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ENHANCEMENT OF BIOAVAILABILITY OF CARVEDILOL USING SOLVENT DEPOSITION TECHNIQUES

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Keywords:

Solvent deposition, Carvedilol, Tablets, Optimization, Solubility enhancement

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ABSTRACT: Objective: Bioavailability is the key determinant of a drug for its therapeutic effectiveness, which in turn depends upon the solubility of that drug in gastro intestinal fluid. Carvedilol is a BCS class II drug. These category of drugs have low solubility and high permeability so their bioavailability is less. Solvent deposition is a promising method to improve the solubility of poorly water soluble drugs. **Methods:** Carvedilol solvent deposition was developed by solvent Evaporation 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 - Solvent deposition was enhanced dramatically. Optimized Carvedilol solvent deposition tablet showed faster drug release in comparison tomarketed tablet. Optimized formulationfollows Higuchi's equation and the release mechanism is super case II transport. **Conclusion:** The present study conclusively indicated that the use of solvent depositionmethod by using water soluble carriers improved the solubility of poorly water soluble drug.

INTRODUCTION: Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption.

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The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced [1].

In this method the rate of dissolution is increased by depositing drug in minuscular form on the surface of an adsorbent. Minuscular form implies the molecularly micronized form of drug, when it is extensively dispersed on the extensive surface of the microparticulate adsorbents. During dissolution the minuscular drug system releases only free, absorbable drug into solution. Hydrogen bonding and van der Waal's forces are accounted for

desorption of the drug from the adsorbent surface. The minuscular drug delivery system can be regarded as drug in a micro particulate form molecularly dispersed on the very extensive surface of carrier. The decrease in particle size and the resulting increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which greatly enhances the rate of solution of the drug. The solvent deposition system is usually prepared by simple evaporation of the solvent used for distribution of the drug on the matrix [2, 3]. The solvent deposition system is a solid preparation in which a drug is deposited from a solvent on the surface of a matrix. This step is usually done by simple evaporation of the solvent used for distribution of the drug onto the matrix. This is accomplished by equilibration of the drug in an organic solvent on water-insoluble excipients with an extensive surface [4].

METERIALS AND METHODS:

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

Preformulation Studies: Preformulation studies were performed on the drug (API), which included solubility, melting point determination and compatibility studies. [5-1]

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.

Preparation of Solvent Deposition System (Sol. D): Method: Solvent Evaporation Method:

Procedure: Dissolve the drug in sufficient quantity of solvent, methanol. To this solution add sufficient amount of polymer. This mixture is stirred well then evaporated in a water bath. Dry this system in a vaccum oven. Keep it in an air tight container and store in dessicator.

Selection of Polymer: In order to select the best polymer for obtaining Solvent depositions, Solvent depositions was prepared by Lactose and MCC.

2.3 Evaluation of Solvent Deposition System:

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]

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

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 ^{0}C. 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]

Optimization of solvent Deposition System: Response surface methodology using factorial design was chosen for the optimization of Solvent deposition because it allows the determination of influence of the factors with a minimum number of experiments. The independent factors were Amount of MCC (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 Solvent deposition and process variables like Amount of polymers and Amount of solvents were optimized.

Characterization of optimized Sol. D:

Dissolution rate: The dissolution studies of Solvent deposition 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 Solvent deposition 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 Solvent deposition 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]

Development of the Optimum Batch: Based on the statistical evaluations the software suggested one optimum batch from each Solvent deposition formulations. These batches of formulations were used for the further studies.

Evaluation of Optimized Solvent Deposition System: 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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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 Solvent deposition 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 a2θ 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]

Evaluation of Pre-Compression Parameters of Optimized Solvent Deposition:

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]

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

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 agraduated 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.

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

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

Preparation of Tablets with Optimized Carvedilol - Solvent Deposition Formulations:

Direct Compression Method: Optimized Carvedilol- Solvent deposition 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]

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 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 ^{o}C. 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 petri dish 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 Solvent deposition 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]

Comparison of optimised solvent Deposition tablets with Marketed Tablet: The dissolution rate of the optimized Solvent deposition tablets was compared with the marketed available tablet of Carvedilol and compare the release profiles.

