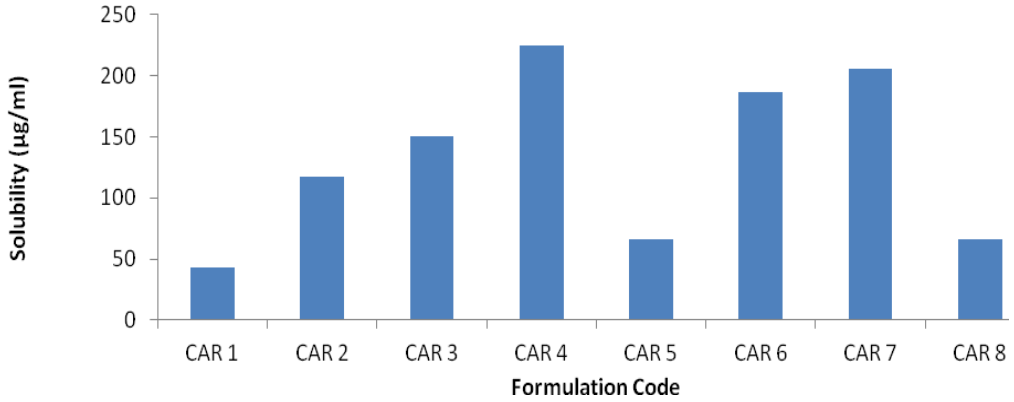

Figure 2: Solubility studies of different solid dispersions of carvedilol

Table 6: Dissolution profile of pure CAR AND SM with rota-evaporation method

	Cumulative Mean Percent Released ± S.D.				
Time (min)	Pure Drug	CAR 1	CAR 2	CAR 3	CAR 4
5	10.8±0.265	20.85±0.422	20.48±0.23	27.23±0.215	23.18±0.225
10	11.69±0.240	27.62±0.340	22.73±0.225	30.38±0.225	33.39±0.127
15	12.82±0.220	30.83±0.450	25.14±0.225	33.76±0.225	33.99±0.23
20	13.72±0.225	31.74±0.22	31.26±0.230	36.54±0.132	39.76±0.127
25	16.03±0.155	34.36±0.341	33.71±0.225	38.11±0.132	42.66±0.098
30	17.55±0.225	38.41±0.345	37.81±0.132	41.11±0.127	44.16±0.132
35	18.69±0.23	39.39±0.225	41.28±0.178	58.6±0.132	67.36±0.132
40	19.8±0.225	40.81±0.341	42.36±0.121	67.98±0.225	69.95±0.250
45	21.6±0.220	41.41±0.225	44.95±0.23	77.88±0.21	88.40±0.127
50	22.93±0.196	49.45±0.346	60.08±0.210	88.11±0.414	90.48±0.215
55	25.03±0.240	54.40±0.853	72.98±0.121	91.71±0.161	94.45±0.127
60	27.23±0.215	65.85±0.127	73.7±0.167	92.86±0.121	96.1±0.215

All results were calculated as mean ± SD, n=3

Table 7: Dissolution profile of pure CAR and SM with lyophilization method

	Cumulative Mean Percent Released ± S.D.				
Time (min)	Pure Drug	CAR 5	CAR 6	CAR 7	CAR 8
5	10.8±0.265	22.73±0.225	20.27±0.2	22.28±0.225	22.73±0.225
10	11.69±0.240	27.91±0.23	22.73±0.225	30.16±0.22	27.91±0.23
15	12.82±0.220	30.18±0.368	25.13±0.341	33.54±0.22	30.01±0.568
20	13.72±0.225	30.61±0.389	31.96±0.225	37.74±0.132	30.9±0.469
25	16.03±0.155	31.74±0.22	37.81±0.225	38.4±0.236	31.96±0.593
30	17.55±0.225	35.48±0.127	40.21±0.127	43.89±0.225	35.56±0.225
35	18.69±0.23	36.76±0.345	42.54±0.225	67.31±0.23	36.76±0.345
40	19.8±0.225	41.26±0.341	45.02±0.23	70.01±0.225	41.26±0.341
45	21.6±0.220	48.62±0.675	49.97±0.225	86.09±0.121	48.62±0.675
50	22.93±0.196	49.82±0.341	65.88±0.127	90.02±0.255	49.96±0.226
55	25.03±0.240	63.56±0.564	67.46±0.132	92.5±0.215	63.56±0.564
60	27.23±0.215	69.56±0.45	76.72±0.127	94.88±0.121	69.56±0.45

All results were calculated as mean ± SD, n=3

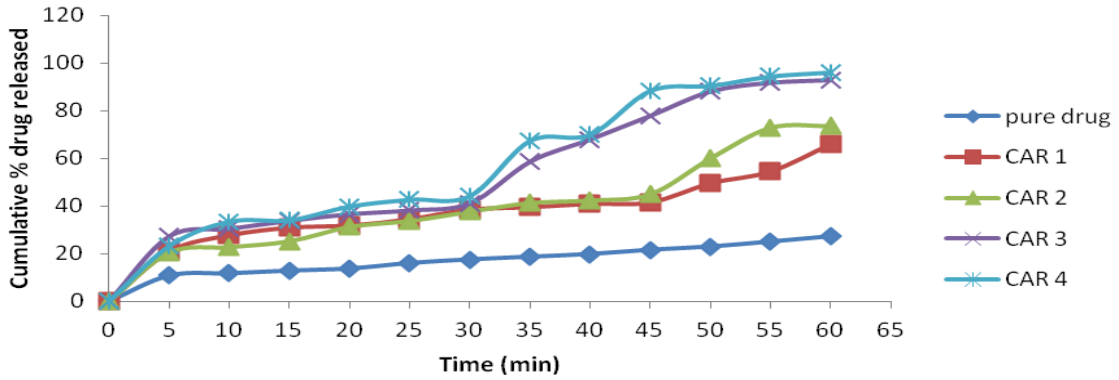

Figure 3: *In vitro* dissolution profile of pure CAR and SM with rota-evaporation method

