International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2651-2662 www.ijprajournal.com ISSN: 2249-7781

Formulation development, optimization and evaluation of carvedilol loaded nanocrystal orodispersıble tablets for the management of hypertension

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Submitted: 20-12-2023 Accepted: 30-12-2023

ABSTRACT: Carvedilol is an antihypertensive drug belonging to BCS II class of drugs. The present research work is focused on the methods to enhance solubility and dissolution rate by decreasing particle size of drug. Carvedilol is converted into Nanocrystals using β Cyclodextrin stabilizer by Anti-solvent precipitation technique. The optimum formulation of Nanocrystals was determined by 3^2 Factorial design. The compatibility studies was done by IR spectroscopy showed no interaction between the drug and stabilizers. It was showed that β Cyclodextrin 1 % w/w concentration gives better drug release profile and enhances the solubility. Dissolution rate of optimized Carvedilol nanocrystals was found to be 96.89 % at 120 mins. The shape and surface morphology of Carvedilol nanocrystals as observed in SEM showed that the Nanocrystals were flaky in shape with rough surface and discrete in morphology without any aggregates or agglomerates. The optimized Carvedilol nanocrystals formulation was further formulated as Orodispersible tablets using suitable, non-interacting excipients by Direct compression technique. Precompression and post compression evaluation studies are also performed. Cumulative % drug release of the Carvedilol nanocrystal Orodispersible tablets was found to be 99.24% at 20 mins. The release kinetics of the Carvedilol nanocrystal Orodispersible tablets was best fitted to First order kinetics, which indicate the immediate release of the drug from CRV Nanocrystal Orodispersible tablets. Stability studies as per ICH guidelines were conducted for a period of 45 days and the tablets were found to be stable. Carvedilol nanocrystal Orodispersible tablet showed better drug release profile when compared to marketed immediate release Carvedilol tablets.

KEYWORDS: Nanocrystals; Carvedilol; Anti-solvent precipitation technique; Orodispersible tablets; in-vitro dissolution rate.

I. INTRODUCTION

Nanotechnology, according to the National Nanotechnology Initiative (NNI), is "research and development at the atomic, molecular, or macromolecular levels in the sub-100-nm range (1-100 nm) to create structures, devices, and systems with novel functional properties"[1]. Nanomedicine is a new discipline that involves using nanotechnology in medication development and offers even more exciting possibilities of novel diagnostics and cures as a result of growing interest in the uses of nanotechnology in the medical industry.[2]

The pharmacy field of nanoparticulate medication delivery system is one in which nanotechnology can be widely used. Nanotechnology has the potential to be used in the pharmaceutical industry for the creation of innovative diagnostic instruments as well as drug carrier systems[3]. Due to the reduction in particle size, drug delivery systems based on nanotechnology have greater advantages over conventional medications. Drug nanocrystals are drug crystals that are smaller than 1mm in size. By reducing the size of the drug's particles to the nanoscale range, the drug's saturation solubility, dissolution velocity, higher adhesiveness to surface and cell membranes, and furthermore, acceptable bioavailability when supplied orally are all improved.[4] Drug nanocrystals, as opposed to polymeric nanoparticles, are produced completely of the drug; there is no carrier material.[5]

Carvedilol is a synthetic member of the carbazole family that acts as both an antihypertensive and an alpha 1-adrenoceptor blocker without any intrinsic sympathomimetic activity. Its effects on beta receptors are stronger than those on alpha 1 receptors. It functions as a vasodilator, an alpha-adrenergic antagonist, a beta-adrenergic antagonist, and an antihypertensive medication. [6]

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Compared to other beta-blockers, carvedilol tends to have fewer frequent side effects, and those that do occur are typically dose-related. [7] Carvedilol is a water insoluble, white, crystalline powder. Although it is easily absorbed from the upper gastrointestinal tract, oral bioavailability is only said to be 25 -30%.

More than 98 % is bound to plasma proteins, primarily with Serum Albumin. Over the therapeutic range, the plasma-protein binding is not reliant on concentration. Excreted primarily as metabolites in the bile and feces; just 2% unaltered in the urine. 16% of CRV is excreted in the urine. It has an elimination half-life of 6 - 8 hours. [8]

It would be simple to synthesize nanocrystals into solid dosage forms like tablets. In general, the direct compression method is the best procedure to use for producing tablets. With the use of Nano- Crystal® Technology, Elan has developed an orally dissolving tablet that may be taken with or without water, making it easier for patients to take their prescription and removing the burden of ingesting big dosage forms. [9]

The present work is focused on solubilization of the poorly soluble BCS Class II drug Carvedilol by converting the drug into Nanocrystals using Antisolvent precipitation technique and optimizing the formulations. Further, the optimized formulation of nanocrystals is formulated as Orodispersible tablets to improve the Oral bioavailability of the drug and patient compliance.