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]

RESULTS AND DISCUSSION:

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

Melting point Determination: Melting point of the drug was found to be 115 ^{0}C which is in conformity with the 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, (Lactose and MCC). 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.

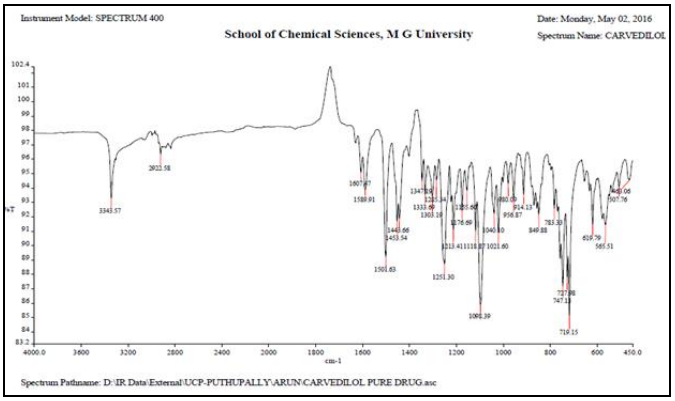

FIG. 1: IR SPECTRUM OF CARVEDILOL

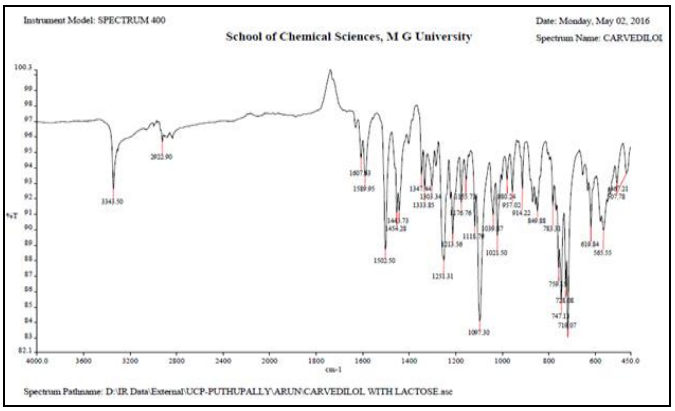

FIG. 2: IR SPECTRUM OF CARVEDILOL + LACTOSE

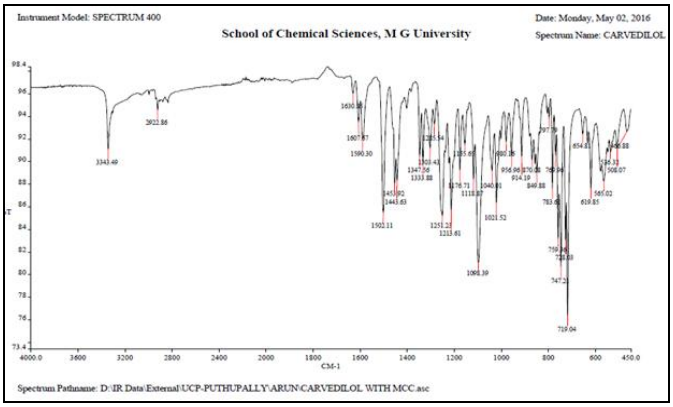

FIG. 3: IR SPECTRUM OF CARVEDILOL + MCC

Preparation of Solvent Deposition System (Sol. D): Solvent depositions of Carvedilol – Lactose, MCC were prepared by using Solvent evaporation method. The composition of Carvedilol Solvent depositions are given below:

TABLE 2: COMPOSITION OF DIFFERENT SOLVENT DEPOSITIONS FORMULATIONS

Code	Composition	Ratio	Method
Sol. D1	Carvedilol:	1:1	Solvent
Sol. D2	Lactose	1:2	Evaporation
Sol. D3		1:3	Method
Sol. D4		1:4	
Sol. D5	Carvedilol: MCC	1:1	Solvent
Sol. D6		1:2	Evaporation
Sol. D7		1:3	Method
Sol. D8		1:4	

Evaluation of Solvent Deposition System (Sol. D)

Percentage Yield: The percentage yield of the prepared Solvent depositions of Carvedilol was in the range of 89.30% to 95.76% being the highest for the formulation Sol. D8 which was prepared by using MCC and the lowest for the formulation Sol. D1 which was prepared by using Lactose. The percentage yield data of all formulation is shown in **Table 2**.