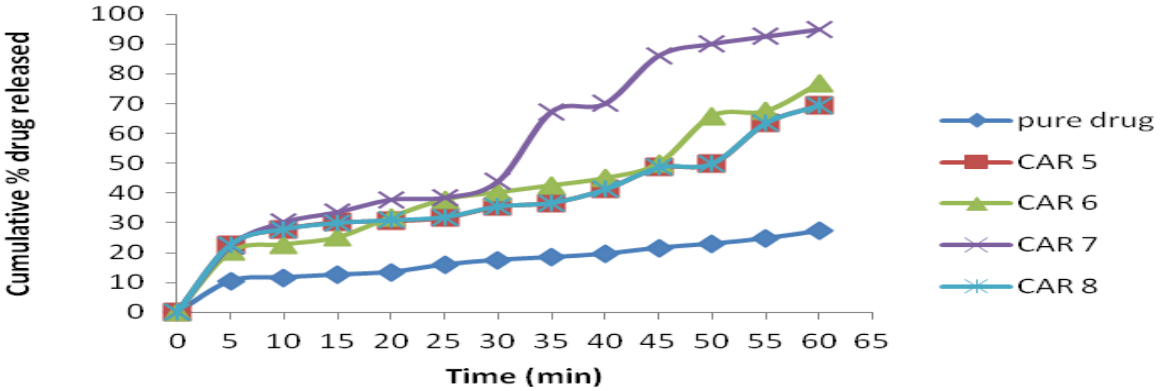

Figure 4: *In Vitro* dissolution profile of pure CAR and SM with lyophilization method

Table 8: Dissolution efficiency of solid dispersions prepared by different methods

Formulation	% DE_{60}
CAR 1	36.83±0.353
CAR 2	39.13±0.191
CAR 3	53.15±0.276
CAR 4	56.31±0.167
CAR 5	37.82±0.356
CAR 6	40.59±0.190
CAR 7	54.92±0.202
CAR 8	39.94±0.409

