Design and evaluation of Carvedilol nanocrystals sustained release tablets

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ABSTRACT

The present study was undertaken to develop and evaluate the carvedilol nanocrystals sustained release (SR) tablets. The tablets were prepared by direct compression method using hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) polymers. The prepared tablets were evaluated in terms of their pre-compression studies, post-compression parameters, *in vitro* dissolution and drug release kinetic. The tableting of blend showed good pre-compression properties and the formulated tablets were exhibited desired post-compression characters. The *in vitro* drug release were performed in the United States pharmacopoeia (USP) apparatus-II (Paddle) using phosphate buffer (pH 6.8). The formulation CT5 was selected as the optimized formulation by an *in vitro* drug release for 24 hrs with the release of 99.46%. Drug release kinetics showed the best fit to Higuchi's equation, and they exhibit diffusion dominated mechanism. The comparative *in vitro* release study showed that the formulation CT5 has better control over the release of drug (99.46%) when compare to reference product (73.64%) for 24 hrs. Thus overall result indicate that the carvedilol nanocrystal using SR tablets is more discriminative approach for better release and prolong action.

INTRODUCTION

Carvedilol is competitive adrenoreceptor antagonist that hinders the activity at the β_1, β_2, and α_1-adrenergic receptors and exhibits a number of ancillary properties, such as antioxidant effects, inhibition of smooth muscle proliferation, and calcium antagonistic blocking activity. The original formulation of carvedilol is approved by the US Food and Drug Administration (FDA) to be administered twice daily and is widely used alone or in combination with other agents for the treatment of essential hypertension, mild-to-severe heart failure and myocardial infraction (Michal *et al.*, 2006). Carvedilol (Biopharmaceutical classification system (BCS) class-II) is practically insoluble in water, highly lipophilic and highly protein bound drug. Carvedilol undergoes significant stereo-selective first-pass metabolism, resulting in low absolute bioavailability (30% or less). However, some sources suggest that this low bioavailability is the result of poor aqueous solubility (Odon *et al*, 2011). Low aqueous solubility puts a large burden on the oral bioavailability and absorption is dissolution rate-limited, which results in uneven and delayed the drug absorption. The solubility was improved by reducing the drug particle size into the nano (sub-micron) range. In this way, saturation solubility was increased, then dissolution rate and bioavailability related to the formulation of poorly soluble drugs could be enhanced (Tuomela *et al.,* 2014; Ali *et al.,* 2011). Consequently, a variety of new drug delivery systems have been investigated to overcome these limitations, such as nanosuspensions, nanoemulsions, solid lipid nanoparticles, solid dispersions, and liposomes (Dandan *et al.,* 2014).

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Among these new formulation approaches, nanosuspensions are considered to be the most promising candidate for poorly water-soluble drugs due to their non-specific applicability. The resulting drug nanoparticles have an increased surface area and an enhanced solubility which in turn could result in substantial increases in drug dissolution rate and oral bioavailability (Sinha *et al.,* 2013; Yu *et al.,* 2015; Ashok Kumar *et al.,* 2015).

Carvedilol nanosuspension could improve drug bioavailability after oral administration it showed fast drug release behavior and extensive fluctuations in plasma concentration (Liu *et al.,* 2012). Conventional solid dosage form with nanocrystals will rise to pronounced fluctuations in plasma concentration and it is definitely harmful to patients with specific disease such as hypertension and diabetes. Therefore, it is necessary to develop a delayed delivery system of nanosuspensions to solve the problem. A once-daily, controlled-release (CR) formulation of carvedilol has been developed that provides levels of exposure similar to those achieved after administration of the current twice-daily formulation. Over a 24-hours period, carvedilol CR has been shown to maintain a steady plasma concentration time profile (Tenero *et al.,* 2006).

Controlled release dosage form slows the discharge of the drug but do not offer a rapid and expected better onset of action (Ritesh *et al.,* 2001). To avoid these limitations by proposing a new solution for poorly water-soluble drug carvedilol to be prepared into sustained release tablets in the form of nanocrystals. The carvedilol nanocrystals sustained release tablets consist of HPMC and EC, which are broadly used as a gelling agent in controlled release preparation. The prime objective of this study was to develop carvedilol nanocrystals SR tablets by adapting direct compression method using various ratio of HPMC and EC polymer for enhanced *in vitro* dissolution, prolong action and better patient compliance.