TABLE 3: PERCENTAGE YIELD AND DRUG CONTENT OF SOLVENT DEPOSITIONS

Formulation	Percentage Yield (%)	Drug Content (%)
Sol. D1	89.30±0.12	63.33±0.32
Sol. D2	92.96±0.15	67.40±0.35
Sol. D3	93.72±0.99	82.97±0.64
Sol. D4	95.51±0.11	86.46±0.26
Sol. D5	91.35±0.16	66.21±0.15
Sol. D6	94.36±0.14	71.71±0.20
Sol. D7	92.48±0.24	84.12±0.34
Sol. D8	95.76±0.48	89.34±0.24

Drug content: The percentage drug content of prepared Solvent depositions of Carvedilol was in the range of 63.33% to 89.34% being the highest for formulation Sol. D8 which was prepared by using MCC and the lowest for the formulation Sol. D1 which was prepared by using Lactose. The percentage drug content data of all formulation was shown in **Table 3.**

Percentage drug release: *In-vitro* dissolution studies showed the effect in drug release from all formulations. Percentage release of Solvent depositions at 1 hr was found to be between 70.23% -95.17%. Cumulative % drug released at various time intervals of all formulations are given in **Table 4** as follows:

TABLE 4: PERCENTAGE DRUG RELEASE OF SOLVENT DEPOSITIONS

Time (min)	Percentage(%) Drug Release							
	Sol. D1	Sol. D2	Sol. D3	Sol. D4	Sol. D5	Sol. D6	Sol. D7	Sol. D8
0	0	0	0	0	0	0	0	0
10	50.07±0.24	71.57±0.23	71.83±0.21	71.57±0.45	56.03±0.44	76.23±0.35	76.75±0.12	75.97±0.46
30	58.68±0.32	72.05±0.13	78.65±0.14	77.87±0.49	63.81±0.34	80.46±0.54	84.09±0.18	84.09±0.02
45	69.10±0.25	76.83±0.45	83.40±0.28	83.65±0.92	65.75±0.22	84.70±0.37	91.70±0.65	90.92±0.16
60	78.06±0.31	86.58±0.12	90.48±0.50	89.45±0.41	70.23±0.18	90.75±0.25	95.17±0.12	94.65±0.33

Optimization of Solvent Deposition System:

Preparation of different formulations of Solvent depositions: Solvent depositions with different ratios were prepared and variables like amount of MCC and amount of methanol were for the best formulation.

TABLE 5: FORMULATION TABLE OF OPTIMIZED SOLVENT DEPOSITIONS

Runs	Formulation Code	Amount of Carvedilol (gm.)	Amount of MCC (gm.)	Amount of methanol (ml)
1	$F_{1\ Sol.D}$	1	2	60
2	$F_{2\ Sol.D}$	1	2	80
3	$F_{3\ Sol.D}$	1	2	100
4	$F_{4\ Sol.D}$	1	3	80

5	$F_{5\ Sol.D}$	1	3	60
6	$F_{6\ Sol.D}$	1	3	100
7	$F_{7\ Sol.D}$	1	4	100
8	$F_{8\ Sol.D}$	1	4	80
9	$F_{9\ Sol.D}$	1	4	60

Characterization of optimized Sol. D:

Dissolution rate of Solvent deposition:

TABLE 6: PERCENTAGE DRUG RELEASE OF SOLVENT DEPOSITION

Time (min)	Percentage(%) drug release								
	$F_{1\ Sol.D}$	$F_{2Sol.D}$	$F_{3Sol.D}$	$F_{4Sol.D}$	$F_{5Sol.D}$	$F_{6Sol.D}$	$F_{7Sol.D}$	$F_{8Sol.D}$	$F_{9Sol.D}$
0	0	0	0	0	0	0	0	0	0
10	74.42±0.18	76.75±0.37	76.75±0.54	74.68±0.51	75.20±0.38	75.97±0.55	76.23±0.36	76.75±0.41	76.75±0.34
15	75.78±0.64	77.33±0.53	77.27±0.49	78.84±0.21	78.62±0.62	79.34±0.35	78.68±0.56	78.75±0.38	78.94±0.38
30	76.32±0.16	78.91±0.69	78.65±0.38	82.31±0.49	84.09±0.31	84.61±0.14	84.09±0.62	84.09±0.22	84.09±0.12
45	82.10±0.92	84.18±0.40	83.66±0.28	88.33±0.84	89.36±0.48	90.40±0.27	87.55±0.16	89.88±0.24	90.92±0.27
60	89.44±0.21	91.53±0.19	91.01±0.81	94.38±0.48	94.65±0.29	95.16±0.17	94.13±0.29	94.91±0.43	94.65±0.22

