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FORMULATION AND EVALUATION OF CARVEDILOL SOLID DISPERSION TABLETS FOR SOLUBILITY ENHANCEMENT

Arun Raj R.* and Dr. Jyoti Harindran

Department of Pharmaceutical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India.

***Corresponding Author: Arun Raj R.**
Department of Pharmaceutical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India.

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ABSTRACT

Objective: This study was mainly designed to solve the drawback of conventional Carvedilol solid dosage form, low bioavailability and limited clinical efficacy, by preparing Solid dispersion. **Methods:** Carvedilol solid dispersionwas developed by kneading method to modify the release and enhance solubility of the drug. The physical state of the dispersed Carvedilol in the polymer matrix was characterized by differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy, Fourier-transform infrared spectroscopy, super saturation solubility testing and dissolution studies. Optimized Carvedilol solid dispersions were formulated into tablets by direct compression method. **Results:** Compared with pure drug and physical mixture, the dissolution of Carvedilol - Solid dispersion was enhanced dramatically. Optimized Carvedilol solid dispersions tablet showed faster drug release in comparison to marketed tablet. Optimized formulation follows Higuchi's equation and the release mechanism is super case II transport. **Conclusion:** The present study conclusively indicated that the use of solid dispersion method by using water soluble carriers improved the solubility of poorly water soluble drug.

KEYWORDS: Solid dispersion, Carvedilol, Tablets, Optimization, Solubility enhancement.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to its convenience and ease of ingestion and it is probable that at least 90% of all drugs used to produce systemic effects administered by oral route. A solid dosage form is a drug delivery system that includes tablets, capsules, sachets, and pills, as well as bulk or unit-dose powders and granules. Among them tablets and capsules are most frequently given by this route. From a patient's perspective, swallowing a dosage form is far more comfortable and a familiar means of taking medication than getting injected. Oral drug administration still continues to be the most preferred route of drug delivery due to its manifold advantages including non-invasiveness, versatility and most important patient compliance. The long and continuing history of the development of new technologies for administration of drugs, the tablet form remains the most commonly used dosage form due to ease of production, inexpensive and patient friendly.[1]

The poor water solubility of many drugs is the major obstruction for the development of highly potent pharmaceutics. Low water solubility tends to the limited bioavailability and absorption of these agents. The developments of a suitable oral formulation for some drugs have always problems, which have very low water solubility. Carvedilol is a poorly water soluble drug having short half-life of 2-8 hours. The aim of the present study is to enhance the solublity of Carvedilol using different solid dispersion techniques with various carriers, which may results in increase absorption and thereby improved bioavailability. Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these orally administered drugs was its low solubility in biological fluids, which results into poor bioavailability after oral administration.[2] Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Is a well-known approach for improvement of the dissolution rate and bioavailability of drugs that are poorly water soluble. The carriers used have to be physiologically inert compounds that are readily water-soluble or water insoluble for fast or controlled dissolution respectively. To achieve faster dissolution rate of poorly water-soluble drug, the drug is dispersed at molecular level in a rapidly water-soluble inert carrier to form a solid dispersion. Successful dispersion of the drug in the carrier, at molecular level, leads to formation of homogeneous phase of the solid dispersion. When such a product comes in contact with gastric fluid, then the water-soluble carrier rapidly dissolves leading to immediate release of the drug at the desired molecular level to cause

dissolution with consequent improvement of bioavailability.[3, 4]

METERIALS AND METHODS

Materials

The following materials were used (Grade-LR): Carvedilol -API (Shasun Pharma, Pondichery), PEG6000, HPMC K100M, Lactose (Yarrow Chem Pvt. Ltd, Mumbai). Crospovidone, Talc, Magnesium Stearate (Chemdyes Corporation, Rajkot), Methanol (Nice Chemicals Pvt. Ltd, Cochin).

2.1. PREFORMULATION STUDIES

Preformulation studies were performed on the drug (API), which included solubility, melting point determination and compatibility studies.[5-12]

Solubility

Solubility of Carvedilol was observed in different solvents such as water, methanol and chloroform.

Melting point Determination

Melting point of the drug was determined by melting point apparatus.

IR Spectroscopy

FTIR spectral analysis of pure drug and polymer was carried out as physical mixtures. Observation was made whether changes in the chemical constitution of drug occurred after combining it with the polymer. The absorption maxima in spectrum were compared with the reference spectrum.

2.2 PREPARATION OF SOLID DISPERSION

Kneading Method

Solid dispersion of Carvedilol - PEG6000 and Carvedilol - HPMC K100M were prepared by kneading method. Polymer was mixed in glass mortar along with solvent to obtain a homogenous paste. The drug was then slowly added to the paste and the mixture was triturated for 1 hr. During the process the water content was empirically adjusted to maintain the consistency of paste. The paste formed was dried under vaccum for 24hrs. Dried powder was passed through specific sieve and stored in a desicator until further evaluation.[13,14]

Selection of Polymer

In order to select the best polymer for obtaining Solid dispersions, Solid dispersions was prepared by PEG 6000 and HPMC K100M.