All results were calculated as mean ± SD, n=3

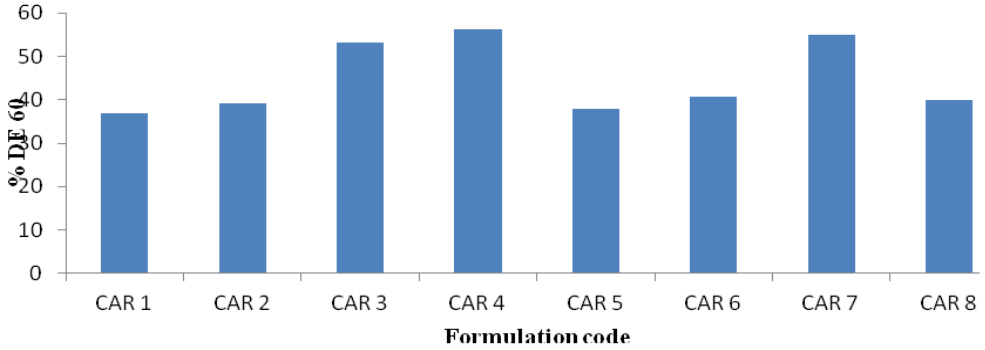

Figure 5: Comparison **of % DE_{60} of different formulations**

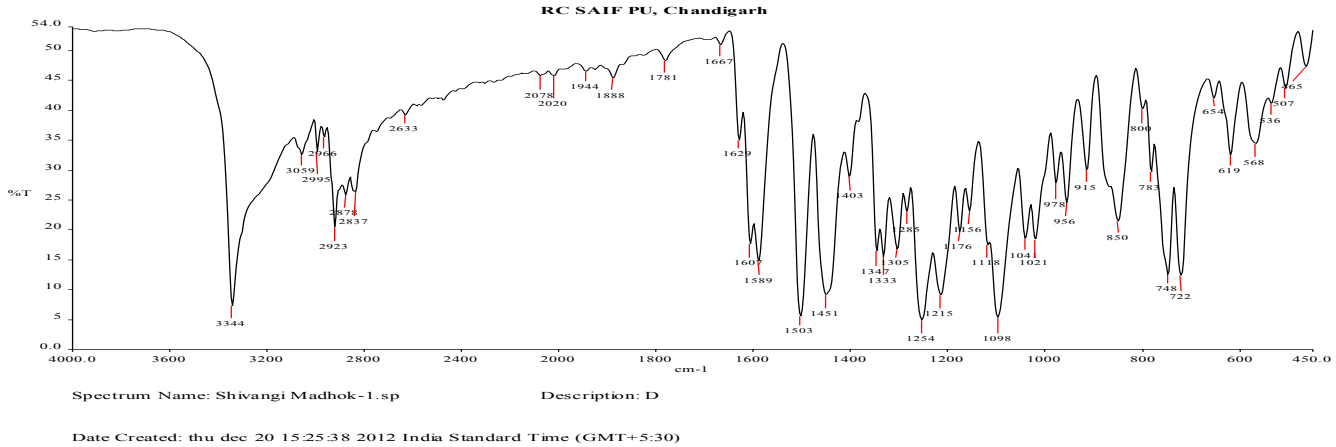

Figure 6: FTIR spectrum of pure carvedilol

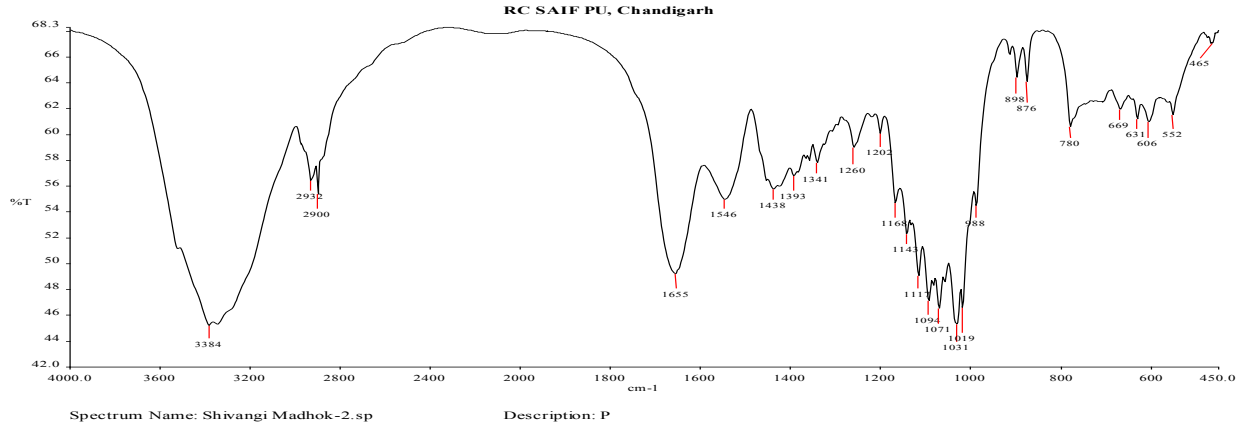

Figure 7: FTIR spectrum of skimmed milk powder

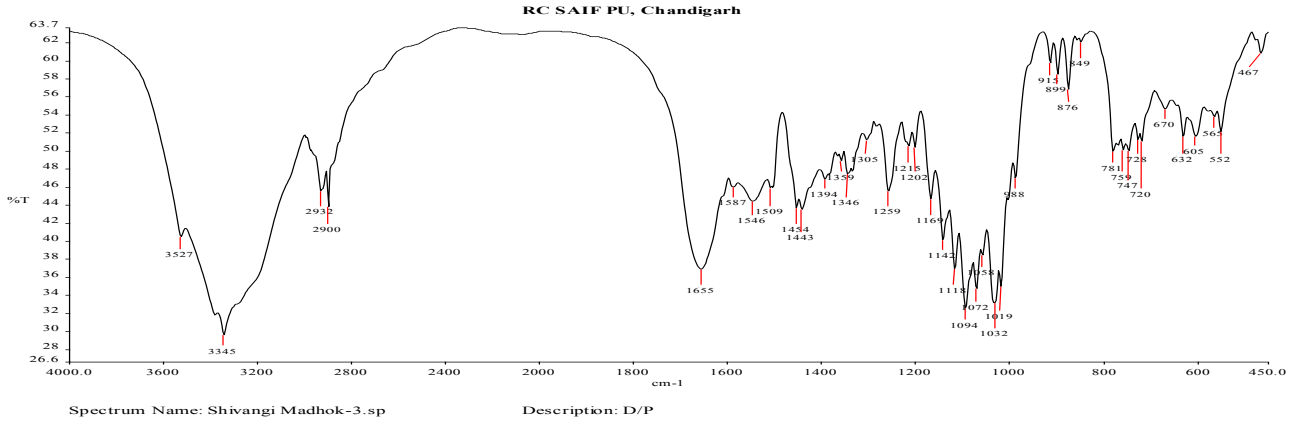

Figure 8: FTIR spectrum of physical mixture