Drug content: The percentage drug content of the solvent depositions 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 SOLVENT DEPOSITIONS

Formulation	Drug Content (%)
$F_{1Sol.D}$	60.93±0.36
$F_{2\ Sol.D}$	66.54±0.14
$F_{3\ Sol.D}$	70.42±0.46
$F_{4\ Sol.D}$	81.24±0.12
$F_{5\ Sol.D}$	84.69±0.23
$F_{6\ Sol.D}$	89.29±0.37
$F_{7\ Sol.D}$	86.46±0.26
$F_{8\ Sol.D}$	84.30±0.41
$F_{9\ Sol.D}$	89.34±0.40

Solubility Analysis: The solubility of the solvent depositions formulations and that of pure Carvedilol in water were given in **Table 8**. According to the table, the solubility of the formulations increases with an increase in concentration of polymer used.

TABLE 8: SOLUBILITY STUDY OF SOLVENT DEPOSITIONS

Formulation	Solubility (mg/ml)	Solubility Enhancement Ratio
Pure drug	0.0093	-
$F_{1Sol.D}$	0.0548	06
$F_{2\ Sol.D}$	0.0641	07
$F_{3\ Sol.D}$	0.0723	08
$F_{4\ Sol.D}$	0.1084	12
$F_{5\ Sol.D}$	0.1266	14
$F_{6\ Sol.D}$	0.1189	13
$F_{7\ Sol.D}$	0.1185	13
$F_{8\ Sol.D}$	0.1410	15
$F_{9\ Sol.D}$	0.1274	14

Development of the Optimums 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 Sol. D 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 SOL. D BATCH BASED ON STATISTICAL EVALUATIONS

Number	Amount of MCC (gm.)	Amount of methanol (ml)	Dissolution at 60^{th} min (%)	Drug content (%)	Solubility Enhancement Ratio
1	3.921	62.28	94.787	88.408	14.559

Evaluation of Optimized Sol. D: The Sol. D formulation was 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 10** and **11**.

TABLE 10: EVALUATION OF OPTIMIZED SOL. D FORMULATIONS

Formulation	Percentage Yield (%)	Drug Content (%)	Solubility (mg/ml)	Solubility Enhancement Ratio
Optimized Sol. D	95.68±0.26	90.29±0.31	0.141	15

TABLE 11: PERCENTAGE DRUG RELEASE OF SOL. D FORMULATIONS

Time (min)	Percentage(%) drug release Optimized Sol. D
0	0
10	76.23±0.27
15	79.82±0.15
30	84.35±0.39
45	91.44±0.56
60	95.94±0.74

Scanning Electron Microscopy Analysis:

The shape and surface morphology of pure drug and Sol. D formulation were as follows. SEM is a qualitative method used to study the structural aspects of Sol. D and drugs, or the products obtained using different methods of preparation. Imaging of solvent deposition 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.

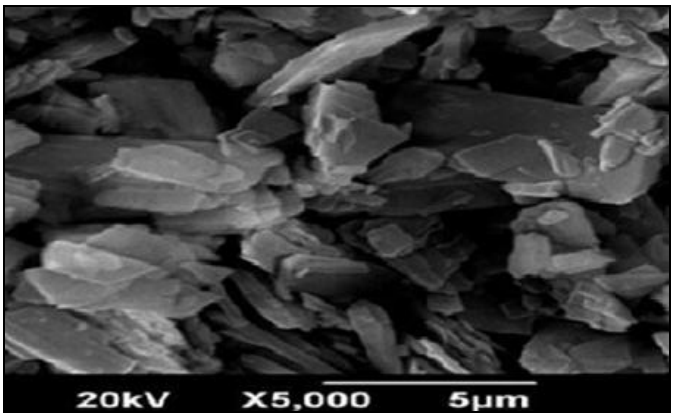

FIG. 4: SEM PICTURE OF PURE DRUG (CARVEDILOL)