II. MATERIALS AND METHODS

Materials:

Carvedilol (API), β Cyclodextrin, Pearlitol 100 SD, Microcrystalline cellulose, Sodium starch glycolate, Aerosil, Talc, Magnesium stearate, Sunset Yellow Lake, Orange flavour, Neotame were obtained as gift samples from Sai Mirrah Innopharm Pvt Ltd. Ethanol was purchased from Lab Chemicals, Chennai. All other reagents were of analytical grade.

Methods:

Preformulation (Compatibility) Studies:

Compatibility studies are carried out by Infrared Spectrophotometer in order to evaluate the drug polymer interaction.

Infrared (IR) spectroscopic studies:

Infrared (IR) spectrum of the drug, excipients and its physical mixtures are obtained using IR spectrophotometer The pellets are prepared on KBr-press under hydraulic pressure of 150kg /cm^2. the spectra is scanned over the wave number range of 4000 to 400 cm^{-1}at the ambient temperature [10]

Standard Curve for Carvedilol

Estimation of absorption maximum (λmax):

A known weight (100 mg) of drug (Cavedilol) is dissolved in sufficient amount of Ethanol in 100ml volumetric flask and 0.1 N HClwas added to make up the volume to give 1000µg/ml solution. The stock solution is further diluted using 0.1 N HCl to prepare 10µg/ml concentration. The resultant solution is scanned in the range of (200- 400nm) by UV Spectrophotometer to get absorption maximum (λ max).

Preparation of Standard calibration curve of Carvedilol:

From the above prepared stock solution, (2 to 10µg/ml) concentration solutions are prepared using the 0.1 N HCl. The absorbance of these solutions was measured at λ max.by UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan). A standard curve is plotted using concentration on X-axis and the absorbance on Y axis.

Formulation of Carvedilol Nanocrystals:

The Carvedilol nanocrystals are formulated by Anti-solvent precipitation technique.

a) Preparation of drug solution:

Adding a precisely weighed sample of the medication (93.75 mg) to 10 ml of ethanol.

b) Adding the drug solution to the stabilizer-containing aqueous solution

With the homogenizer running continuously at 1000 rpm for 1 hour, the produced drug solution is added dropwise at a rate of 2 ml/min into the appropriate volume (150 ml) of water with different stabilizer concentrations.

c) Removal of solvent:

The organic solvent is removed by continuous stirring for 2 hours at 500 rpm

d) Filter & oven dry the solution at 60 ^{0}C for 12 hrs to collect the nanocrystals.

Optimization of Carvedilol nanocrystals

The optimization of CRV Nanocrystals was done using 3^2 Factorial design in Design Expert® Software Version 13.

Characterization of Carvedilol nanocrystals:

Determination of Particle size and Zeta Potential:

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Volume 8, Issue 6 Nov-Dec 2023, pp: 2651-2662 www.ijprajournal.com ISSN: 2249-7781

The mean particle size (z-average), and zeta potential of Carvedilol nanocrystal formulations were determined by dynamic light scattering technique using a zeta size analyzer (Horiba Scientific SZ -100). The nanocrystals are redispersed with water to obtain a proper scattering intensity before measurement (Manish)

Determination of Drug Content

10 mg of CRV nanocrystal powder is dissolved in 5 ml methanol and by using 0.1 N HCl, the volume was made up to mark in 100 ml volumetric flask. Then the above solution was diluted and analysed spectrophotometrically at 285nm. [11]

Saturation solubility studies:

The Higuchi and Connors method was used to assess how the nanocrystals affected the solubility of CRV. To put it briefly, too much pure CRV, CRV mixed with stabilizers, and CRV nanocrystals are taken in 10 mL of distilled water and stored in separate screw-capped vials for 48 hours at 25°C±0.5°C in a thermostatically controlled shaking water bath. Every day up until equilibrium was established, samples were examined. Aliquots were then taken out, filtered using a 0.22 m filter, and their drug content was measured spectrophotometrically at 285 nm. [9]

In vitro dissolution studies:

All nanocrystal formulations were tested for drug dissolution in vitro using the USP dissolution device Type I (Basket method) at a rotation speed of 50 rpm. For each batch, sample of 3.125mg equivalent Carvedilol nanocrystals were taken and subjected to dissolution studies with 900 ml of 0.1 N HCl as dissolution medium. The bath was maintained at 37±0.5°C throughout the experiment. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at predetermined time intervals of 15, 30, 45, 60, 90 and 120 mins. The samples were replaced with fresh dissolution medium and absorbance values of sample solutions are measured at λmax in UV Spectrophotometer. The cumulative percentage drug release was calculated. [3]