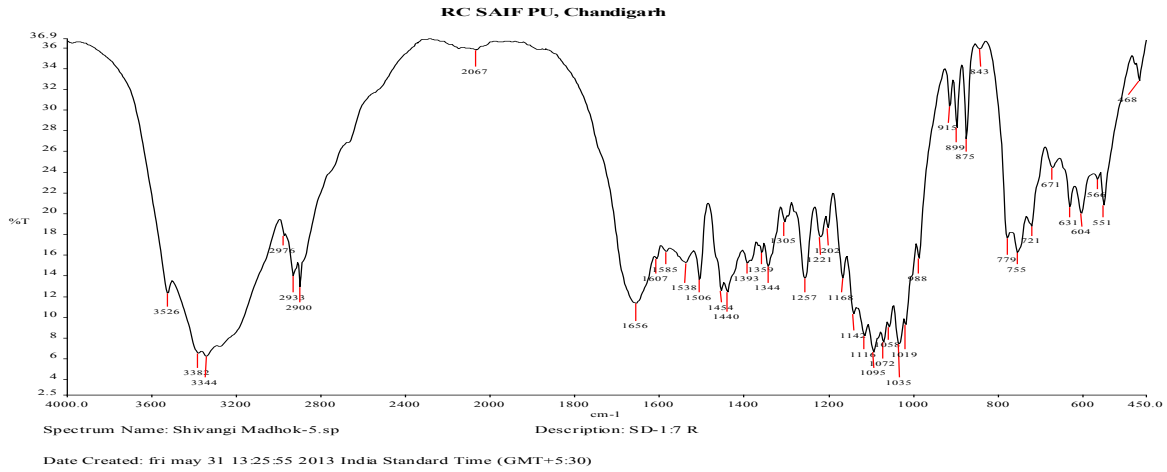

Figure 9: FTIR spectrum of CAR 4

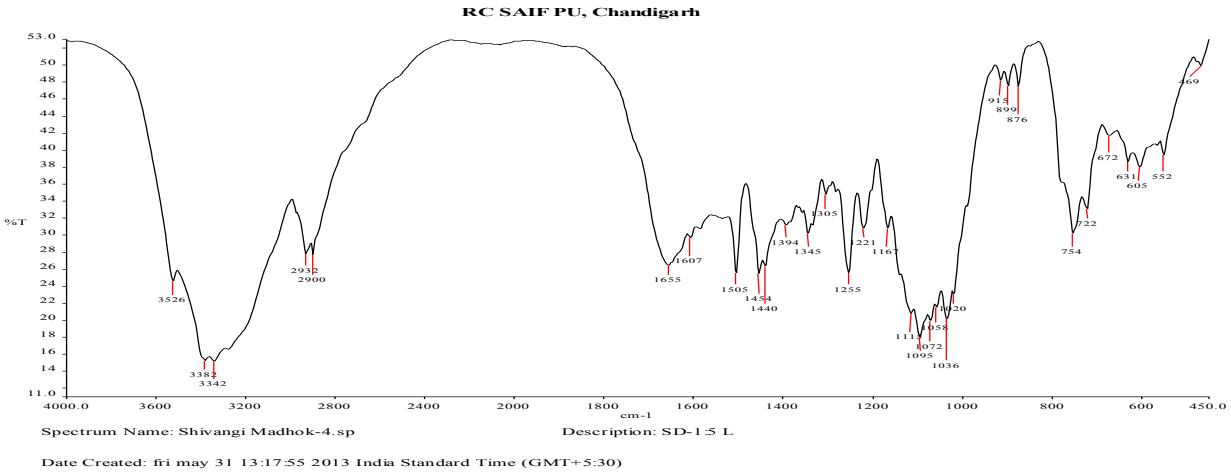

Figure 10: FTIR spectrum of CAR 7

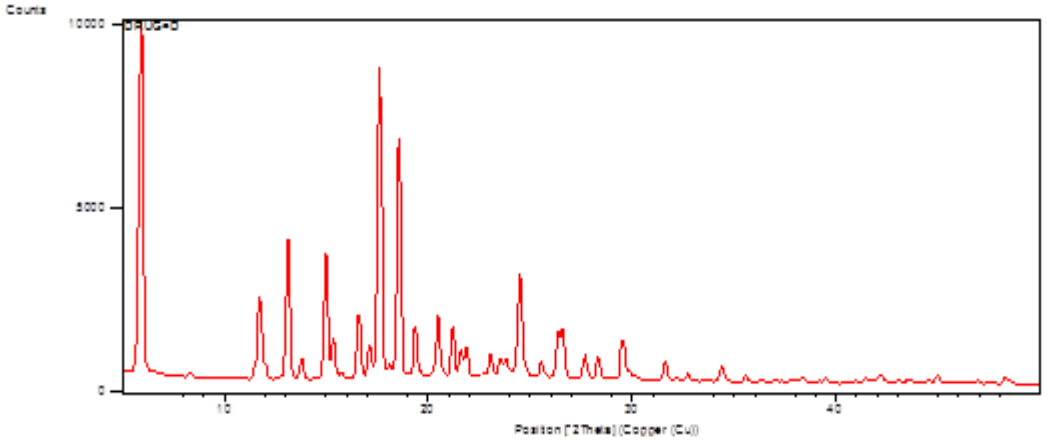

Figure 11: X-RD pattern of Carvedilol

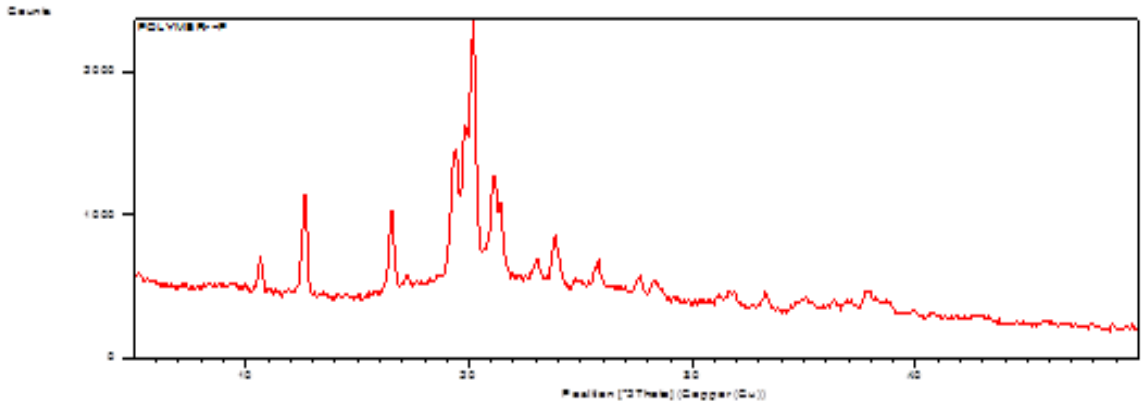

Figure 12: X-RD pattern of skimmed milk powder

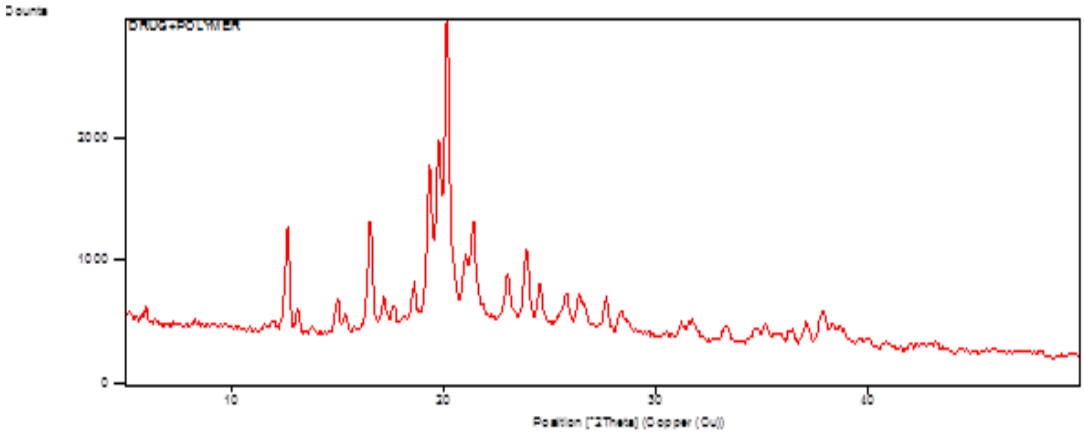

Figure 13: X-RD pattern of physical mixture