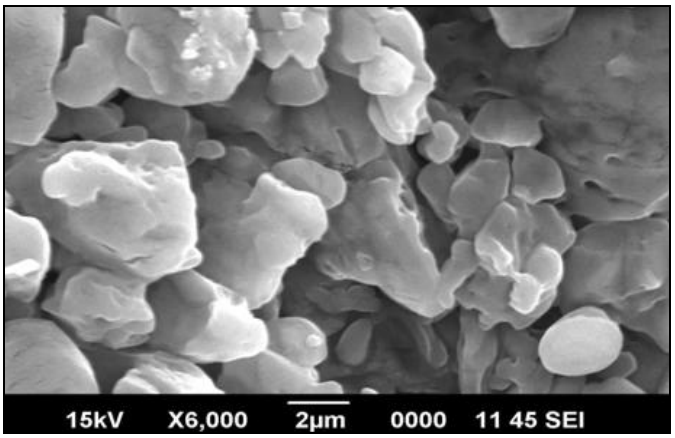

FIG. 5: SEM PICTURE OF SOLVENT DEPOSITIONS

X-ray diffraction study: The X-Ray diffraction diagram of Carvedilol (**Fig. 6**) was compared with that of the solvent deposition. 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 solvent deposition 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.

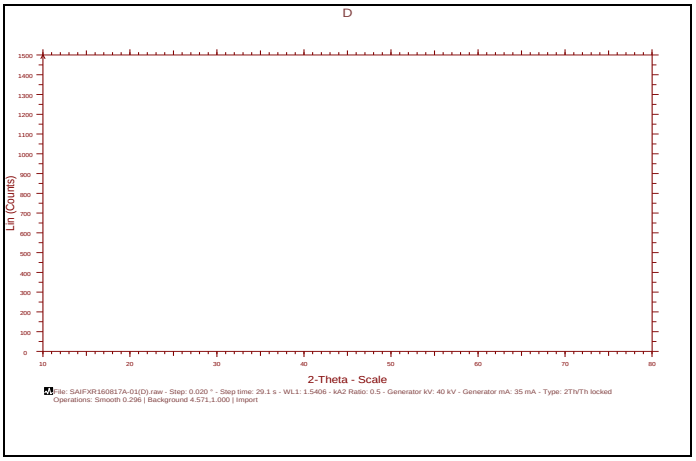

FIG. 6: X-RAY DIFFRACTION OF CARVEDILOL

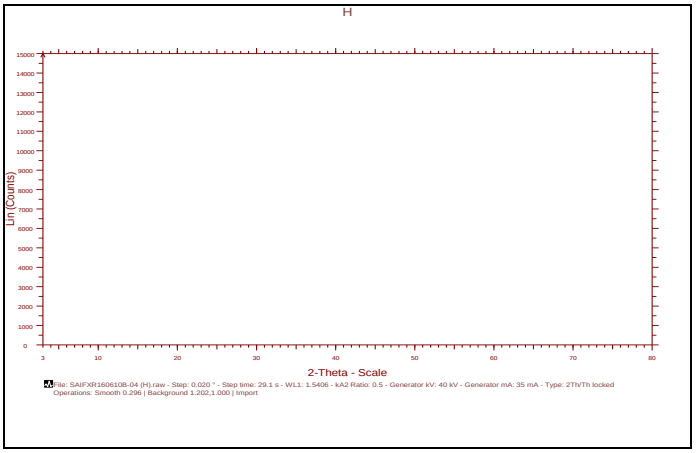

FIG. 7: X-RAY DIFFRACTION OF SOLVENT DEPOSITIONS

Differential Scanning Calorimetry Study (DSC):

The pure drug and the solvent deposition formulation were analyzed by DSC to study the thermal behaviour. DSC thermogram of drug and solvent deposition are shown in the **Fig. 8** and **Fig. 9**. The DSC analysis provided additional evidence that solid dispersions were formed. When solvent deposition was formed, their melting, boiling, and sublimation points shifted to different temperatures or disappear. DSC thermogram of Carvedilol pure

drug shows an endothermic peak at120 ^{0}C, 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 solvent deposition sharp endothermic peak was absent, which is different from pure drug, suggesting that there is formation of the solvent deposition.