Scanning electron microscopy (SEM):

The optimized CRV Nanocrystal formulation was examined for its surface characteristics and by using scanning electron microscopy. The detailed particle structural characterization was conducted at different acceleration voltage and the surface morphology of the CRV nanocrystals was observed. [11]

Formulation of CRV loaded nanocrystal Orodispersible tablets:

CRV nanocrystal Orodispersible tablets were formulated by direct compression method. Pearlitol 100 SD was used as a diluent and Microcrystalline cellulose was used as binder. Aerosil was used as Glidant. Sodium Starch Glycolate was used as the super-disintegrant. Talc was used as a Glidant and Magnesium Stearate was used as a Lubricant. All the ingredients were passed through #60mesh separately. Then the ingredients were weighed and mixed in geometrical dilution and after sufficient mixing of drug with the other excipients, the blend is directly compressed into tablets. Composition of formulation shown in (table I)

Table I: Composition of Carvedilol loaded nanocrystal Orodispersible tablets

INGREDIENTS	**FOR 1 TABLET (mg)**	**FOR 100 TABLETS (mg)**
CRV nanocrystals equivalent to 3.125 mg drug	53.125	5312.5
Pearlitol 100 SD	112.375	11237.5
Microcrystalline Cellulose	20	2000.0
Aerosil	1	100.0
Sodium Starch Glycolate	8	800.0
Magnesium stearate	2	200.0
Talc	2	200.0
Neotame	0.5	50.0
Orange flavour	0.5	50.0
Sunset yellow lake	0.5	50.0

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Preformulatıon study of the blend [12]

Angle of repose (θ):

Angle of repose is defined as maximum possible angle between the surface of the pile of powder and the horizontal plane. The friction force in a loose powder can be measured by the angle of repose (θ). It indicates the flow properties of the powder/granules. The formula for calculating angle of repose is,

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

Where, θ = Angle of repose; h = height of the heap in cm; r = radius of the heap in cm

Bulk density:

The ratio of a powder's total mass to its bulk volume is known as bulk density. A graduated measuring cylinder with a 10ml capacity was used to pour the precisely weighed 5g of powder blend (passed through a 20 grit screen) into. The initial volume, also known as the bulk volume, was then seen. The formula, which is used to calculate bulk density is,

$\rho b = M / Vb$

Where, ρb = Bulk density; M= Mass of the blend; Vb = Bulk volume of the blend

Tapped Density:

The ratio of a powder's total mass to its tapped volume is known as the powder's tapped density. A precisely weighed quantity of the powder mixture was put in a measuring cylinder, and the volume was determined by tapping the powder 100 times, recording the volume each time. Using the formula, the tapped density was obtained.

$\rho t = M / Vt$

Where, ρt = Tapped density; M = Mass of the blend; Vt = Tapped volume of the blend

Compressibility index:

The powder flow qualities are shown by the compressibility index. It is outlined as a percentage. Bulk density and tapped density serve as the foundation for compressibility index. Compressibility index or Carr's index (CI) was used to calculate the compressibility index of the powder blends. Three determinations were done

$I = (\rho t - \rho b)/\rho b \times 100$

Where, I = Compressibility index; ρt = Tapped density of the blend; ρb = Bulk density of the blend.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow and is calculated by

Hausner ratio = Dt / Db

Where, Dt = tapped density; Db = bulk density.

Post compression evaluation of tablets:

General appearance: [3]

The formulated tablets are evaluated for general appearance viz., colour, shape, odour etc.

Uniformity of weight: [13]

20 tablets are selected randomly from the compressed tablets and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in the table.

Table II: Weight variation specification as per I.P

Average weight of tablets	% deviation
80mg or less	< 10%
More than 80mg but less than 250mg	<7.5%
250mg or more	<5%

Thickness and diameter: [13]

CRV nanocrystal ODTs thickness and diameter are important characteristics in reproducing appearance of the tablets. Three tablets were taken and their thickness and diameter was recorded using digital Vernier Caliper.

Hardness: [13]

In order to prevent tablet breaking during shipping, handling, and storage, hardness is a crucial and essential factor. To encourage early disintegration in the mouth, the crushing intensity limit for CRV nanocrystal ODT is normally maintained in a lower range. The tablet's hardness was measured with a Monsanto hardness tester and represented in kg/cm^2. Three observations on average are given.