MATERIALS AND METHODS

Materials used

Carvedilol was obtained as a gift sample from Dr Reddy's laboratory limited, (Hyderabad, India), Ethyl cellulose and Microcrystalline cellulose (MCC) were obtained from Loba chemicals, (Mumbai, India). Hydroxy propyl methyl cellulose (HPMC) obtained from High media chemicals, (Bangalore, India), Magnesium stearate and Talc obtained from SD Fine chemicals (Mumbai, India). All other chemicals and reagent were of analytical grade.

Methods
Preparation and physiochemical characterization of carvedilol nanocrystals

Carvedilol nanocrystals were prepared by emulsion-diffusion (solvent exchange) method followed by high pressure homogenization with stabilizers. The prepared nanosuspension was oven-dried at 60°C for 12 hrs. The yield of the dried

carvedilol nanocrystals were approximately 80%. Physicochemical parameters such as appearance, color, odor, pH, melting point, LOD, partition co-efficient, saturation solubility at various pH and morphology (SEM image) of carvedilol nanocrystals were described in our previous report, which shows significant results. (Ashok Kumar *et al.,* 2015)

Drug-excipient compatibility study

Fourier transform infrared (FT-IR) spectrum of drug (carvedilol nanocrystals) and the combination of drug with excipients (physical mixture) were taken individually. Samples were compressed with potassium bromide and scanned between 4000-400 cm^{-1} in FT-IR (Analytical 2500, Germany). The change in spectra of the drug in the presence of excipients was investigated to identify the interaction of drug molecule with the excipients if any (Mutalik *et al.,* 2007).

Preparation of carvedilol nanocrystals SR tablets

Carvedilol nanocrystals were prepared by emulsion-diffusion (solvent exchange) method (Quintanar *et al.,* 2005) followed by high pressure homogenization with stabilizers (Dolenc *et al.,* 2009). Carvedilol nanocrystals SR tablets were prepared by direct compression method using the varying proportions of polymers in combination. The composition of various formulations of the tablets with their codes is listed in Table 1. The excipients and active ingredients were individually passed through 60 mesh and 40 mesh sieve respectively. Calculated amount of the drug, polymers (HPMC and EC) and filler (MCC) was mixed thoroughly. Magnesium stearate and talc was added as lubricant and mixed for 10 minutes; the appropriate amount of the mixture was weighed and then compressed using a an eight station rotary press (Rimek Minipress, Ahmadabad, India) at a constant compression force equipped with a 12 mm flat-faced punches. The weight of all the tablets were kept constant i.e., 300 mg and stored in airtight containers for further study. Prior to compression, the blends were evaluated for their flow and compressibility characteristics.

Pre-compression studies
Angle of repose

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to interparticulate friction or resistance to movement between particles. A funnel was fixed at a height approximately 2-4 cm over the platform. The loose powder blend was slowly passed through the wall of the funnel, till the tip of powder cone formed just touched the tip of funnel stem. The height of the heap and radius was measured by using scale, the value of angle of repose is calculated by using the following formula (Rockville, 2002).

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, θ is angle of repose, h is the height of heap, and r is the radius of base of heap circle.

Total porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V) of blend (Martin, 2001).

$$Porosity\ (\%) = \frac{V_o - V_f}{V_o}$$

Where, V_o is the initial volume of blend in graduated cylinder, and V_f is the final volume of blend in graduated cylinder.

Moisture content

The moisture content values of the physical mixture (blend) were determined using a moisture balance (Sartorius MA 150, Germany) fitted with an infrared heating unit. The balance was preheated to 80 ^{o}C for 10 minutes and the drug sample (~1 gm) was heated for a further 30 minutes at this temperature and record the moisture content (Pather *et al.,* 1998).

Post-compression parameters

The prepared tablets were characterized for general appearance, weight variation, friability, drug content, tensile strength and elastic recovery to meet the pharmacopoeial standards and/or in house specification (Martin, 2001; Wells, 2002).

Tensile strength

Tensile strength is the stress at which a material breaks or permanently deforms. It is an intensive property independent of the size of the tested tablet (Andrej *et al.,* 2009). It was measured diametrically using tablet hardness tester (Campbell electronics, Mumbai, India). The tensile strength of the tablets was calculated by formula.

$$Tensile\ strength = \frac{2F}{\pi dh}$$

Where, F is the rushing force of tablets, d is the diameter of tablets, and h is the thickness of tablets.