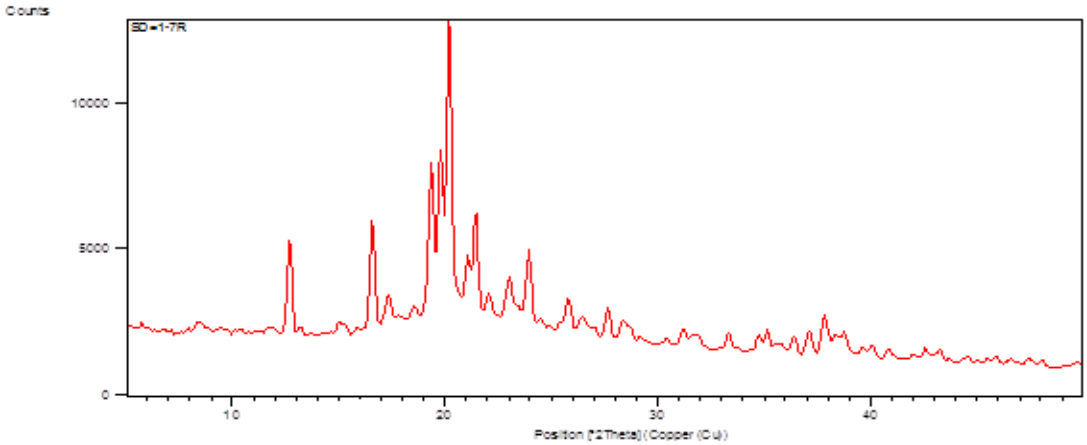

Figure 14: X- Ray diffraction of S.D. CAR 4

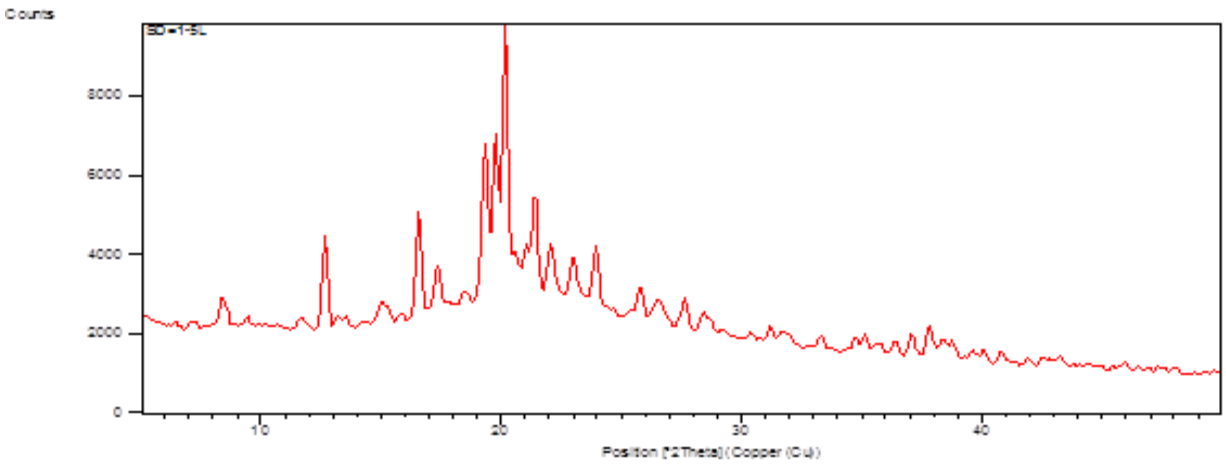

Figure 15: X- Ray diffraction of S.D. of CAR 7

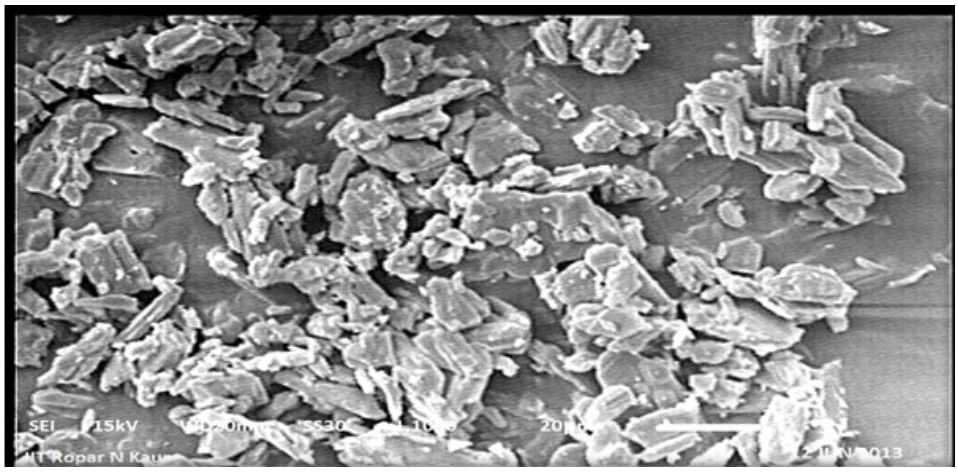

Figure 16: SEM image of CAR at 1,000 X

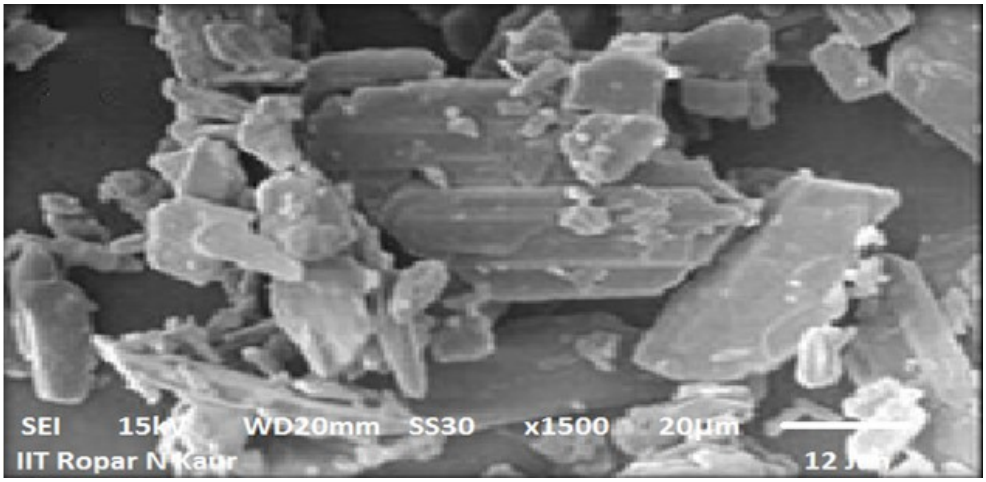

Figure 17: SEM image of CAR at 1,500 X

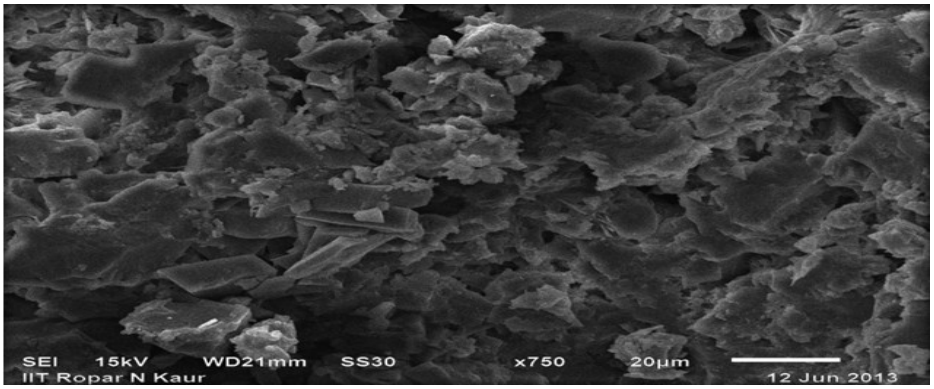