Friability: [13]

Friability was assessed using the Roche friabilator. Six pre-weighed tablets were put in the friabilator, which was rotated for four minutes at a speed of 25 rpm, or up to 100 rotations. Every rotation, the tablets are dropped from a distance of 6 inches. After the fines had been removed, the tablets were reweighed, and the percentage of weight reduction was determined. Friablity can be calculated by,

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% Friability = $\frac{\text{Weight before friabilation} - \text{Weight after friabilation}}{\text{Weight before friabilation}}$ **x 100**

In-vitro disintegration time: [13]

In each tube of the disintegration test apparatus (Lab care instruments) basket, the disc and six CRV nanocrystal ODTs were introduced. A beaker containing 900ml of 0.1 N HCl and set to 37±2°C was used to contain the basket. The tablet's timing of disintegration was noted. SD and the average time were computed.

Fineness of dispersion: [14]

Two CRV nanocrystal ODTs were placed in 100 ml of water for this test, and the mixture was gently stirred until the tablets totally dissolved. Following that, a sieve screen with a nominal mesh aperture of 710 m is used to filter the dispersion.

In-vitro dispersion time: [14]

One CRV nanocrystal ODT was added to 100 ml of Phosphate buffer pH 6.8 (pH of saliva) at 37±0.5°C. Time required for complete dispersion of tablet was measured. The test was performed in triplicate.

Wetting Time: [13]

A Petri dish with a 10 cm diameter is filled with five round tissue papers. Amaranth, a water-soluble color, is applied to a Petri dish in an amount of 10 ml. One CRV nanocrystal ODT is carefully placed on the tissue paper's surface, and the amount of time it takes for water to reach the tablet's upper surface is recorded as the wetting time. Three ODTs for CRV nanocrystals are put through this test.

Water absorption ratio (R): [13]

A piece of tissue paper folded twice was placed in a petri dish (internal diameter = 10 cm) containing 5 ml of distilled water. One CRV nanocrystal ODT was placed on the tissue paper. The wetted tablet was weighed. The test was done for three tablets. The water absorption ratio (R) was determined by the equation,

Water absorption ratio = $\frac{Wa - Wb}{Wb}$ **x 100**

Where, Wa is the weight of the tablets before and Wb is the weight of the tablet after water absorption.

Moisture uptake studies: [15]

To ascertain the formulation's stability, moisture uptake tests for CRV nanocrystal ODT should be conducted. Ten tablets were placed in a desiccator with calcium chloride and 37°C for 24 hours. The tablets were then weighed and kept at room temperature with a 75% RH for two weeks. By leaving saturated sodium chloride solution at the bottom of the solution in the desiccator for three days, the required humidity was attained. Weighing the tablets, a percentage increase in weight was calculated.

Drug content/ Assay: [13]

Twenty CRV nanocrystal ODTs were ground, and 3.125 mg equivalent weight of CRV was measured out of the ODT powder and placed into a volumetric flask with a volume of 100 ml. 5ml of ethanol was first added, and it was shook for 10 minutes. Then, 0.1 N HCl solution was added to the volume to get it to 100 ml. The solution is next filtered, appropriately diluted, and spectrophotometrically analyzed at 285 nm.

In-vitro dissolution studies: [13]

Thermonik dissolution apparatus with a paddle stirrer (Type II) was used for the dissolution investigations for CRV nanocrystal ODT in 0.1 N HCl. At 50 rpm, the paddles were permitted to spin. At intervals of five minutes, samples were taken out and their volume was replaced with new dissolution media in order to keep the sink conditions constant. The dissolution medium was kept at a temperature of 37±0.5°C. The withdrawn samples were filtered, and a UV-visible spectrophotometer was used to detect absorbance at 285 nm.

Release kinetics studies on in-vitro drug release data of the CRV nanocrystal ODTs [3]

To study the kinetics, data obtained from in-vitro release of CRV nanocrystal ODTs were fitted to zero order kinetics, first order kinetics, Higuchi's model and Korsmeyer-Peppas model to characterize in-vitro drug release mechanism. The results were tabulated and graphs were plotted.

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Table III: Diffusion exponent and solute release mechanism

Diffusion coefficient	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anamolous (non-fickian diffusion)
0.89	Case II transport
n>0.89	Super case II transport

Stability study of CRV nanocrystal ODTs as per ICH Guidelines [13]

Stability testing used to demonstrate how a drug substance's or formulation's quality changes over time under the effect of numerous environmental conditions, including temperature, humidity, and light. The ICH Guidelines were followed for conducting stability studies.

The CRV nanocrystal ODTs were held at accelerated circumstances (temperature $40^{o}C\pm2^{o}C$ and RH 75±5%) utilizing a stability chamber and refrigerated temperature ($4^{o}C\pm2^{o}C$) for a period of one and a half months. They were then placed in airtight screw cap vials that were amber in color. At 15, 30, and 45 days, they were periodically taken out and examined for their physical condition, in-vitro dissolution investigations, and drug content.