2.3 EVALUATION OF SOLID DISPERSION

Percentage Yield

The prepared powders were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds which were used for preparation.[15-17]

$$\% \text{ Yield} = \frac{\text{Weight of Powder}}{\text{Weight of solid starting materials}} \times 100$$

Drug content

An accurately weighed 100 mg of formulations was taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1N HCl and assayed for drug content using the UV spectrophotometric method at 241 nm.[15-17]

Percentage drug release

Dissolution studies were carried for all the formulations, employing USP dissolution apparatus type I, using 900 ml 0.1N HCl as the dissolution medium at 50 rpm and 37 ± 0.5^0C. The samples were periodically withdrawn at suitable time intervals 5, 10, 15, 30, 45 & 60 minutes and volume replaced with equivalent amount of plain dissolution medium. The samples were filtered and diluted. Absorbance of the resulting solution at 241 nm using UV-visible spectrophotometer.[15-17]

2.4 OPTIMIZATION OF SOLID DISPERSION

Response surface methodology using factorial design was chosen for the optimization of spherical agglomerates because it allows the determination of influence of the factors with a minimum number of experiments. The independent factors were Amount of PEG 6000 (X1), Amount of methanol (X2). The response variables were dissolution at 60th min (%) (Y1), Drug content (Y2) and solubility enhancement ratio (Y3). Nine formulations were prepared according to Factorial design. The formulations were F1 to F9. The responses obtained from the design matrix were statistically evaluated using Design expert 10 statistical software trial package, Stat – Ease 10.0.3.1.[18]

Preparation of different formulations by Solid dispersion

Carvedilol formulations were prepared by Solid dispersion and process variables like Amount of polymers and Amount of solvents were optimized.

Characterization of optimized SD, Sol. D and IC

Dissolution rate

The dissolution studies of Solid dispersions were performed using USP dissolution apparatus type I. Dissolution study was performed in 900 ml 0.1N HCl. The stirring speed was 50 rpm, and the temperature was maintained at 37°C±0.5°C. The samples were withdrawn periodically and were replenished with fresh dissolution medium. The samples were filtered, diluted and analyzed by UV spectrophotometer at 241 nm using 0.1 N HCL as blank.[15-17]

Drug content

An accurately weighed 100 mg of Solid dispersion formulations was taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1N HCl and assayed for drug content using the UV spectrophotometric method at 241 nm.[15-17]

Solubility Analysis

To evaluate increase in solubility of Carvedilol after forming Solid dispersion saturation solubility measurements were carried out as follows: known excess of formulations was added to 10 ml of distilled water. Samples were shaken for 24 hours at room temperature in a rotary flask shaker. Samples were then filtered through No. 41 whatman filter paper and the filtrate was suitably diluted and analyzed spectrophotometrically at 241 nm. Saturation solubility of the pure drug was also determined.[15]

2.5 DEVELOPMENT OF THE OPTIMUM BATCH

Based on the statistical evaluations the software suggested one optimum batch from each Solid dispersion formulations. These batches of formulations were used for the further studies

2.6 EVALUATION OF OPTIMIZED SOLID DISPERSION

Percentage Yield

The prepared powders were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds which were used for preparation.[15-17]

Drug content

An accurately weighed 100 mg of optimized formulation were taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1N HCl and assayed for drug content using the UV spectrophotometric method at 241 nm.[15-17]

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Solubility Analysis

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IR Spectroscopy

IR spectral analysis of optimized formulations were carried out. Observation was made whether changes in the chemical constitution of drug occurred after combining it with the polymers. The absorption maxima in spectrum were compared with the reference spectrum.[5-12]

Scanning Electron Microscopy Analysis

The obtained agglomerates were subjected to Surface Electron Microscopy (SEM) analysis in order to check whether the obtained crystal had become spherical in shape.[19]

X-Ray Diffraction Study

X-ray powder diffraction patterns of Carvedilol, optimized formulations were conducted with a Phillips X'pert Pro P analytical diffractometer using a copper Kα target with a nickel filter at 45 kV voltage, 30 mA current and at scanning speed of 0.05s over a 2θ range of 5°-60°.[19]

Differential scanning calorimetry

DSC thermogram of carvedilol and optimized formulations were recorded on the DSC (Perkin Elmer Pyris1 DSC). Samples were sealed in pans and scanned at a heating rate of 10^{o}C min-1 over a temperature range of 50-300^{o}C under nitrogen gas stream.[16]

2.7 EVALUATION OF PRE-COMPRESSION PARAMETERS OF OPTIMIZED SOLID DISPERSION

Angle of repose

Angle of repose was determined by using fixed funnel method. The powders were allowed to flow through the funnel fixed on a burette stand at definite height (h). The angle of repose (θ) was then calculated by measuring the height (h) and radius(r) of the heap of granules formed.[20]

$\tan\theta = h/r$ or **$\theta = \tan^{-1}(h/r)$**

Bulk density

The bulk density of powder is dependent on particle packing and changes as powder consolidates. Apparent bulk density was determined by pouring a weighed quantity of powder into a graduated cylinder and measuring the volume of packing.[20]

Bulk density = Weight of the powder / Volume of the packing

Tapped density

Tapped density is defined as the mass of a powder divided by the tapped volume. Tapped density was determined by tapping method. Weighed quantity of powder was placed in a graduated cylinder and tapped until no further change in volume of powder was noted and the volume of tapped packing was noted.[20]

Tapped density = weight of the powder / volume of the tapped packing

Compressibility index: The compressibility of the powder was calculated by determining the Carr's index and Hausner's ratio.

$$\text{Car's consolidation index \%} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