Elastic recovery

This quantity, the degree of the expansion after removal of the compression forces and it was measured one day after compression (Andrej *et al.,* 2009). Elastic recovery was calculated using the formula.

$$Elastic\ recovery = \frac{h\ punch - h\ tablet}{h\ punch}\ X\ 100$$

Where, h_{punch} is the distance between punches (upper and lower), and h_{tablet} is the weight of the tablet measured 1 day after compression.

In vitro dissolution study

The *in vitro* dissolution of carvedilol nanocrystals SR tablets were performed using USP dissolution apparatus (Electrolab, Mumbai, India) type-II (Paddle). The studies were carried out using 900 ml of phosphate buffer solution (pH 6.8) as dissolution medium. The studies were performed at a temperature of 37±0.5 °C with 100 rpm speed for 24 hrs. The tablets were placed in dissolution jar and an aliquot of 5 ml was withdrawn at an interval of 1 hr, 4 hrs, 8 hrs, 12 hrs, 16 hrs, 20 hrs and 24 hrs respectively. The same volume of pre warmed (37±0.5 ℃) fresh dissolution medium was replaced each time. The samples were filtered through 0.45μm membrane filter. Samples were suitably diluted with phosphate buffer solution and assayed for carvedilol nanocrystals concentration using HPLC method. Drug dissolved in specified time periods were plotted as cumulative percentage drug release versus time (hrs) curve. *In vitro* dissolution of reference product (carvedilol SR tablets were prepared by using optimized batch excipient concentration) was carried out in the similar manner and the results were compared with optimized formula.

Drug release kinetics

The dissolution data obtained was fitted to zero order (cumulative amount of drug released vs time), first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), Hixson-Crowell (cubic root of percent drug release vs time) and Korsmeyer-Peppas (log cumulative percentage of drug released vs log time) equations to understand the rate and mechanism of carvedilol nanocrystals release from the prepared formulations. The PSP-DISSO V2 software, developed in-house was used to study the release kinetics parameters for formulation in phosphate buffer (pH 6.8). The correlation coefficients were calculated and used to find the fitness of the data. The diffusion exponent (n) for different batches of tablets, the value of $n \leq 0.45$ indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion-controlled drug release (Shato *et al.,* 1997).

Accelerated stability studies

The accelerated stability study (40±2°C/75±5 % RH) of the CT5 formulation tablets were carried out according to ICH guideline for six months by storing the sample in stability chamber. At the interval of 1, 2, 3 and 6 months, tablets were withdrawn and evaluated for physical appearance, weight variation, thickness, friability, drug content, tensile strength and *in vitro* dissolution rate by the method described previously.

RESULT AND DISCUSSION
Drug-excipient compatibility study

The development of successful formulation depends only on the suitable selection of excipients. The compatibility study was performed to analyze the drug interaction with the excipients by FT-IR spectrum were shown in Figure 1. The different peaks of drug and their physical mixture indicate that all functional groups and characteristics of the drug were not altered. From the observation, it was conclude that there was no interference in the functional group as the principle peaks of carvedilol nanocrystals were found to be unaltered in the drug-excipient physical mixture.
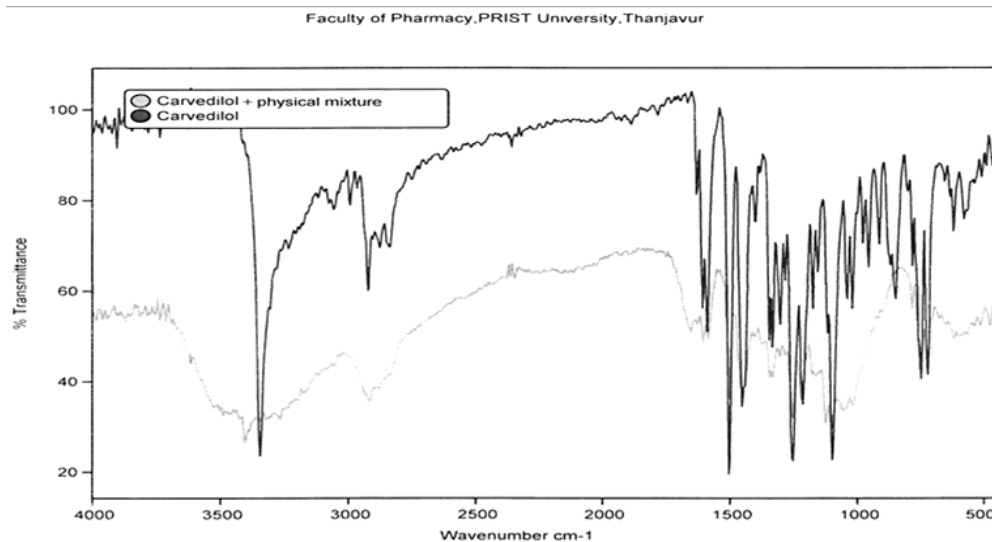
Faculty of Pharmacy,PRIST University,Thanjavur