Comparison of in vitro drug release studies of CRV nanocrystal ODTs with Marketed tablets [3]

Invitro drug release of CRV nanocrystal ODTs are compared to commercially available tablets. A spinning paddle is used to mix the 900 ml of 0.1 N HCl at 37°C±0.5°C while adding tablets. 5 ml samples are taken every 1,2,3,4,5, 10, 15, 20, 30, and 45 minutes. After each sampling, an equal volume of fresh medium is added to the dissolution medium to maintain the same volume throughout the test. Utilizing a UV spectrophotometer set to 285 nm, the test is run.

III. RESULTS AND DISCUSSIONS

Drug – excipients compatibility study

FTIR spectroscopy gives the possible information about the interaction between the drug and polymers. The pure drug shows N-H stretching, O-H stretching, C-H stretching of aromatics, C=C stretching, C-N stretching and C-O stretching in the wave numbers of 3456.18, 3348.18, 2923.87, 1504.37, 1342.36, 1257.50cm^{-1} respectively. The final formulation of Carvedilol loaded nanocrystal Orodispersible tablets showed peaks at 3457.50, 3348.18, 2923.87, 1589.23, 1342.36, 1257.50 which implies there is no significant difference in the original peaks of the pure drug. This suggests that there is no interaction between the drug and the excipients.

Determination of λmax for Carvedilol

The maximum absorbance of Carvedilol was studied and was found to be 285 nm. Hence the wavelength of 285 nm was selected for analysis of drug in dissolution media.

Standard Calibration Curve of Carvedilol

The UV Spectrophotometric method was used to analyze the calibration curve of Carvedilol. It was found that the solutions show linearity (r^2 = 0.9995) in absorbance at a concentration of 2-10 µg/ml in 0.1 N HCland obeys Beer Lambert's law at 285nm.

Factorial design

A two factor, three level (3^2)Full Factorial Design was used to optimize the main effects, interaction effects and fit statistics of the formulation parameters on the performance of Carvedilol loaded Nanocrystals. The significant parameters such as stabilizer concentration and stirring speed and the significant response factors such as Particle size and percentage dissolution rate were used to access the quality of Carvedilol loaded Nanocrystals.

Table IV: Actual summary of Factorial design for CRV Nanocrystals

Run	Factor 1	Factor 2	Response 1	Response 2
	A: BCD concn	B: Stirring speed	Particle size	Dissolution rate
	% w/v	Rpm	nm	%
1	1	500	401.2	69.61
2	0.5	1500	160	90.20
3	0.5	500	457	66.74
4	1.5	1500	191	84.63
5	1	1000	232	79.34

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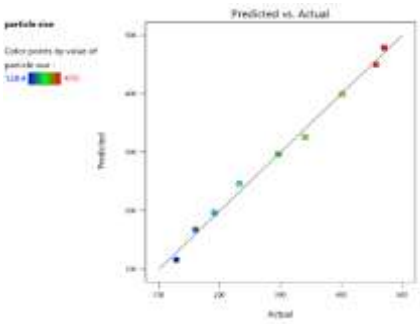
6	0.5	1000	297	74.83
7	1.5	500	470	62.16
8	1	1500	128.4	96.89
9	1.5	1000	340	76.14

Response 1: Particle size (PS) (nm)

The particle size was found to be in the range of **128.4 to 470nm**. Increase in the stirring speed decreases the particle size of nanocrystals.



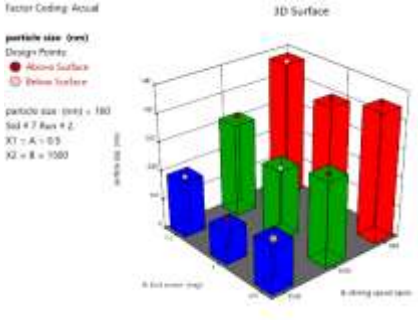
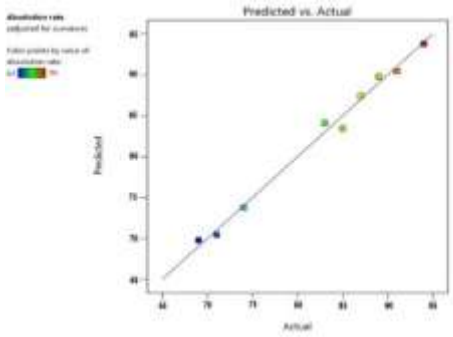


Fig 1: Perturbation of Response 1 (PS)Fig 2: 3D surface plot of PS

Response 2:Dissolution rate (%) (DR)

The cumulative percentage drug release for the nanocrystals was found to be in the range of **63.55** to **96.77%** at 120 mins. Increase in the concentration of stabilizer increases the drug release of the formulation.



