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Impact analysis of inclusion complexation on micromeritic properties and dissolution behavior of carvedilol

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ABSTRACT

The study aimed at investigating an inclusion complexation technique to improve solubility and dissolution characteristics of carvedilol by successful complexation with β-cyclodextrin. Inclusion complexes (ICs) of drug and β-cyclodextrin were prepared by kneading method in four different ratios. Physical mixtures were also prepared in identical ratios to compare the efficacy of prepared ICs. The preparations were subjected to rheological studies, drug loading, in vitro release study, FT-IR spectroscopy, thermal events analysis by DSC, X-ray diffraction, scanning electron microscopy (SEM) and accelerated stability study. IC granules were free flowing and compressible. FT-IR study denoted to absence of any chemical interactions between drug and carrier. DSC and X-ray diffraction suggested the presence of crystalline drug in the complexes. Dissolution of ICs revealed significant enhancement of release rate and extent compared to untreated drug. MDT, %DE and $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ indicated marked improvement in release rate from complexes. Kinetic modeling suggested that fickian diffusion was the predominant mechanism of drug release from solid complexes. Stability samples showed no significant alterations in DSC and FT-IR studies that referred to the stability of ICs. ICs were compatible, effective and stable over time. Further studies can be planned to investigate their therapeutic efficacy.

INTRODUCTION

Cyclodextrins are classes of ring structured molecules primarily formed by bonded or cross linked sugar molecules. These are starch derivative products, produced by enzymatic conversion. Their molecular arrangements permit them a unique feature of entrapping hydrophobic molecule into their internal cavities to form host-guest complexes (Liu *et al*., 2013). Complexation with cyclodextrins has come out as a potential approach to improving solubility of a number of poorly soluble bioactive compounds (Del Valle, 2004). They can offer significant advances in pharmaceutical formulations by improving solubility of poorly aqueous soluble drugs, enhancing bioavailability of scarcely absorbed drug by rendering them more lipophilic and stabilizing drug molecules from oxidative, light or thermal degradations. For their diverse advantages, they could attract attention of scientists all over the world to invent newer applications and assess their impacts on different drug particles. Carvedilol is a non-selective antihypertensive agent. It competitively blocks the receptors of norepinephrine, which is responsible for elevating blood pressure.

Blocking adrenergic β_1 and β_2 receptors cause slow down of heart rhythm and significant reduction in cardiac muscle contraction that result in decrease in pumped blood volume and in turn blood pressure falls down to normal level.

Besides, it's binding with α_1 adrenergic receptors causes vasodilatation that also lowers the blood pressure. Carvedilol has been shown to be effective in the treatment of patients with essential and renal hypertension, and angina pectoris (Kramer *et al*., 1992), where it requires immediate action. Though it is

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extensively absorbed after an oral dose, still it takes 1 to 2 hours to reach peak plasma drug concentration (Abdel-Razek *et al.*, 2010). This longer T_{max} can be caused by the delay of releasing the active ingredient from conventional dosage forms or discharging the drug beyond its narrow absorption window i.e. upper part of gastrointestinal tract (GIT) (Shilpa *et al*., 2012). Furthermore, the inability of released drug to be dissolved and permeate the mucosal cell membrane is another contributing factor for such a practically water insoluble drug (USP, 2009). Besides, carvedilol is poorly flowable and compressible drug (Tapas *et al*., 2012a). Attempts to improve solubility behavior and rheological properties of such a drug are thus rational and challenging. In various approaches of enhancing solubility and wetting properties of poorly soluble drugs, cyclodextrin inclusion complexation is renowned for its efficacy, simplicity and suitability (Srikanth *et al*., 2010; Pooja *et al*., 2011; Loh *et al*., 2016). In this study, the water insoluble carvedilol has been complexed molecularly with β-cyclodextrin and the impact of the complexation on physical properties and release behavior has been evaluated. The impact analysis of the inclusion complexes on micromeritic properties as well as the dissolution behavior of poorly water soluble drugs may play a very important role in understanding the mechanism of increased solubility of the complexes.