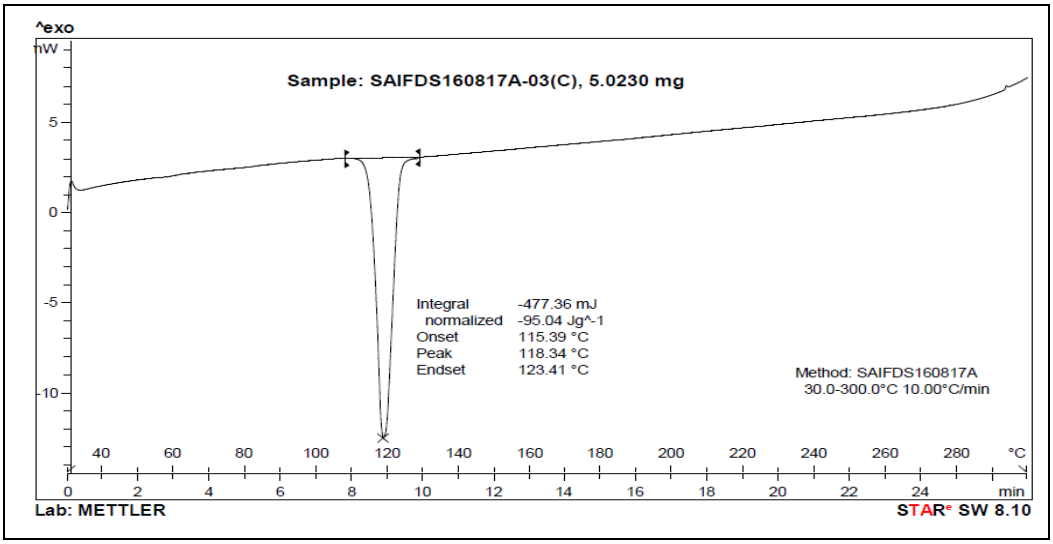

FIG. 8: DSC THERMOGRAM OF CARVEDILOL

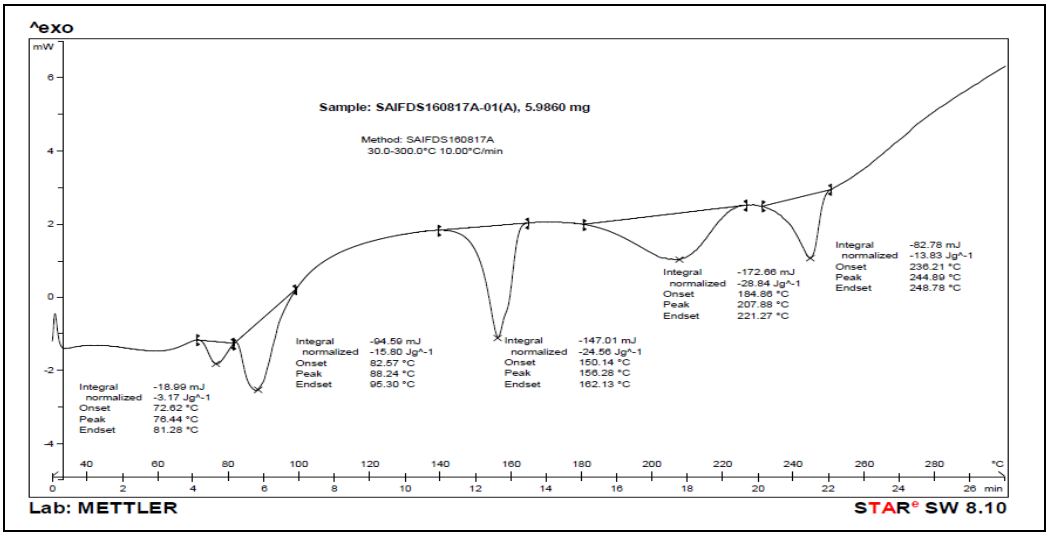

FIG. 9: DSC THERMOGRAM OF SOLVENT DEPOSITION

Precompression Evaluation of Optimized Sol. D:

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 Sol. D	0.63	0.76	17.65	1.21	29.09