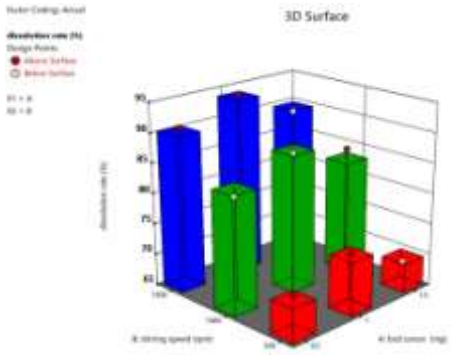


Fig 3: Perturbation of Response 2 (DR)Fig 4: 3D surface plot of DR

Formulation of Optimized Carvedilol loaded nanocrystals

Optimized Carvedilol loaded nanocrystals were prepared by Anti-solvent precipitation technique using β Cyclodextrin 1 % w/w and stirring speed 1500 rpm.

Table V:Comparison of Predicted and Actual values of optimized CRV Nanocrystal formulation

Parameters	Predicted Value	Actual value	SE Mean
Particle size	116.26	128.4	10.2365
Dissolution rate	96.78	96.89	0.895806

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The formulation F8 was found to be optimized and further studies were carried out using this F8 CRV nanocrystals formulation.

Characterization of OptimizedCarvedilol loaded nanocrystals

Particle size and Poludispersity index and Zeta potential:

The Particle size of the optimized F8 CRV Nanocrystal formulation was found to be 128.4 nm. Polydispersity index of optimized formulation is found to be 0.453 which indicates uniformity of particle size within the formulation. The Zeta potential of the optimized F8 CRV Nanocrystal formulation was found to be 25.8 mV and hence the formulation is stable.

Drug content:

The UV- Visible spectrophotometric method was used to determine the drug content of optimized formulation. The drug content was found to be 97.58 ± 0.18 % w/w.

Saturation solubility study:

The saturation solubility study by UV spectroscopy showed that the solubility of the pure drug was 2.46 ± 4.45µg/ml, Physical mixture of CRV+β CD was 4.63 ± 3.67µg/ml and that of Optimized F8 CRV Nanocrystals 53.58 ± 2.23µg/ml in distilled water.

Surface morphology by Scanning Electron Microscopy (SEM) analysis:

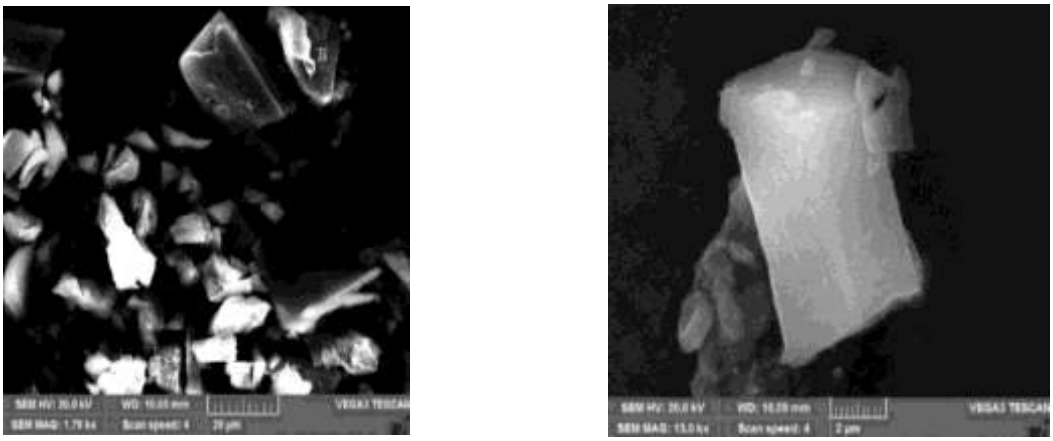

Figure 5: a) SEM image of CRV NCs at 1.79 kx b) SEM image of CRV NCs at 13.0 kx

The SEM images of the optimized F8 CRV Nanocrystals at different magnifications was recorded and observed. The particles are almost flaky. The results shows that CRV Nanocrystals have flaky shape or appearance without any aggregation or agglomeration.

In vitro Drug Release study:

In vitro drug release study for Optimized Formulation and pure drug were studied and their percentage drug release were shown in the table

Table VI: In vitro Drug Release study for Optimized Formulation and Pure drug

Time (mins)	Cumulative percentage drug release	
	Optimized formulation	Pure drug
15	39.45	2.33
30	54.20	4.84
45	66.39	7.28
60	72.64	10.52
90	84.42	13.97

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The in vitro drug release study of the CRV Nanocrystal formulations F1 to F9 were performed, in which the formulation F8 showed maximum cumulative percentage drug release of 96.89%, while formulation F7 showed least release of 62.16% at the end of 120 mins.