MATERIALS AND METHODS

Materials

Carvedilol was collected from ACI Limited, Bangladesh as kind gift sample. β-cyclodextrin was obtained from Popular Pharmaceuticals Ltd., Bangladesh. Other reagents and materials were of analytical grade and procured from the local market.

Preparation of inclusion complexes

Inclusion complexes (ICs) were prepared by kneading method at drug: carrier ratio of 1:0.5, 1:1, 1:2 and 1:3. β-cyclodextrin and carvedilol were weighed accurately in specified quantity and mixed well in a mortar and pestle. The mixture was wetted by minimum amount methanol and kneaded thoroughly for 15 min in the glass mortar. The paste was dried at room temperature for 72 hours, grinded and passed through '30' mesh sieve. The inclusion complexes were stored in glass vials in a desiccator.

Preparation of physical mixtures

Physical mixtures (PMs) were prepared at same molar ratio as the solid complexes by thorough blending in a glass mortar. Appropriate amount of drug and carrier was mixed thoroughly for 10 minutes. The mixtures were coded according to Table 1. The mixtures were milled, passed through '30' mesh screen and stored in glass vials in a desiccator.

Percentage yield calculation

Percent yield was calculated by comparing the obtained weight of IC granules with total weight of starting materials. The following formula was followed for calculating the yield. It is an indication of suitability of a production process and process loss.

$$\text{Percentage yield} = \frac{\text{Weight of obtained inclusion complexes}}{\text{Total amount of drug and carrier}} \times 100$$

Bulk density and tapped density measurement

Bulk density (BD) and tapped density (TD) of ICs were calculated by comparing the total mass of powder to the bulk and tapped volume respectively.

Determination of Carr's index and Hausner ratio

Carr's index is an indication to the flow property of solid masses. It is expressed as percent density variation and was calculated by the following formula (Tapas *et al.*, 2012b).

$$\text{Carr's index (CI)} = \frac{\text{Tapped density (TD)} - \text{Bulk density (BD)}}{\text{Tapped density (TD)}} \times 100$$

Hausner ratio (HR) is another expression of flow ability and compressibility of powders. It is simply a comparison of powder densities and calculated by the following formula (Tapas *et al.*, 2012b).

$$\text{Hausner's ratio (HR)} = \frac{\text{Tapped density (TD)}}{\text{Bulk density (BD)}}$$

Assay of samples

ICs and PMs were analyzed for determination of drug content using by UV-spectrophotometer (UV mini 1240, Shimadzu) according to the method of Tapas *et al.* (2012b). 25 mg equivalent sample was dissolved in 10 ml methanol which was diluted by distilled water up to 500 ml. Standard solution was prepared by dissolving 10 mg of untreated carvedilol in equal volume of same solvent composition to produce identical concentration. The absorbance of the solutions were measured at 286 nm against appropriate blank solution and compared to determine drug loading.

Fourier transform infrared (FT-IR) spectroscopy

FT-IR spectrum of untreated drug was obtained by Shimadzu FT-IR spectrophotometer (Japan) by scanning the samples in KBr discs. In a similar way, FT-IR spectra of inclusion complexes of 1:1 and 1:3 ratios, their physical mixtures and stability samples were also taken. The samples were scanned over the frequency range 4000 cm^{-1} to 400 cm^{-1}. The spectra were compared with that of pure drug for any possible interaction.

Differential scanning calorimetry (DSC) study

Untreated drug, inclusion complex of 1:3 ratio, physical mixture and stability sample of same proportion were undertaken to thermal study by Shimadzu DSC-60 analyzer with TA60W trend line software. Samples of 3-5 mg were taken in aluminum pans and lids and heated at ascending rate of 10°C per minute under dry nitrogen environment. Thermal events of each sample were observed between 30°C and 500°C.