Preparation of Tablets with Optimized Carvedilol- Sd, Sol. D And IC Formulations:

TABLE 13: FORMULATION CODE OF OPTIMIZED SD, SOL. D AND IC FORMULATIONS TABLETS AND PURE DRUG TABLET

Ingredients (mg)	Formulations			
	Optimized SD	Optimized Sol. D	Optimized IC	Carvedilol Pure drug
Carvedilol	-	-	-	12.5
Solvent depositions of carvedilol eqvlnt to	-	68.84	-	-

12.5 mg				
Crosspovidone (5%)	10	10	10	10
Talc (2%)	4	4	4	4
Magnesium stearate (5%)	10	10	10	10
Lactose	163.5	107.16		163.5
Total weight (mg)	200	200	200	200

3.9 Evaluation of Carvedilol- Sol. D Tablets:

Physicochemical properties of tablets: The Sol. D formulation 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 SOL. D TABLET AND PURE DRUG TABLET

Formulation	Thickness (mm)*	Hardness (kg/cm^2)*	Weight variation (mg)**	Friability (%)	Drug content (%)*
Optimized Sol. D	4.4 ± 0.15	4.46±0.14	200.1±0.89	0.416	98.89±0.45
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 Sol. D	32±1.26	42±0.50	59±1.5
Pure drug tablet	31±0.19	38±0.20	48±2.0

S.D., n=3

Comparison of Optimised Sol. D Tablet with Marketed Tablet:

TABLE 16: COMPARISON OF DISSOLUTION PROFILE OF TABLET PREPARED FROM SOL. D AND PURE DRUG WITH MARKETED FORM

Time (min)	Carvedilol Tablet (%CDR)		
	Optimized Sol. D	Pure drug	Marketed
0	0	0	0
10	33.41±0.26	9.61±0.34	51.43±0.28
15	60.43±0.63	13.77±0.14	63.97±0.35
30	83.23±0.21	16.90±0.68	71.28±0.68
45	89.57±0.17	21.05±0.25	85.85±0.43
60	94.87±0.64	24.19±0.73	92.15±0.27

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 17**.

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 %

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 1.2718 which means that it follows super case II transport.

CONCLUSION: From this study, the increase in dissolution rates of carvedilol solvent deposition can be observed. Solubility studies showed a solubilizing effect of carriers on carvedilol. XRD, DSC and SEM studies of carvedilol solvent deposition 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 solvent deposition could be formulated into tablets by direct compression method. Optimized formulation showed faster drug release in comparison tomarketed tablet. It follows Higuchi's equation and the release mechanism is super case II trasnsport. It is clear from the data obtained that a higher polymer concentration gives faster drug

release. Hence solvent deposition is one of most promising technique used in enhancing the solubility of poorly water soluble drug.

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REFERENCES:

1. Kulkarni, A. S., Aloorkar, N. H., Mane, M. S. & Gaja, J. B. Liquisolid Systems : A review. International Journal of Pharmaceutical Sciences and Nanotechnology : 2010; 3: 795–802.
2. Sonam Jain, Premjeet Sandhu1, Manisha Gurjar and Reetesh Malvi, Solubility Enhancement by Solvent Deposition Technique: An Overview. Asian Journal of Pharmaceutical and Clinical Research, 2012; 5(4):15-19.
3. Nikhil K. Sachan, Seema Pushkar, S.S Solanki and Dagendra S. Bhatere, Enhancement of solubility of Acyclovir by solid dispersion and inclusion complexation methods. World Applied Science Journal 2010; 11(7): 857-864.
4. Philip. J. Carloson, Lori A. Pretzer and Joel E. Boyd, Solvent deposition of Titaninum Dioxide on Acrylic for Photocatalytic Application, 2007, page. No: 7970- 7976.
5. Rajput N, Thakare VM, Tejade BW, Chaudari KP, Jadhao UT. Formulation and evaluation of fast dissolving tablet by inclusion complexation. Asian J Pharm Sci Technol 2014; 4: 15-20.
6. Azharuddin M, Kamath K, Shabaraya AR. Design and evaluation of fast dissolving tablets of carvedilol using sublimation technique. Indian J Pharm Sci Res 2012; 3: 3788-94.
7. Rao PM, Babu AM, Sree KN, Rameswarapu NS, Mallikharjunarao KL, Prasanna Kumar Desu. Formulation Development and *in-vitro* evaluation of immediate release tablets of biperiden HCl cyclodextrin complexes. Int J Res Pharm Nanosci 2013; 2: 757-67.
8. Giri TK, Biswanath SA. Preparation and evaluation of rapidly disintegrating Fast release tablet of Diazepam -Hydroxypropyl-β-Cyclo dextrin inclusion Complex. Sci Res Pharmacol Pharm 2010; 1: 18-26.
9. Bhanja SB, Ellaiah P, Nayak BS, Mahapatra DK, Sahu A, Padhy SK, *et al*., Enhancement of dissolution properties, preparation and evaluation of immediate release tablets of poorly soluble drug-repaglinide. Int J Pharm Technol 2011; 3: 2961-91.
10. Ratna JV, Sywalini V, Akshara T, Subbiah UV, Devi GS. Effect of hydrophilic polymers on solid dispersions of carvedilol for enhancing its dissolution rate. J Glob Trends Pharm Sci 2012; 3: 708-13.
11. Loyd V Allen. Remington-The Science & Practice of Pharmacy. 22nd Edition. The Pharmaceutical press, 2012; 687-690, 1313.
12. Aulton ME, Taylor KM. Aultons Pharmaceutics. The Design and Manufacturing Medicines. Third Edition. Elsevier publication, 2007. p. 329, 335, 353.
13. Nadia Saffoon, Riaz Uddin, Naz Hasan Huda and Kumar Bishwajit Sutradhar, Enhancement of Oral Bioavailability and Solid Dispersion: A Review, Journal of Applied Pharmaceutical Science 2011; 1(7): 13-20.
14. Hind Al Zein, Khalil Sakeer, Fars K Alanazi. Desiging an extended release waxy matrix tablets containing Nicardipine–hydroxy propyl β cyclodextrin. Saudi pharmaceutical journal 2011; 19: 245-253.
15. Shah M, Mehta T, Amin A. Preparation and characterization of inclusion complex of a calcium channel blocker. Int J Res Pharm Biomed Sci 2011; 2: 1731-8.
16. Shah SS, Pasha TY, Behera AK, Bhandari A. Solubility enhancement and physicochemical characterization of inclusion complexes of itraconazole. Sch Res Libr Pharm Lett 2012; 4: 354-66.
17. Rani P, Murthy VS, Madhavi BR. Comparative Study on the Preparation and characterization of Inclusion Complexes of BCS Class II drug with cyclodextrins. Adv Res Pharm Biol 2013; 3: 420-5.
18. P. Szabo´-Re´ve´sz a, H. Go¨czo˜, K. Pintye-Ho´di, P. Ka´sajr, I. Ero˜s, M. Hasznos-Nezdei, B. Farkas, Development of spherical crystal agglomerates of an aspartic acid saltfor direct tablet making. Powder Technology 2001; 114: 118–124.
19. Zhou Q, Wei X, Dou W, Chou G, Wang Z. Preparation and characterization of inclusion complexes formed between baicalein and cyclodextrins. Carbohydr Polym 2013; 95: 733-9. Available from: http://www.elsevier.com.
20. Metkari VB, Kulkarni LV, Patil PS, Jadhav PA, Jadhav PH, Yadav PS. Formulation and evaluation of fast dissolving tablets of carbamazepine using solid dispersion. Int J Pharm Res Sci 2014; 2: 47-59.
21. Hydroxy Propyl Beta Cyclodextrin. An Enabling Technology for Challenging Pharmaceutical Formulations; 2009. Available from: http:// www.Pharma-Mag.com.
22. Shirse P, Rao KS, Iqbal MM. Formulation and evaluation of cyclodextrin inclusion complex tablets of water insoluble drug-glimipiride. Int J Res Pharm Chem 2012; 2: 222-8.
23. Walter Lund. The Pharmaceutical Codex. Principles and Practice of Pharmaceutics. Twelth Edition. The Pharmaceutical press, 1994; 6: 244-245.
24. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13: 123-33.
25. Singhvi G, Singh M. Review article on *in-vitro* drug release characterization models. Int J Pharm Stud Res 2011; 2: 77-84.

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