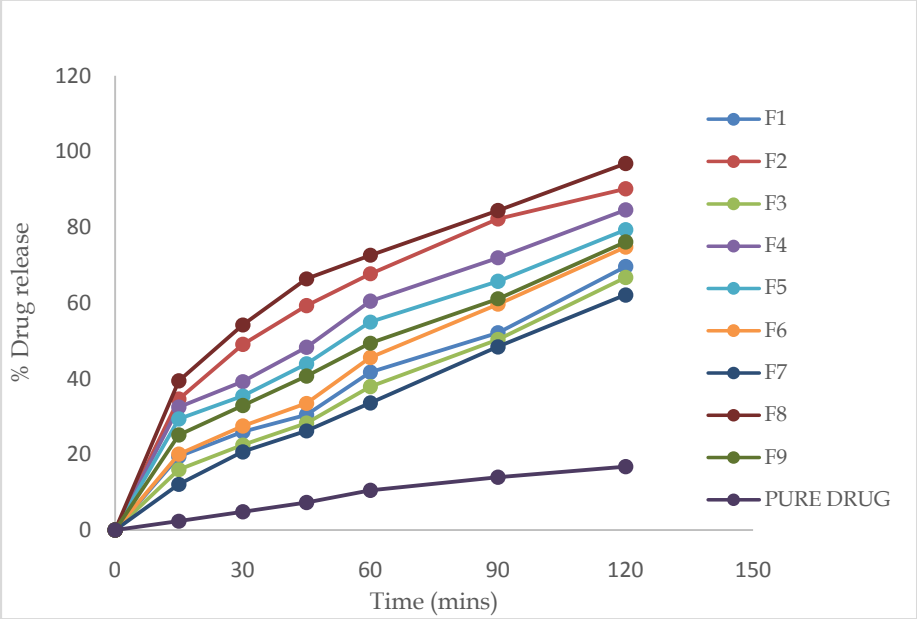

Figure 6: Comparison of dissolution profiles of F1 - F9 with pure drug

Formulation of optimized Carvedilol loaded nanocrystal Orodispersible tablets

The optimized Carvedilol loaded nanocrystal orodispersible tablets were formulated with the suitable excipients and directly compressed using 8mm punch using 10 station Tablet punching machine (Jaguar company)

Figure 7: Compressed CRV loaded nanocrystal Orodispersible tablets

Preformulation studies of the blend

The Carvedilol Nanocrystals excipient powder blend was subjected to Pre-compression evaluation parameters and was observed to have good flow property.

Table VII: Preformulation studies of the blend

Parameters	Bulk density (g/ml) ±SD	Tapped density (g/ml) ±SD	Compressibility index %±SD	Hausner'sratio±SD	Angle of repose (θ) ±SD
Values	0.576 ± 0.002	0.673 ± 0.001	15.916 ± 0.309	1.183 ± 0.005	30.02 ± 0.709

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Evaluation of the compressed CRV nanocrystal ODTs

Appearance:

The tablets were light orange coloured, circular, uncoated with scoring on one side.

Uniformity of weight:

The weight uniformity of the tablets was evaluated and the values of were found to be in the range of 0.206 g to 0.214 g. It was observed that all the tablets passed the test for uniformity of weight. All the tablets complies with the uniformity of weight. i.e., <7.5% of the weight of the tablet.

Diameter and Thickness:

The average diameter and thickness of three CRV nanocrystal ODTs were found to be around 8.00 ± 0.02 mm and 3.50 ± 0.02 mm respectively, which means there is no significant change in the diameter and thickness of the tablets.

Hardness:

Hardness test indicates good mechanical strength, as the average hardness of three CRV nanocrystal ODTs was found in the range of 3.5 ± 0.01 kg/cm^2. High hardness values increase the disintegration time and reduced dissolution values.

Friability:

Friability observed was 0.53 %w/w ± 0.03 % w/w, i.e., less than 1% w/w as per the IP standards and indicated that CRV nanocrystal ODTs have a good mechanical resistance.

In-vitro Disintegration time:

The average disintegration time of six CRV nanocrystal ODTs were found to be in the range of 24 sec ± 3 secs. The tablet complies with the test for disintegration time s per USP.

Fineness of Dispersion:

The fineness of dispersion test was carried out as per USP for two CRV nanocrystal ODTs and they passed the test.

In-vitro Dispersion time:

The average in-vitro dispersion time of three CRV Nanocrystal ODTs were noted to be 25 sec ± 4 sec in 100 ml distilled water and complies with the standards as per USP

Wetting time:

The average wetting time of the CRV nanocrystal ODTs was rapid in all the three tablets taken and was found to be 20 sec ± 5 sec. The wetting of CRV Nanocrystal ODT at different time periods is shown.