X-ray powder diffractometry

Powder X-ray diffraction patterns of untreated CVD and ICs of 1:2 ratio were recorded by D8 ADVANCE X-ray diffractometer (Bruker, Germany). Cu was used as anode material and operated at a voltage of 35 kV, 20 mA current. The samples were analyzed over 2θ angle range of 5°–70° with scanning step size of 0.02° (2θ) and scan step time of 0.5 degree per minute.

Scanning electron microscopy

Carvedilol, β-cyclodextrin and IC of 1:3 ratio were studied for morphological pattern by scanning electron microscopy (SEM). Each Sample was accumulated in the aluminum stabs which were coated with a double sided sticking tape. These were then sealed and finally coated with platinum under reduced pressure for 15 minutes using Hitachi Ion Sputter. Then the coated samples were analyzed by scanning electron microscope (Hitachi S-3400N, Germany) under different magnification to observe surface characteristics.

Stability study

Accurately weighed amount of ICs (ratio 1:1 and 1:3) were taken in glass vials and placed at 40°C±2°C and 75% RH stability chamber for 3 months for accelerated stability study. The effect of time, temperature and humidity on stability samples were evaluated by assessing drug content, FT-IR and DSC studies according to methods described in above sections.

Preparation of dissolution media

Simulated gastric fluid without enzyme was chosen as the dissolution medium for the preparations as per USP test II for carvedilol tablet. 2 g of sodium chloride and 7 ml of hydrochloric acid per liter of distilled water was the composition of dissolution media. The media had pH around 1.2.

Drug release studies

Solid complexes equivalent to 25 mg of CVD was subjected to in vitro dissolution study. The study was carried out in USP XXI six station dissolution test apparatus VDA-8 DR, India using 900 ml of dissolution fluid, paddle (II) apparatus with rotation speed of 50 rpm at temperature of 37°C ±0.5°C. Aliquots were withdrawn at 5, 10, 15, 30, 45 and 60 minutes interval and followed by immediate replacement of fresh medium to keep the volume constant. The concentration of CVD was determined using UV spectroscopy (UV mini 1240, Shimadzu) at 286 nm by comparing with obtained standard curve (Tapas *et al.*, 2012b). The test was performed six times for each sample.

Characterization of release records

In order to categorize release pattern from the solid complexes, mean dissolution time (MDT), % percent dissolution efficiency (%DE) and fractional dissolution time points ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) were calculated by different equations stated by Masum *et al*. (2012). From the release data, percent dissolved drug in 60 minutes (DP_{60}) were also determined (Tapas *et al.*, 2012b).

Kinetic modeling

To predict the mechanism of drug release from the solid complexes, in vitro drug dissolution data were fitted to various mathematical models including zero order, first order, Higuchi, Hixon Crowell and Korsmeyer-Peppas models (Hussain *et al*., 2012). Linearity to the best suitable model was determined from the regression coefficient value obtained from the equations of each graph.

RESULTS

Carvedilol was white crystalline fluffy powder having very poor flow property. On the other hand, β-cyclodextrin was white granular powder having good rheological property. When the drug was treated with cyclodextrin to form ICs, the carrier rendered the drug more flow-able without altering physical appearances. Compressibility of the complexes was far better than the pure drug as suggested by the Carr's index (CI) and Hausner ratio (HR) in Table 1. Powder flow defines powders having Carr's index 32 to 37 as very poor flow ability. Untreated carvedilol was found to have CI ratio of 32.50 that signals to its lack of flow properties. But cyclodextrin complexation improved rheological properties to fair or excellent level as proposed by the lower CI ratio.