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

2.8 PREPARATION OF TABLETS WITH OPTIMIZED CARVEDILOL- SOLID DISPERSION FORMULATIONS

DIRECT COMPRESSION METHOD

Optimized Carvedilol- Solid dispersion formulations were formulated into tablets by direct compression method. In the case of direct compression, lactose, a directly compressible vehicle was used as filler. Crospovidone (5%), talc (2%), and magnesium stearate (5%) were incorporated, respectively as disintegrant and lubricants. All the ingredients were blended thoroughly in a closed dry plastic container. The blend of powders was compressed in to tablets on a single punch tablet machine having diameter 7mm.[21-23]

2.9 EVALUATION OF TABLETS

PHYSICO-CHEMICAL PROPERTIES

Thickness: The tablet thickness was calculated using Vernier calipers. It is expressed as mm.[5-12]

Hardness: The hardness of the prepared tablets was estimated using Monsanto hardness tester. Three tablets from each formulation batch were selected and force is applied diametrically. It is expressed in kg/cm^2.[5-12]

Friability: Roche friabilator was used for testing the friability of prepared fast dissolving tablets. It subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes or 100 revolutions. Pre weighed sample (Wi) of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed (Wf). The friability (F) is given by the formula.[5-12]

$$F = \frac{Wi - Wf}{Wi} \times 100$$

Weight Variation test: The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with IP Limits, variation within the I.P limits; it passes the weight variation test.[5-12]

Drug Content: Five tablets were weighed and powdered using a glass mortar and pestle. An accurately weighed 100 mg of powder was taken into 50 ml volumetric flask, dissolved in methanol and the solution was filtered through what man filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of

Melting point Determination: Melting point of the drug was found to be 115^0 C which is in conformity with the pH 1.2. The drug content was determined at 241 nm by UV-spectrophotometer.[15-17]

Disintegration time: The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus. 900 ml Distilled water was used as a disintegrating media at 37 ± 0.2^oC. The time required to obtain complete disintegration of all the tablets were noted.[5-12]

Wetting time and water absorption ratio: Tablets were separately weighed (Wa) and carefully placed onto the surface of a piece of tissue paper twice folded in a 5 cm diameter petridish containing 6 ml of water. The time for complete wetting (water reaches the upper surface of the tablet) was noted and recorded as the wetting time. The wetted tablet was carefully removed and reweighed (Wb). Water absorption ratio (R) through the tablet was then determined according to equation below.[5-12]

$$R = 100 \times (Wb - Wa)/Wb$$

In-vitro drug release study: The dissolution studies of pure drug and optimized Solid dispersion tablets were performed using USP dissolution apparatus type I. Dissolution study was performed in 900 mL 0.1N HCl. The stirring speed was 50 rpm, and the temperature was maintained at 37°C±0.5°C. The samples were withdrawn periodically and were replenished with fresh dissolution medium. The samples were filtered, diluted and analyzed by UV spectrophotometer at 241 nm.[15-17]

2.10 COMPARISON OF OPTIMISED SOLID DISPERSION TABLETS WITH MARKETED TABLET

The dissolution rate of the optimized Solid dispersion tablets was compared with the marketed available tablet of Carvedilol and compare the release profiles.

2.11 KINETICS OF IN-VITRO DRUG RELEASE

To study the release kinetics of in-vitro drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer- Peppas as log %drug released Vs log time.[24, 25]

3. RESULTS AND DISCUSSION

3.1 PREFORMULATION STUDIES

Solubility study: Solubility of the drug Sample in Water, Chloroform and Methanol was examined.

Table 1: Solubility profile of the drug

Drug	Water	Methanol	Chloroform
Carvedilol	Insoluble	Freely Soluble	Soluble

reported range. It indicates the purity of the drug sample. If any impurity is present, it will cause variation in the melting point of given substance.

FTIR Spectroscopy: IR spectrum of Carvedilol was compared with the spectra of Physical mixtures of Carvedilol with different polymers used, (PEG 6000 and HPMC K100M). There was no disappearance of any characteristic peaks. This shows that there is no chemical interaction between drug and polymers used. The presence of characteristic peaks confirmed that the drug and polymers used were compatible.