Water absorption ratio:

Water absorption ratio is closely related to the inner structure of tablets. The average water absorption ratio values for three CRV nanocrystal ODTs was found to be 62 ± 5 % w/w.

Moisture uptake:

Moisture uptake study was performed for ten CRV nanocrystal ODTs at 75% RH and the results were in the range of 0.2% - 0.45%.

Uniformity of content/Assay:

The drug content of CRV nanocrystal ODTs was studied by using UV Spectroscopy at the wavelength of 285 nm. The drug content was found to be 96.4 ± 0.7 % w/w indicating uniform distribution of drug in the formulated tablets as per pharmacopeia specification. The official limits for CRV content in CRV tablets as per IP is 90% to 110%.

In-vitro Drug release study:

The cumulative drug release from CRV Nanocrystal ODTs was found to be 99.24% at 20 mins.

Table VIII: In-vitro drug release of CRV Nanocrystal ODTs

Time (mins)	Cumulative % drug release	
	CRV Nanocrystal ODTs	Marketed tablets
1	30.26	5.23
2	51.14	9.34
3	60.59	13.12
4	68.73	19.62
5	75.86	24.51
10	83.91	35.18
15	90.43	47.82
20	99.24	58.12

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2651-2662 www.ijprajournal.com ISSN: 2249-7781

Release kinetics studies on in-vitro drug release data of the CRV nanocrystal ODTs:

The data from in vitro release of optimized formulation was fit into various kinetic models to find out the mechanism of drug release from CRV Nanocrystal ODTs. Good linearity was observed with the first-order (r2=0.9125), the First order kinetics explains the immediate release of the drug from CRV Nanocrystal ODTs. The slope of the Korsmeyer Peppas plot (n= 0.8987) was found to be more than 0.89 indicating the diffusion was Super Case II transport. Thus, the release kinetics showed first-order drug release with Super Case II transport.

Stability study of the CRV nanocrystal ODT formulation as per ICH Guidelines:

No significant changes in physical appearance, Percentage drug release at 20 mins and drug content at storage condition of 40°C ± 2°C / 75 ± 5% RH, 4°C ±2°C and at room temperature after the end of 45 days.

Comparison of in vitro drug release studies of CRV nanocrystal tablets with marketed tablets:

Invitro drug release profile of Carvedilol nanocrystal Orodispersible tablets [best formulation (F8) showed better dissolution rate (99.24%) when compared with the marketed immediate release Carvedilol tablets (58.12%) at 20 mins. The results were shown in the figure 8.

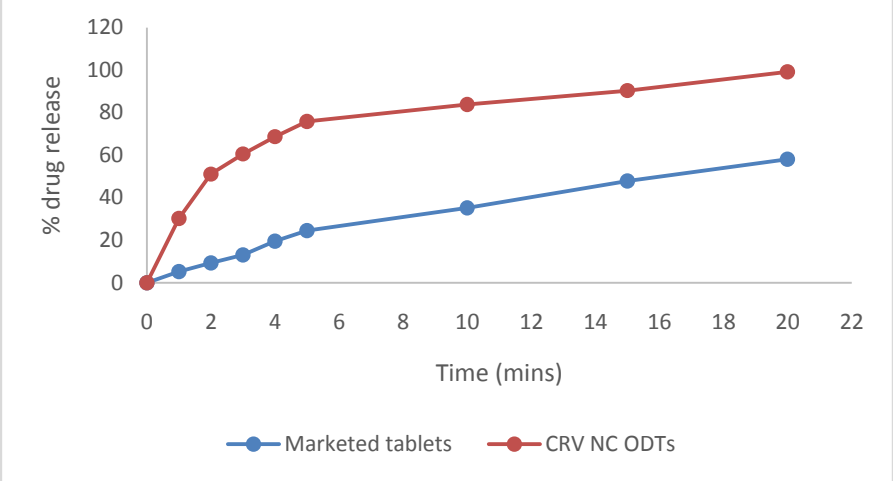

Figure 8: Comparison of in vitro dissolution profiles of CRV nanocrystal tablets with marketed tablets

IV. CONCLUSION

Hence it was concluded that conversion of drug to nanocrystals is a good approach to enhance the solubility of poorly water soluble BCS Class II drug, Carvedilol by the bottom up approach, Anti-solvent precipitation technique. The saturation solubility studies and in-vitro dissolution studies suggested that the Carvedilol loaded nanocrystal Orodispersible tablets can help to maximize the therapeutic effect of the drug by increasing the solubility of the drug, thereby enhancing the oral bioavailability of the drug due to decreased first pass metabolism of the drug owing to oral administration, reduce side effects.

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