Hausner ratio (HR) of drug and solid complexes also pointed towards the similar findings. The drug had a larger HR ratio that is a sign of poor flow. While the complexes had shown significant reduction of the HR values that denoted to better flow characteristics. As per USP-33 NF 28, HR values 1.00-1.11 denotes to excellent, 1.12-1.18 to good and 1.19-1.25 indicates to fair flow characteristics. Thus ICs of all ratios were found to have fair to excellent flow properties. Higher the carrier content, better the flow ability of complexes was found.

Inclusion complex system was found to yield 95% to 97% of theoretical amount. The yield ratio was moderately acceptable because of the process loss during preparation of small scale batches. Assay of the complexes was found adjacent to the theoretical values. It indicates to the suitability and effectiveness of the manufacturing technique to produce uniform complexes.

Table 1: Ratio, code names, percentage yield, drug content and micromeritic properties of carvedilol and inclusion complexes.

Ratio	Untreated Drug	1:0.5	1:1	1:2	1:3
Code for inclusion complex	Carvedilol	IC½	IC1	IC2	IC3
Code for physical mixture	-	PM½	PM1	PM2	PM3
Bulk density (g/ml)	0.27	0.42	0.48	0.53	0.56
Tapped density (g/ml)	0.40	0.53	0.55	0.57	0.61
Carr's index (CI)	32.50	20.75	12.73	7.02	8.33
Hausner ratio (HR)	1.48	1.26	1.15	1.08	1.09
Percentage yield	-	95.32	96.14	96.65	97.01
Calculated drug content (%)	-	65.25	48.97	32.14	24.51
Theoretical drug content (%)	100.00	66.67	50.00	33.33	25.00

In FT-IR spectra of pure drug (Fig. 1a), carvedilol showed characteristic peaks at 3345.59 cm^{-1} (for merged peak of O-H bending and N-H stretching of aromatic amine), 2924.13 cm^{-1}

(due to C-H stretching vibrations in methyl group), 1592.26 cm^{-1} (of N-H bending vibrations), 1101.37 cm^{-1} and 1252.79 cm^{-1} (for O-H bending and C-O stretching vibrations). The IR spectrum of β- cyclodextrin (Fig. 1b) is characterized by vibration of the –CH and $–CH_2$ groups in the 2800–3000 cm^{-1} region and intense bands at 3300–3500 cm^{-1} associated with the absorption of the hydrogen bonded -OH groups of β-cyclodextrin.

The IR spectra of the ICs prepared by kneading method (IC1 and IC3) showed small differences when compared with pure drug, like decreased intensity of the NH deformation band at 1501.61 cm^{-1} and a reduced intensity peak at 2924.13 cm^{-1} for methyl stretching (Fig. 1c & d). FT-IR spectrum of physical mixtures PM1 and PM3 (Fig. 2e & f) corresponds simply to the superposition of the IR spectra of the pure carvedilol and raw β-cyclodestrin. Even the samples which were studied for stability SIC1 and SIC3 showed no significant alteration in peak position and intensities (Fig. 2g & h).

X-ray powder diffractometry patterns of carvedilol and its complexes are illustrated in Fig. 3. Intense peaks of the drug was observed at 2θ of 12.74°, 15.16°, 17.44°, 18.76°, 20.32°, 23.02°, 24.37°, 27.69°, 28.29° and 31.29°. Similarly, the diffractogram of solid complex revealed presence of sharp peaks at similar positions. Rather, it was composed of some additional peaks that were probably contributed by the crystalline carrier.