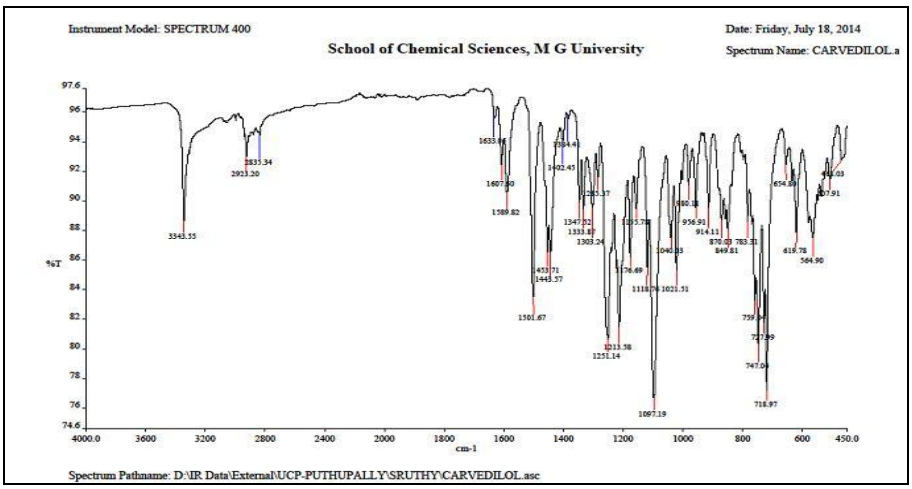

Figure 1: IR Spectrum of Carvedilol

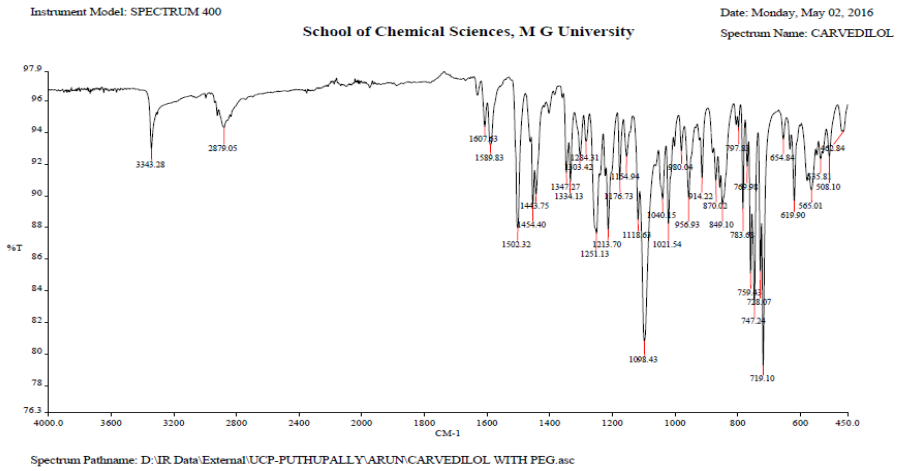

Figure 2: IR spectrum of Carvedilol + PEG 6000

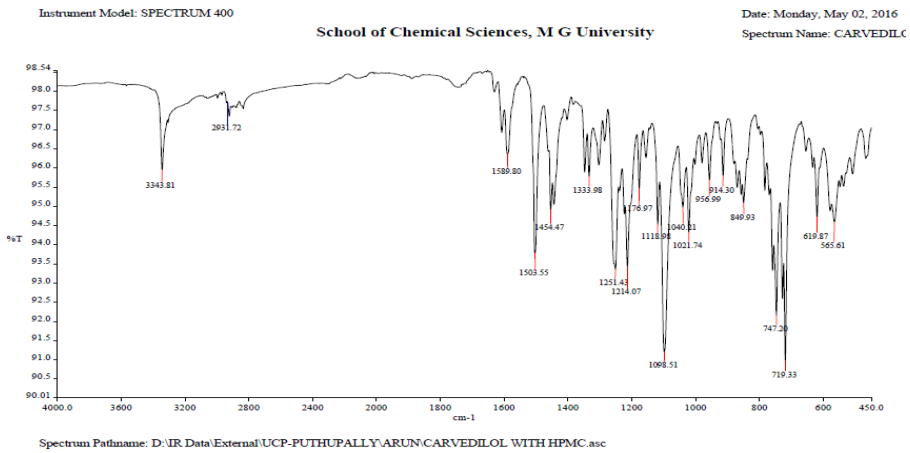

Figure 3: IR spectrum of Carvedilol + HPMC K100M

3.2 PREPARATION OF SOLID DISPERION (SD)

Solid dispersions of Carvedilol – PEG 6000, HPMC K100M were prepared by using kneading method. The composition of Carvedilol solid dispersions are given below.

Table 2: Composition of different solid dispersion formulations

CODE	COMPOSITION	RATIO	METHOD
SD1 SD2 SD3 SD4	CARVEDILOL: PEG6000	1:1 1:2 1:3 1:4	KNEADINGMETHOD
SD5 SD6 SD7 SD8	CARVEDILOL: HPMCK 100M	1:1 1:2 1:3 1:4	KNEADING METHOD

3.3 EVALUATION OF SOLID DISPERION (SD)

Percentage Yield: The percentage yield of the prepared Solid dispersions of Carvedilol was in the range of 91.50% to 97.81% being the highest for the formulation SD4 which was prepared by using PEG 6000 and the lowest for the formulation SD5 which was prepared by using HPMC K100M. The percentage yield data of all formulation is shown in Table 3.

Drug content: The percentage drug content of prepared Solid dispersions of Carvedilol was in the range of 70.16% to 94.77% being the highest for formulation SD4 which was prepared by using PEG 6000 and the lowest for the formulation SD5 which was prepared by using HPMC K100M. The percentage drug content data of all formulation was shown in Table 3.

Table 3: Percentage yield and drug content of Solid dispersions

Formulation	Percentage yield (%)	Drug Content (%)
SD1	93.21±0.17	71.22±0.05
SD2	93.39±0.03	76.11±0.55
SD3	95.63±0.07	87.55±0.76
SD4	97.81±0.11	94.77±0.44
SD5	91.50±0.06	70.16±0.63
SD6	92.23±0.01	74.69±0.58
SD7	95.68±0.44	84.39±0.64
SD8	96.72±0.76	93.29±0.13

Percentage drug release: *In-vitro* dissolution studies showed the effect in drug release from all formulations. Percentage release of Solid dispersions at 1 hr was found to be between 80.10%-95.63%. Cumulative % drug released at various time intervals of all formulations are given in Table 4 as follows.