Fig. 1: FT-IR spectrum of drug-excipient compatibility

Table 1: Formulation composition.

Ingredients (mg/tablet)	CT1	CT2	CT3	CT4	CT5	CT6	CT7	CT8	CT9
Carvedilol nanocrystals	60	60	60	60	60	60	60	60	60
HPMC	45	45	45	60	60	60	75	75	75
EC	6	9	12	6	9	12	6	9	12
MCC	180	177	174	165	162	159	150	147	144
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6

Preparation of carvedilol nanocrystals SR tablets

In the present study carvedilol nanocrystals SR tablets were prepared by direct compression process as is known to be more economical than wet granulation and also avoid heat and moisture, which may affect the drug stability. A total number of nine formulations (CT1 to CT9) were prepared and evaluated for its pre-compression and post-compression parameters.

Pre-compression studies

Pre-compression parameters report were shown in Table 2. Angle of repose for various batches of the blend is found to be less than 28.81 ± 0.04^{o}, it indicate the good flow property. Angle of repose value more than 30° indicate unsatisfactory flow properties of granules (Rashid *et al.,* 2009).

The percentage porosity values of the granules ranged from 26.55 ± 0.04 to $29.56\pm0.06\%$, indicating that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26% shows that the particles in the powders are of greatly different sizes and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates. The proposed tablets components (blend) had moisture content value of less than 2%, this property was not expected to adversely influence flowability. It is unlikely that the high moisture content of the excipients influences tableting characteristics. All these results indicate that the granules (blend) possessed satisfactory flow properties,

compressibility, and moisture content were within the acceptable limits.

Table 2: Pre-compression stidies data

| Formulation code	Angle of Repose (degrees)	Total porosity (%)	Moisture content (%)
CT1	28.34±0.02	29.50±0.08	1.25±0.01
CT2	27.28±0.05	27.23±0.07	1.56±0.03
CT3	28.36±0.03	28.23±0.06	1.54±0.02
CT4	28.81±0.04	29.56±0.06	1.63±0.04
CT5	26.85±0.03	26.55±0.04	1.75±0.02
CT6	27.41±0.02	27.33±0.05	1.80±0.01
CT7	25.94±0.04	29.50±0.06	1.78±0.03
CT8	26.98±0.01	27.24±0.08	1.86±0.01
CT9	27.30±0.03	28.23±0.07	1.97±0.02

Mean ± standard deviation, n=3

Post-compression parameters

The tablets weight variation, friability, drug content, tensile strength and elastic recovery of each formulation are presented in Table 3. In determination of the tablet weights (n=10), all formulations weights were found to be with in USP pharmacopoeial specification of 285 to 315 mg. The drug content uniformity of all tablet formulation was found to be 97.46±0.15 to 101.43±0.16 %, which was within the limit of 90-110 %, and hence all the formulations passed the content uniformity as per USP pharmacopeia. The manufactured tablets showed low weight variation and a high degree of drug content uniformity in all