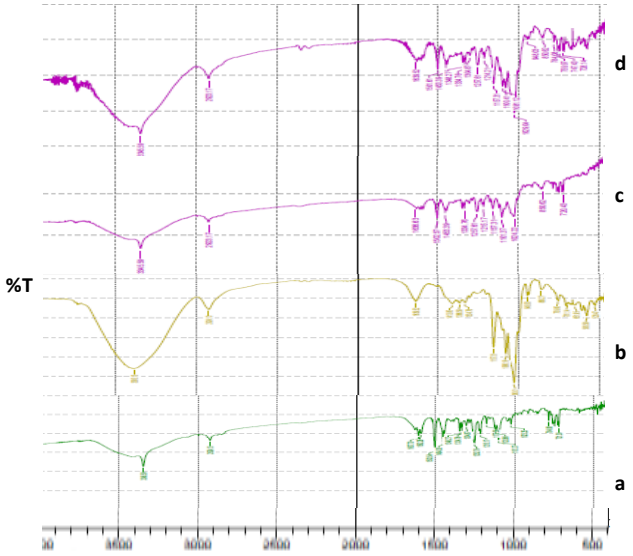

Fig. 1: FT-IR spectra of: a) pure carvedilol, b) β- cyclodextrin, c) IC1 and d) IC3 obtained by kneading method.

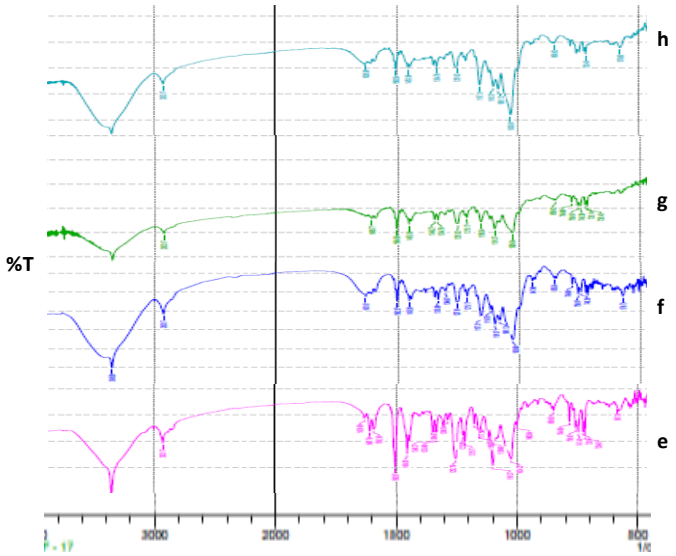

Fig. 2: FT-IR spectra of: e) physical mixture PM1, f) PM3, g) stability sample SIC1 and h) SIC3.