Table 4: Percentage drug release of Solid dispersions

Time (min)	Percentage(%) drug release							
	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
0	0	0	0	0	0	0	0	0
10	25.07±0.26	27.48±0.12	29.99±0.35	33.55±0.41	24.80±0.37	25.25±0.64	28.72±0.75	32.54±0.38
30	64.38±0.18	68.94±0.22	71.47±0.47	74.36±0.12	64.05±0.21	65.11±0.69	68.50±0.45	70.61±0.53
45	70.81±0.34	73.48±0.48	77.81±0.14	80.37±0.53	69.08±0.72	70.35±0.25	73.96±0.58	78.28±0.25
60	81.24±0.62	83.94±0.38	87.85±0.64	95.63±0.16	80.10±0.25	82.65±0.38	85.14±0.22	94.17±0.43

Selection of Polymer: In order to select the best polymer for obtaining Solid dispersions, SD1, SD2, SD3, SD4 were prepared by using PEG 6000 and SD5, SD6, SD7, SD8 were prepared by using HPMC K100M. From the above analyses of SD, it was found that the Solid dispersions prepared by using PEG 6000 showed better results in comparison to other formulations. The formulation were further statistically optimized using Design expert 10 statistical software trial package, Stat – Ease 10.0.3.1.

3.4 OPTIMIZATION OF SOLID DISPERION

Preparation of different formulations of Solid dispersions: Solid dispersions with different ratios were prepared and variables like amount of PEG 6000 and amount of methanol were for the best formulation.

Table 5: Formulation Table of optimized Solid dispersions

Runs	Formulation Code	Amount of Carvedilol (gm.)	Amount of PEG 6000 (gm.)	Amount of methanol (ml)
1	$F_{1\ SD}$	1	2	3
2	$F_{2\ SD}$	1	2	4
3	$F_{3\ SD}$	1	2	5
4	$F_{4\ SD}$	1	3	4
5	$F_{5\ SD}$	1	3	3
6	$F_{6\ SD}$	1	3	5
7	$F_{7\ SD}$	1	4	5
8	$F_{8\ SD}$	1	4	4
9	$F_{9\ SD}$	1	4	3

Characterization of optimized SD

Dissolution rate of Solid dispersions

Table 6: Percentage drug release of Solid dispersions

Time (min)	Percentage(%) drug release								
	$F_{1\ SD}$	$F_{2\ SD}$	$F_{3\ SD}$	$F_{4\ SD}$	$F_{5\ SD}$	$F_{6\ SD}$	$F_{7\ SD}$	$F_{8\ SD}$	$F_{9\ SD}$
0	0	0	0	0	0	0	0	0	0
10	26.17±0.15	28.24±0.34	27.20±0.22	31.34±0.18	29.27±0.46	30.31±0.32	32.38±0.42	33.41±0.27	33.41±0.33
15	48.32±0.54	50.06±0.13	46.88±0.38	53.17±0.29	51.10±0.31	52.13±0.28	54.42±0.44	56.29±0.15	55.24±0.51
30	68.76±0.14	69.76±0.32	67.67±0.58	71.88±0.39	70.84±0.22	71.88±0.27	72.93±0.38	75.00±0.17	73.96±0.25
45	74.04±0.63	75.04±0.35	72.95±0.29	78.17±0.73	76.10±0.58	77.14±0.46	79.92±0.24	81.30±0.56	80.26±0.14
60	83.33±0.75	84.41±0.68	83.36±0.49	88.63±0.52	86.50±0.23	87.59±0.48	93.82±0.55	95.89±0.39	94.85±0.23

Drug content: The percentage drug content of the solid dispersions formulations were given in table 7. It can be seen that the formulations in small polymer ratio which gave comparatively low drug content. The formulation with higher polymer ratio gave high drug content.

Table 7: Percentage drug content of Solid dispersions

Formulation	Drug Content (%)
$F_{1\ SD}$	72.78±0.12
$F_{2\ SD}$	78.10±0.27
$F_{3\ SD}$	77.10±0.22
$F_{4\ SD}$	88.88±0.43
$F_{5\ SD}$	84.00±0.36
$F_{6\ SD}$	87.01±0.25
$F_{7\ SD}$	93.20±0.31
$F_{8\ SD}$	95.21±0.14
$F_{9\ SD}$	94.06±0.46

Solubility Analysis: The solubility of the solid dispersions formulations and that of pure Carvedilol in water were given in table no 8. According to the table, the solubility of the formulations increases with an increase in concentration of polymer used.

Table 8: Solubility study of Solid dispersions

Formulation	Solubility (mg/ml)	Solubility enhancement ratio
Pure drug	0.0093	-
$F_{1\ SD}$	0.0597	06
$F_{2\ SD}$	0.0798	08
$F_{3\ SD}$	0.0697	07
$F_{4\ SD}$	0.1013	11
$F_{5\ SD}$	0.0855	09
$F_{6\ SD}$	0.0913	10
$F_{7\ SD}$	0.1100	12
$F_{8\ SD}$	0.1350	15
$F_{9\ SD}$	0.1287	14

3.5 DEVELOPMENT OF THE OPTIMUM SD BATCH

Based on the statistical evaluations the software gave a solution for obtaining maximum percentage drug release**,** drug content and solubility enhancement ratio of the SD formulations. The formula opted for the further studies were given along with percentage drug release**,** drug content and solubility enhancement ratio.

Table 9: Formula for optimum SD batch based on statistical evaluations.