Table 3: Post-compression parameters data

Formulation code	Weight variation (mg)	Tensile strength (MPa)	Elastic recovery (%)	Friability (%)	Drug content (%)
CT1	293.34 ±0.77	1.98 ±0.01	46±0.12	0.89 ±0.01	98.50 ±0.12
CT2	296.55 ±0.75	2.13 ±0.02	42±0.17	0.76 ±0.02	99.02 ±0.18
CT3	297.73 ±0.77	2.12 ±0.01	34±0.11	0.82 ±0.01	97.82 ±0.22
CT4	296.84 ±1.17	2.18 ±0.03	38±0.24	0.76 ±0.01	98.46 ±0.14
CT5	297.32 ±0.75	2.31 ±0.01	34±0.18	0.73 ±0.02	98.25 ±0.18
CT6	300.56 ±2.26	2.38 ±0.02	38±0.16	0.74 ±0.02	101.43 ±0.16
CT7	296.54 ±1.18	2.43 ±0.02	36±0.22	0.73 ±0.01	98.28 ±0.14
CT8	296.2 5±2.14	2.48 ±0.01	38±0.16	0.75 ±0.02	99.76 ±0.16
CT9	297.34 ±1.43	2.62 ±0.03	37±0.18	0.68 ±0.01	97.46 ±0.15

Mean ± standard deviation
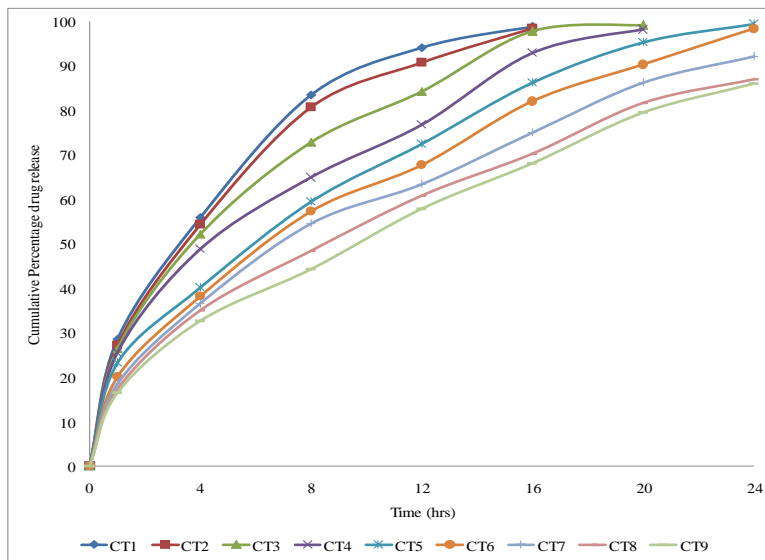
Fig. 2: *In vitro* drug release of carvedilol nanocrystals SR tablets

batches of the tablet formulation. Friability of the tablets was found to be 0.68±0.01 to 0.89±0.01 %, well within acceptable range of 1 % and indicate that tablets surface are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed (Lachman *et al.,* 1986).

The tensile strength of the tablet was predominantly affected by the applied compression force. An increase in compression force resulted in much higher tensile strengths. As tensile strengths were closely correlated to dissolution rates and disintegration times (Esezobo and Pilple, 1977), there was hence a need to minimize the response. Tensile strength of carvedilol nanocrystals tablets were improved as the HPMC polymer concentration was increased. The amount of insoluble diluent (i.e microcrystalline cellulose) in the formulation also affected the tablet's tensile strength. The tensile strength of the all formulated batches was ranges from 1.98±0.01 to 2.62±0.03 MPa, which were capable for withstanding the abrasion force during transit. Microcrystalline cellulose has been known to be a highly compactable excipient conferring strength to a tablet (Edge *et al.,* 2001). Elastic recovery value ranges from 34±0.11 to 46±0.12% in the case of tablet formulations compacted with carvedilol nanocrystals. This average value indicates that carvedilol nanocrystals interact with microcrystalline cellulose filler strongly. Tablets containing carvedilol nanocrystals need to be compacted

with average force to reach pharmacopoeial standard. Higher forces result in greater deformation and more elastic behavior of tablets after the compacting force is removed. No increase in diameter of tablet after being expulsed from the matrix was observed, which indicate that no elastic recovery occurred after tablets ejection. Post-compression evaluation of carvedilol nanocrystal SR tablets complies with the standard pharmacopoeial limit and in-house specifications (IHS).