Figure 18: SEM image of S.D. of CAR 4 with rota evaporation method at 750 X

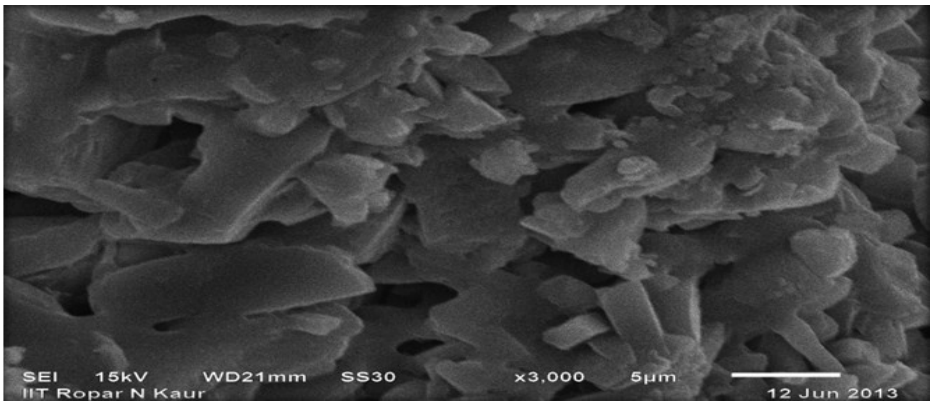

Figure 19: SEM image of S.D. of CAR 4 WITH rota evaporation method at 3,000 X

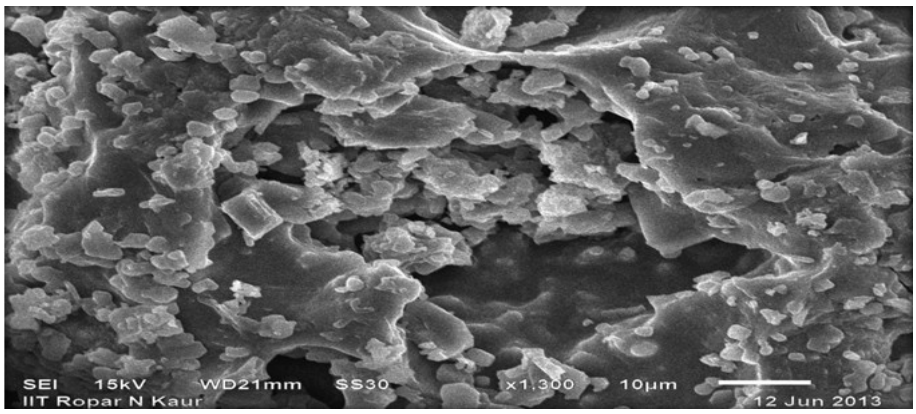

Figure 20: SEM image of S.D. of CAR 7 with lyophilization method at 1,300X

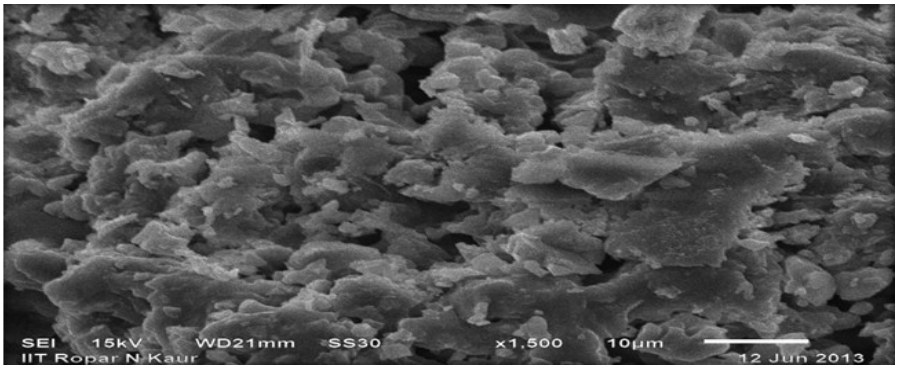

Figure 21: SEM image of S.D. of CAR: SM (1:5) with lyophilization method at 1500 X