Number	Amount of PEG 6000 (gm.)	Amount of methanol (ml)	Dissolution at 60^{th} min (%)	Drug content (%)	Solubility enhancement ratio
1	4	3.825	95.788	95.915	14.858

3.6 EVALUATION OF OPTIMIZED SD

The SD formulations were evaluated for Percentage yield, Drug content, Dissolution at 60^{th} min, Solubility analysis, FTIR, SEM, Powder X-ray diffraction, DSC. The evaluation is depicted in Table.

Table 10: Evaluation of optimized SD formulation

Formulation	Percentage yield (%)	Drug content (%)	Solubility (mg/ml)	Solubility enhancement ratio
Optimized SD	96.64±0.38	95.81±0.22	0.135	15

Table 11: Percentage drug release of SD formulation

Time (min)	Percentage(%) drug release of Optimized SD
0	0
10	33.41
15	54.21
30	73.96
45	81.30
60	95.89

Scanning Electron Microscopy Analysis: The shape and surface morphology of pure drug and SD formulation were as follows. SEM is a qualitative method used to study the structural aspects of SD and drugs, or the products obtained using different methods of preparation. Imaging of solid dispersion by SEM is expected to provide information on the surface morphology. Morphological changes of these structures can be taken as a proof of the formation of a solid dispersion. The study shows change in crystal pattern of drug to amorphous form. This change in crystal pattern accounts for increased solubility. Drug and Solid dispersion of drug showed significant difference in the microscopic structure.

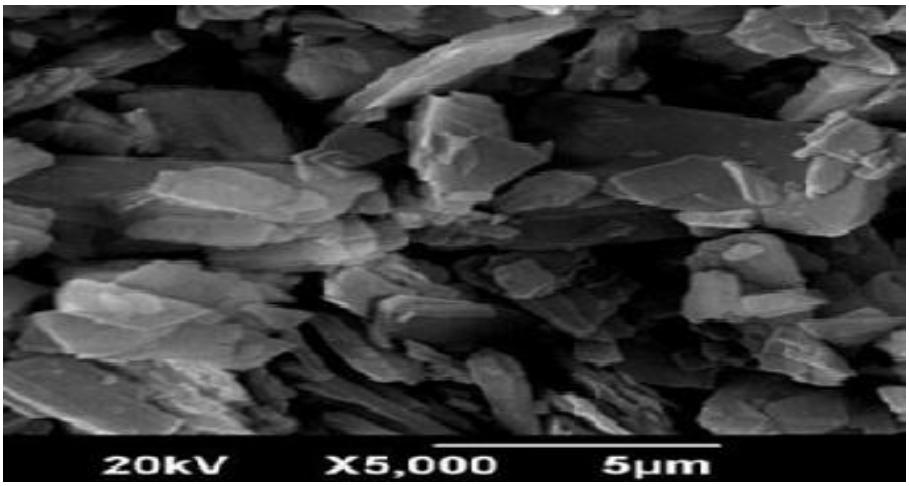

Figure 4: SEM picture of Pure drug (Carvedilol)

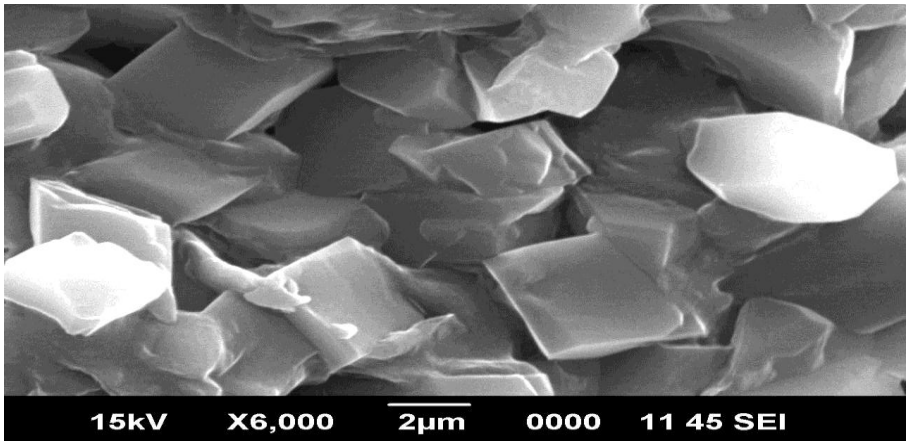

Figure 5: SEM picture of Solid dispersions

X-ray diffraction study: The X-Ray diffraction diagram of Carvedilol (figure) was compared with that of the solid dispersions. The XRD pattern of pure drug Carvedilol shows peaks which are intense and sharp shows the crystalline nature of the drug. The XRD pattern of solid dispersions showed undefined, broad peaks with less intensity. The peak of diminished intensity shows the decrease in Crystallinity of the drug and the nature of the drug converted to amorphous form and thus improved solubility of the drug.