In vitro **dissolution study**

To establish the sink condition, we did not carry out the experiment directly, but in some reports (Odon *et al.,* 2011) have stated that the drug does not possess sufficient solubility on acidic buffer (pH 1.2), whereas it shows satisfactory solubility in phosphate buffer. For this reason, the phosphate buffer pH 6.8 was chosen as dissolution medium. The *in vitro* dissolution profile of carvedilol nanocrystal SR tablets formulation CT1 to CT9 were shown in Figure 2. The *in vitro* dissolution results indicate that the release rate decreased as the concentration of HPMC increased. At higher polymer loading, the viscosity of gel matrix is increased which results in decrease in the effective diffusion coefficient of the drug and is more likely to be resistant to drug diffusion and erosion (Skoug *et al.,* 1993; Wan *et al.,* 1993).This indicates that drug/polymer ratio is important factor affecting the rate of release

drugs from polymer matrices. Among the all formulations, the tablets prepared with HPMC 20 to 25% and EC 2 to 4% have shown greater drug release of not more than (NMT) 24% and not less than (NLT) 80% in 1 hr and 20 hrs respectively. Rate of drug release tend to decrease with increase in the content of either HPMC and/or EC. This finding similar with the literatures (Vazques *et al.,* 1992; Ford *et al.,* 1985), that the viscosity of the gel layer around the tablet increase with increase in the hydrogel concentration, thus limiting the release of the active ingredient.

Drug release kinetics

As data indicated in Table 4, the formulations did not follow a zero order pattern where the regression value of 0.7478-0.9824. When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.8796 and 0.9868. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid, depending on the concentration. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics. In this experiments, the *in vitro* release profiles of drug from all the formulations showed high linearity with regression value of 0.9306 to 0.9988, indicating that the drug release follows the Higuchi's equation, and diffusion is the dominating drug release mechanism. This finding is similar that of previously investigated work (Reza *et al.,* 2003; Shanmugam *et al.,* 2011). To confirm the diffusion mechanism, the dissolution data were fit into Korsmeyer-Peppas equation, which is often used to describe the drug release behavior from polymeric system. As indicated in Table 4, CT1 to CT9 formulations showed good linearity ($R2$: 0.9527 to 0.9991), with slope (*n*) values ranging from 0.3140 to 0.5556, in which CT1 to CT5 exhibited Fickian type drug release, whereas CT6 to CT9 exhibited non-Fickian (anomalous) drug release.

Table 4: Drug release kinetic data.

Formulation Code	Zero order Plot (R^2)	First order Plot (R^2)	Higuchi plot (R^2)	Korsmeyer-Peppas plot		Hixon-Crowel cube root law (R^2)
				(n)	(R^2)	
CT1	0.7478	0.9226	0.9306	0.3140	0.9527	0.9070
CT2	0.7775	0.9227	0.9435	0.3331	0.9621	0.9217
CT3	0.8538	0.9469	0.9705	0.3748	0.9836	0.9633
CT4	0.9119	0.9448	0.9863	0.4176	0.9939	0.9754
CT5	0.9578	0.9852	0.9970	0.4304	0.9945	0.9861
CT6	0.9662	0.8796	0.9988	0.5272	0.9982	0.9801
CT7	0.9648	0.9727	0.9986	0.5151	0.9986	0.9907
CT8	0.9711	0.9868	0.9986	0.5195	0.9991	0.9904
CT9	0.9824	0.9827	0.9955	0.5556	0.9962	0.9924

Selection criteria for best formulation

All formulations showed incomplete drug release of 100 % at the end of 24 hrs, except CT5 and CT6. According to the pharmacopoeial specification, it is seen that NMT 25 % of the labeled amount of drug is getting released in first 1 hr, NLT 40 % and NMT 60 % of the labeled amount of drug in 8 hrs. NLT 80 % of the labeled amount drug in 20 hrs, which were observed with CT5, CT6, CT7 and CT8 formulation. From the *in vitro* release data, CT5 formulation was best and its cumulative drug release was 99.46 %, when compare to other formulation. Concluded that, CT5 is showed the proper SR profile according to the pharmacopoeial limit. In addition CT5 formulation could be best expressed by Higuchi's equation, as the plot showed regression value of 0.9970 and also fitted to the exponential equation (R^2: 0.9945 and n=0.4304). The carvedilol nanocrystals SR tablets formulation CT5 consisting HPMC and EC ratio of 22:3 showed suitable *in vitro* drug release and this batch was optimized for stability studies.

Comparative *in vitro* drug release

Reference product was subjected to evaluation of weight variation, tensile strength, friability and their value were shown in Table 5. The weight variation, tensile strength and friability of reference product tablets were found to be within the acceptable official limits.