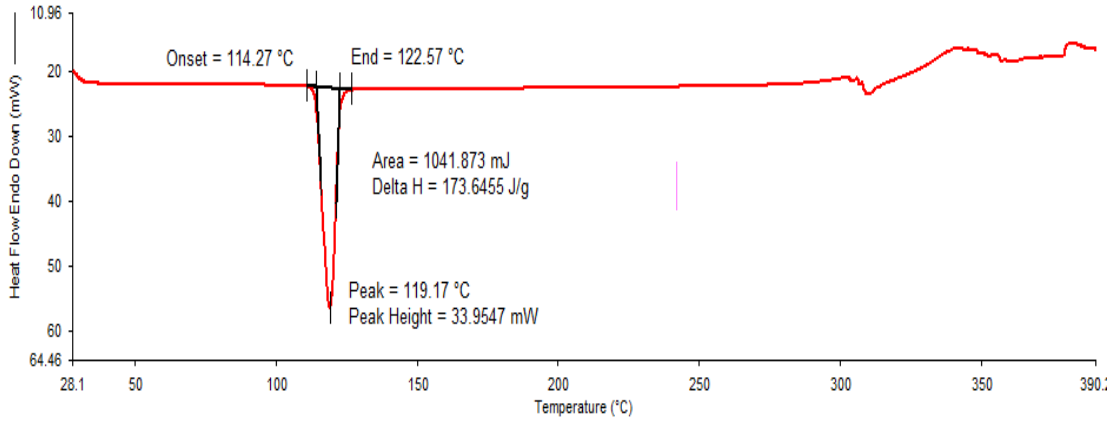

Figure 22: DSC Themogram of carvedilol

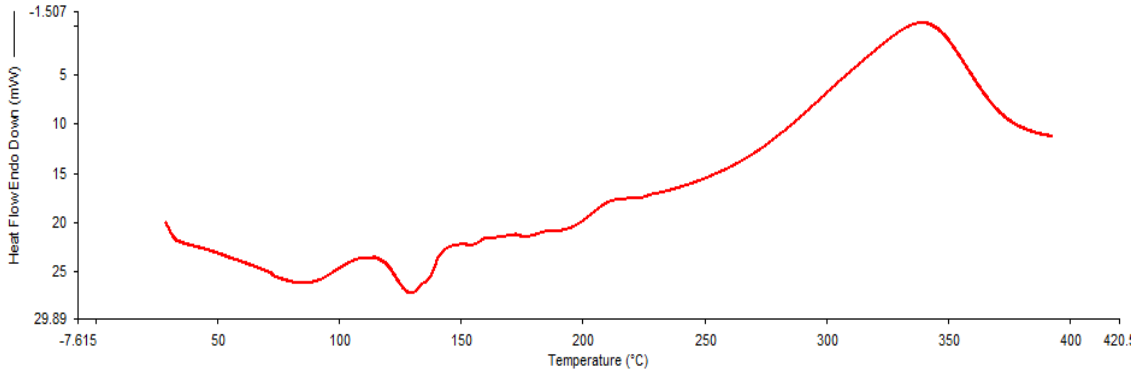

Figure 23: DSC Themogram of Skimmed Milk Powder

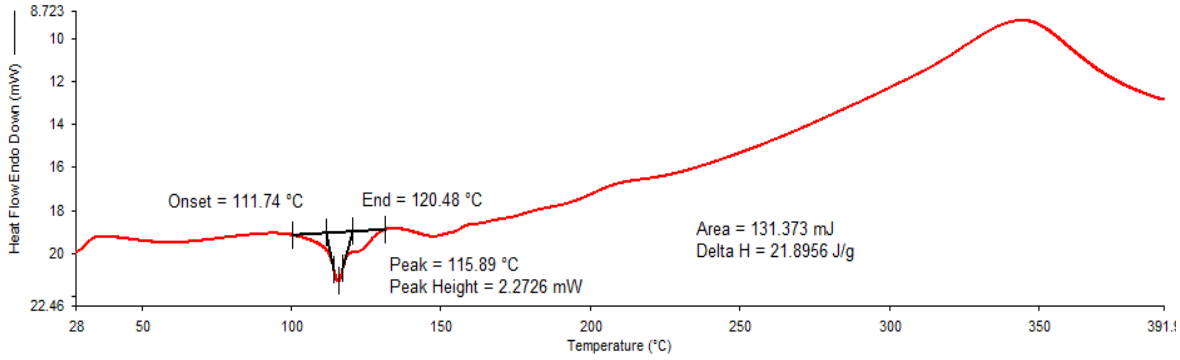

Figure 24: DSC Themogram of physical mixture

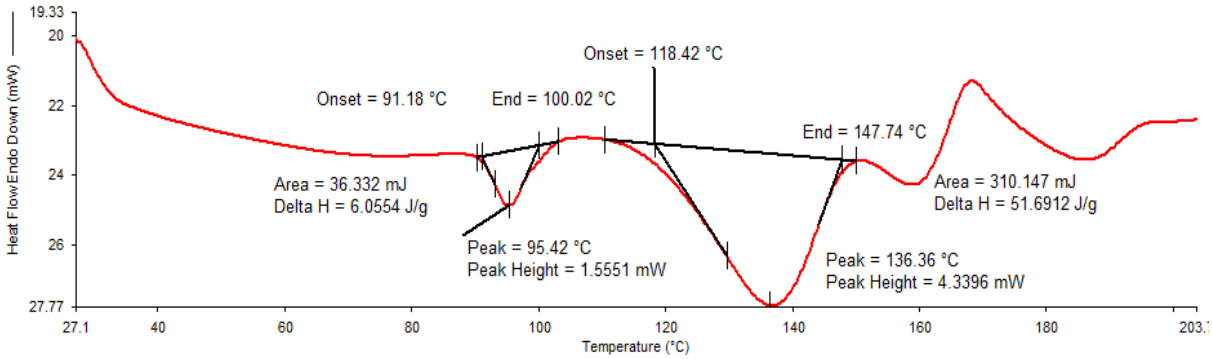

Figure 25: DSC Themogram of CAR 4

Table 9: Characterization of blends of selected SD tablets

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner's Ratio (Hr)	Compressibility Index (%) (CI)	Angle of Repose (^{0})
T1	0.532 ± 0.62	0.637 ± 0.18	1.079 ± 0.67	12.26 ± 0.53	28.09 ± 0.17
T2	0.567 ± 0.04	0.641 ± 0.03	1.130 ± 0.15	11.54 ± 0.01	27.88 ± 0.01

Data is expressed in mean ± S.D (n=3)

Table 10: Characterization of selected solid dispersion tablets

Formulation Code	Thickness (mm)	Hardness ($kg/cm^{2)}$	Weight Variation (mg)	Friability (%)	Disintegration Time (minutes)
T1	3.32 ± 0.76	3.4 ± 0.58	193 ± 1.98	0.50 ± 0.19	6 ± 0.01
T2	3.36 ± 0.70	3.3 ± 0.59	191 ± 1.96	0.51 ± 0.12	5 ± 0.01

Data is expressed in mean ± S.D (n=3)

Table 11: Drug content in the selected solid dispersion tablets

Formulation Code	Drug Content (mg/tablet)	Drug Content (%)
T1	9.72 ± 0.022	97.2
T2	9.85 ± 0.013	98.5

Data is expressed as mean ± S.D (n=3)

Table 12: Dissolution efficiency of selected formulation tablets and marketed tablet