D

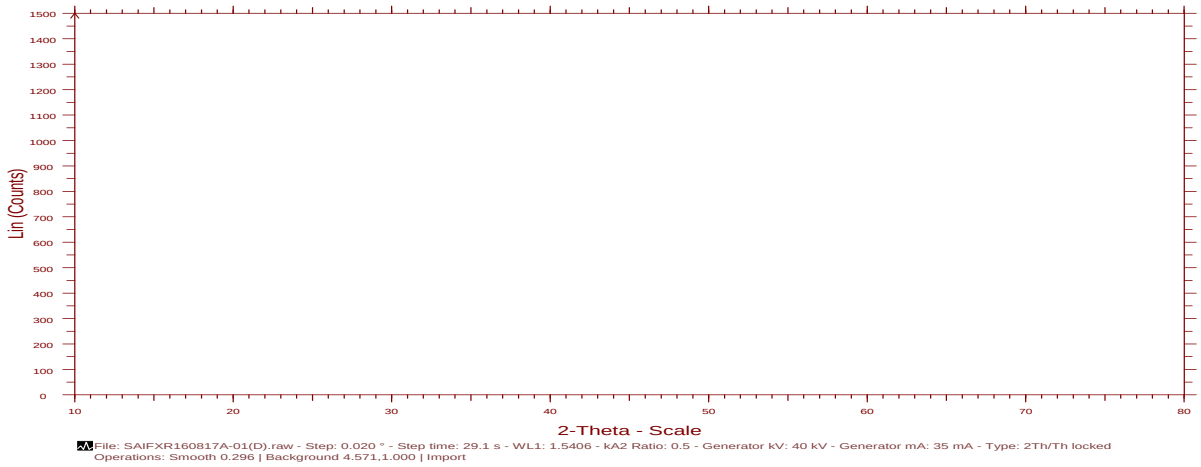

Figure 6: X-ray diffraction of Carvedilol

F

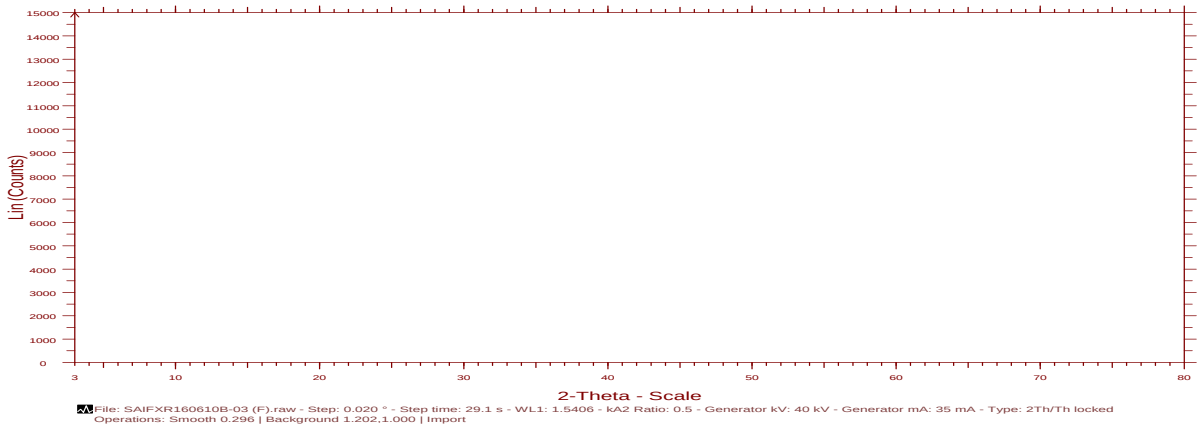

Figure 7: X-ray diffraction of Solid dispersions

Differential scanning calorimetry study (DSC): The pure drug and the solid dispersion formulation were analyzed by DSC to study the thermal behaviour. DSC thermogram of drug and solid dispersion are shown in the fig 8 & fig 9. The DSC analysis provided additional evidence that solid dispersions were formed. When solid dispersions were formed, their melting, boiling, and sublimation points shifted to different temperatures or disappear. DSC thermogram of Carvedilol pure drug shows an endothermic peak at 120^0c, which is related to the Melting point of the pure drug. It indicates that the drug carvedilol used was in pure crystalline state. In DSC thermogram of carvedilol solid dispersion sharp endothermic peak was absent, which is different from pure drug, suggesting that there is formation of the solid dispersion.