Table 5: Reference product data.

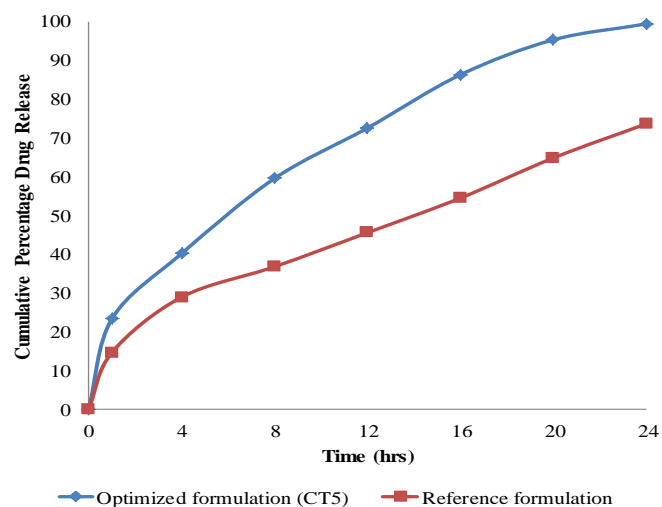| Parameters	Observation
Tablet weight (mg)	298±0.14
Tensile strength (MPa)	2.45±0.01
Friability (%)	0.72±0.01

Fig. 3: Comparative *in vitro* drug release data.

The optimized carvedilol nanocrystals SR tablets (CT5) in vitro dissolution release profile was compared with reference product using same experimental condition as described previously. The comparative *in vitro* release studies results in Figure 3 indicate that the optimized carvedilol nanocrystals SR tablets (CT5) have shown a cumulative percent release of 99.46% in 24 hrs, while the opposite result found only 73.64%. Furthermore, CT5 showed significantly higher *in vitro* dissolution rate as compare to reference product, due to enhanced surface area (nanocrystals) and sustained release.

Table 6: Accelerated stability studies data.

Parameters	Specification	Initial	40±2°C/ 75±5 % RH			
			1 Month	2 Months	3 Months	6 Months
Physical appearance*	White, circular tablet, plain on both side	Complies	Complies	Complies	Complies	Complies
Weight variation (mg)	285-315	Complies	Complies	Complies	Complies	Complies
Thickness (mm)*	2.60±0.10	Complies	Complies	Complies	Complies	Complies
Tensile strength (MPa)*	2.50±0.50	Complies	Complies	Complies	Complies	Complies
Friability (%)**	< 1	Complies	Complies	Complies	Complies	Complies
Drug content (%)**	90-110	98.25±0.18	97.81±0.23	98.31±0.12	97.28±0.26	96.48±0.14
In vitro dissolution (%)**	NLT 80	99.46	98.62	98.18	97.35	96.88

* IHS, ** Revision Bulletin, United States Pharmacopoeial Convention. January 1, 2011.

Accelerated stability studies

Stability studies for optimized formulation (CT5) was carried out based on the accelerated condition at 1, 2, 3 and 6 months and the data were shown in Table 6. The results found satisfactory and revealed that the optimized formulation was stable up to 6 months as per ICH guidelines.

CONCLUSION

The finding of the study concluded that the precompression and post-compression parameters values are falling within the acceptable pharmacopoeial and IHS limits. *In vitro* dissolution study of CT5 formulation showed the maximum drug release (99.46 %) within 24 hrs, when compare to other formulations. According to the *in vitro* release studies, the decrease in release rate was observed with an increase the concentration of polymers. Diffusion might be the drug release mechanism for all prepared tablets, which can be expressed by Higuchi's equation. The comparative *in vitro* release studies revealed that the release rate was depends on the polymers, particle size and physical nature of active ingredient. Special features of carvedilol nanocrystals are: further enlargement in surface area as compared to micronized powders, the increase in dissolution velocity and both leading to overcoming the rate-limiting step of oral absorption for BCS class II drug, carvedilol. Use of once-daily carvedilol nanocrystals tablets will provide the opportunity to simplify treatment regimens without sacrificing efficacy or tolerability, with important implications for improving blood pressure controls in patients with hypertension. Further studies will be conducted to evaluate thus SR tablets *in vivo* study for better therapy and improved patient compliance.

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