S. No.	Formulation code	Dissolution efficiency (% DE_{60})
1	Marketed tablet	28.67
2	T1	54.25
3	T2	58.61

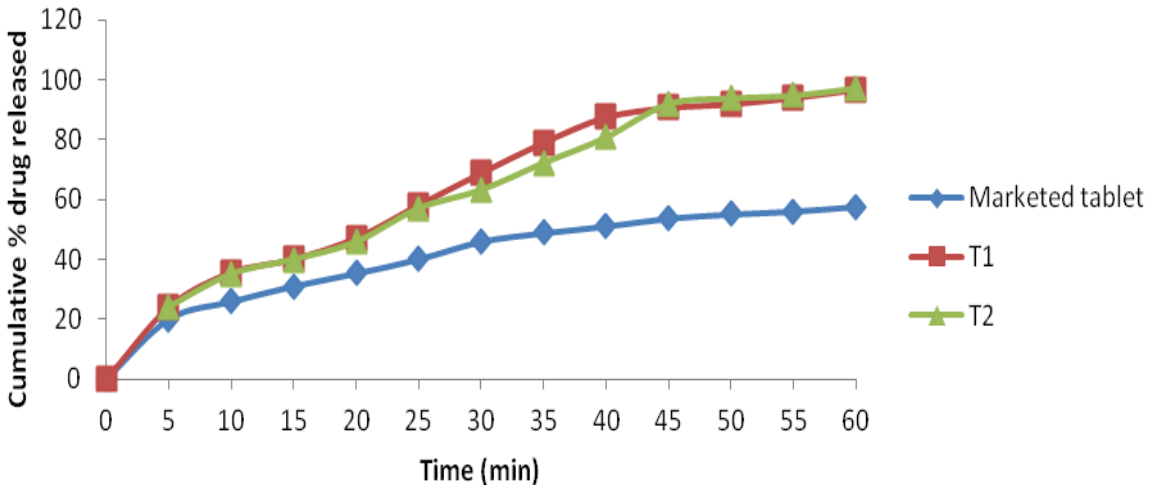

Figure 27: Dissolution profile of carvedilol from marketed tablet and best formulations (T1 AND T2)

Table 13: Dissolution profile of carvedilol from marketed tablet and selected solid dispersion tablets before stability studies

Time (min)	Cumulative mean percent released ± S.D.		
	Marketed Tablet	T1 Tablets	T2 Tablets
5	20.03 ± 0.230	24.10 ± 0.215	23.86 ± 0.230
10	25.89 ± 0.340	35.66 ± 0.641	34.98 ± 0.589
15	31.08 ± 0.389	40.09 ± 0.220	39.89 ± 0.230
20	35.34 ± 0.127	47.19 ± 0.240	45.76 ± 0.125
25	40.07 ± 0.121	58.19 ± 0.564	56.98 ± 0.161
30	45.98 ± 0.230	68.9 ± 0.220	63.18 ± 0.240
35	48.85 ± 0.568	79.10 ± 0.230	72.19 ± 0.422
40	51.08 ± 0.564	87.58 ± 0.230	80.76 ± 0.220
45	53.76 ± 0.161	90.73 ± 0.121	91.98 ± 0.230
50	55.16 ± 0.422	91.99 ± 0.125	93.88 ± 0.340
55	56.10 ± 0.122	94.12 ± 0.340	94.78 ± 0.240
60	57.66 ± 0.265	96.81 ± 0.215	97.26 ± 0.161

Data is expressed as mean ± S.D (n=3)

Table 14: Evaluation parameters after stability studies for T2

Parameters	Conditions 40 ± 2 °C and 75 ± 5 % RH						
Time period (days)	0	15	30	45	60	75	90
Color appearance	White	White	White	White	White	White	White
Drug content	97.3	98.7	99.1	97.5	98.8	96.9	97.2
Hardness ($kg/cm^{2)}$	3.5	3.1	3.4	3.1	2.9	3.3	3.5
Disintegration time (mins)	6	6.5	6	6	5	6	6.6

Table 15: Dissolution profile of carvedilol from marketed product and solid dispersion tablets after stability studies

Time (min)	Cumulative mean percent released ± S.D.		
	Marketed	T2 Tablets	S2 Tablets
5	20.03 ± 0.23	23.86 ± 0.23	23.32 ± 0.34
10	25.89 ± 0.34	34.98 ± 0.589	33.87 ± 0.161
15	31.08 ± 0.389	39.89 ± 0.23	38.9 ± 0.22
20	35.34 ± 0.127	45.76 ± 0.125	45.87 ± 0.126
25	40.07 ± 0.121	56.98 ± 0.161	55.99 ± 0.389
30	45.98 ± 0.23	63.18 ± 0.24	64.17 ± 0.23
35	48.85 ± 0.568	72.19 ± 0.422	73.10 ± 0.48
40	51.08 ± 0.564	80.76 ± 0.22	81.22 ± 0.96
45	53.76 ± 0.161	91.98 ± 0.23	91.84 ± 0.27
50	55.16 ± 0.422	93.88 ± 0.34	94.20 ± 0.58
55	56.10 ± 0.122	94.78 ± 0.24	95.90 ± 0.84
60	57.66 ± 0.265	97.26 ± 0.161	98.66 ± 0.71

Data is expressed as mean ± S.D (n=3)

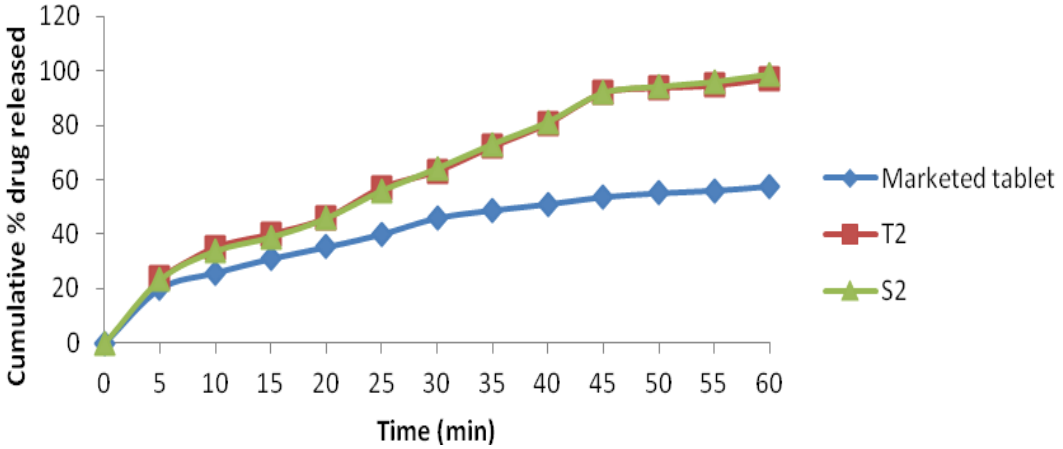

Figure 28: Dissolution profile of selected solid dispersion tablets before and after stability studies

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