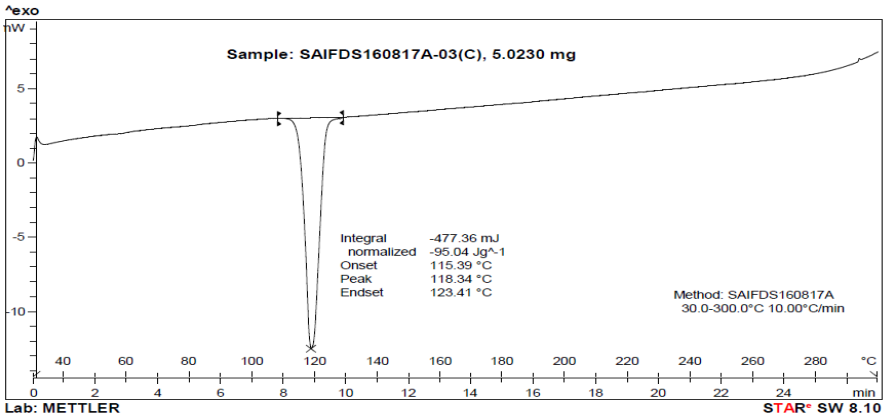

Figure 8: DSC thermogram of Carvedilol

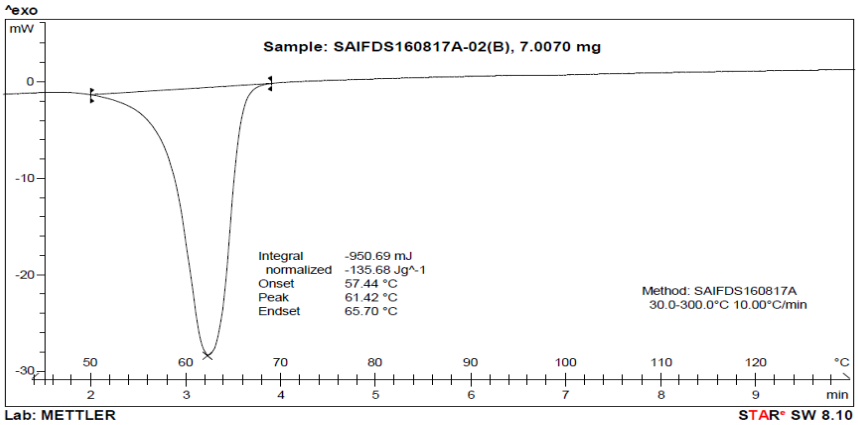

Figure 9: DSC thermogram of Solid dispersions

3.7 PRECOMPRESSION EVALUATION OF OPTIMIZED SD

Table 12: Micrometric properties of the powder

Formulation	Bulk Density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (CI)	Hausner Ratio (HR)	Angle of Repose (θ)
Optimized SD	0.54	0.65	16.92	1.20	28.92

3.8 PREPARATION OF TABLETS WITH OPTIMIZED CARVEDILOL- SD FORMULATION

Table 13: Formulation Code of optimized SD formulation tablet and pure drug Tablet

Ingredients (mg)	Formulations	
	Optimized SD	Carvedilol Pure drug
Carvedilol	-	12.5
Solid dispersions of carvedilol eqvlnt to 12.5 mg	65.23	-
Crosspovidone (5%)	10	10
Talc (2%)	4	4
Magnesium stearate (5%)	10	10
Lactose	163.5	163.5
Total weight (mg)	**200**	**200**

3.9 EVALUATION OF CARVEDILOL- SD TABLETS

Physicochemical properties of tablets: The SD formulations tablets and pure drug Tablet were prepared by direct compression technique. The tablets were evaluated for thickness, hardness, friability and weight variation and % Drug content.

Table 14: Physicochemical properties of SD tablets and pure drug Tablet

Formulation	Thickness (mm)*	Hardness (kg/cm^2)*	Weight variation (mg)**	Friability (%)	Drug content (%)*
Optimized SD	4.4 ± 0.17	4.46±0.17	200.6±0.16	0.370	99.22 ±0.62
Pure drug tablet	4.3 ± 0.83	4.51±0.13	200.6±0.36	0.412	99.16±0.1

* Values are expressed as mean ± S.D., n=3.
**Values are expressed as mean ± S.D., n=10.

Table 15: Results of disintegration time, wetting time and water absorption ratio

Formulation	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio
Optimized SD	34 ±0.46	44±0.30	55±1.0
Pure drug tablet	31±0.19	38±0.20	48±2.0

S.D., n=3.

3.10 COMPARISON OF OPTIMISED SD TABLETS WITH MARKETED TABLET

Table 16: Comparison of dissolution profile of tablet prepared from SD and pure drug with marketed form

Time (min)	Carvedilol Tablet (%CDR)		
	Optimized SD	Pure drug	Marketed
0	0	0	0
10	33.41±	9.61±	51.43±
15	53.17±	13.77±	63.97±
30	75.00±	16.90±	71.28±
45	80.26±	21.05±	85.85±
60	93.82±	24.19±	92.15±

The optimized formulations were compared with marketed tablet for different tests like hardness, friability, thickness, uniformity of drug content, and *in-vitro* dissolution study. The results are tabulated in table.

Table 17: Details of Marketed product

Sl. No.	Evaluation parameter	Observations
1	Hardness (kg/cm^2)	5 ± 0.17 kg/cm^2
2	Thickness (mm)	3.9 ± 0.34 mm
3	Friability (%)	0.595%
4	Weight Variation	pass
5	Percentage Drug content (%)	98.78 ± 0.11 %

3.11 KINETICS OF IN-VITRO DRUG RELEASE

The data were processed for regression analysis using MS-EXCEL statistical functions. Evaluation of release kinetics and application of best fit by correlation coefficient shows that the drug release follows Higuchi's equation. And their high Regression coefficient indicating the mechanism of release was diffusion controlled. From Korsemeyer-Peppas equation, release exponent was found to be 1.1219 which means that it follows super case II transport.

4. CONCLUSION

From this study, the increase in dissolution rates of carvedilol solid dispersions can be observed. Solubility studies showed a solubilizing effect of carriers on carvedilol. XRD, DSC and SEM studies of carvedilol solid dispersions indicated that the drug was entrapped within the carrier matrix and was present in amorphous form. In these systems drug carrier interaction was shown with the use of FTIR. The dissolution rates of physical mixtures were higher than those of pure drug, which was possibly caused by increased drug wettability. The pre-compression and post compression evaluations results are within the limit. Optimized carvedilol solid dispersions could be formulated into tablets by direct compression method. Optimized formulation showed faster drug release in comparison to marketed tablet. It follows Higuchi's equation and the release mechanism is super case II transport. It is clear from the data obtained that a higher polymer concentration gives faster drug release. Hence solid dispersion is one of most promising technique used in enhancing the solubility of poorly water soluble drug.

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