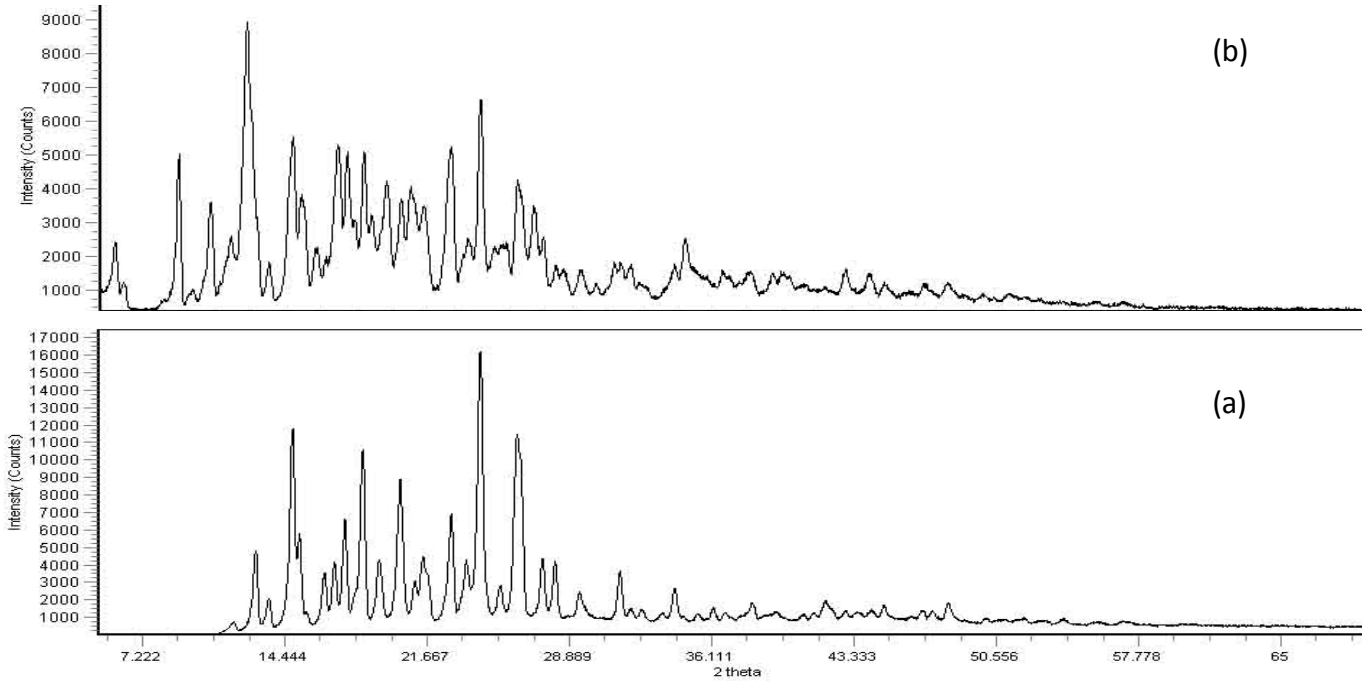

Fig. 3: Diffraction spectra of a) carvedilol and b) inclusion complex of ratio 1:2 (IC2).

DSC thermograms of drug, carrier, physical mixture, inclusion complex and stability sample have been presented in Fig. 4 & 5. The thermogram of untreated carvedilol demonstrated a sharp endothermic peak at 117.66 °C corresponding to the melting of the drug at that temperature. DSC thermogram of β-cyclodextrin revealed an endothermic peak at 110.33 °C that corresponds to release of water molecules (Bhutani *et al.*, 2007), a small peak at 226.30 °C and a large decomposition peak at higher temperature over 300°C. The physical mixture, inclusion complex and the stability sample of ICs were found to contain two distinguishable peaks one around 100 °C and one in 117 °C.

Scanning electron micrographs of untreated drug showed oval to spherical crystals (Fig. 6a). β-cyclodextrin revealed irregular shaped crystalline structures. The kneaded samples (IC3) illustrated uniform dispersion of drug crystals in the continuous irregular shaped carrier particles (Fig. 6c). Carvedilol was still in crystalline form in the inclusion complexes that was further confirmed by 2500 magnification.

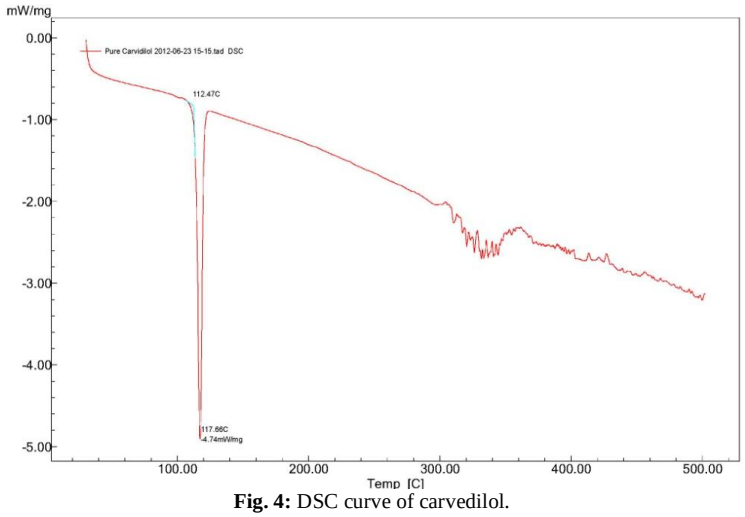

Fig. 4: DSC curve of carvedilol.

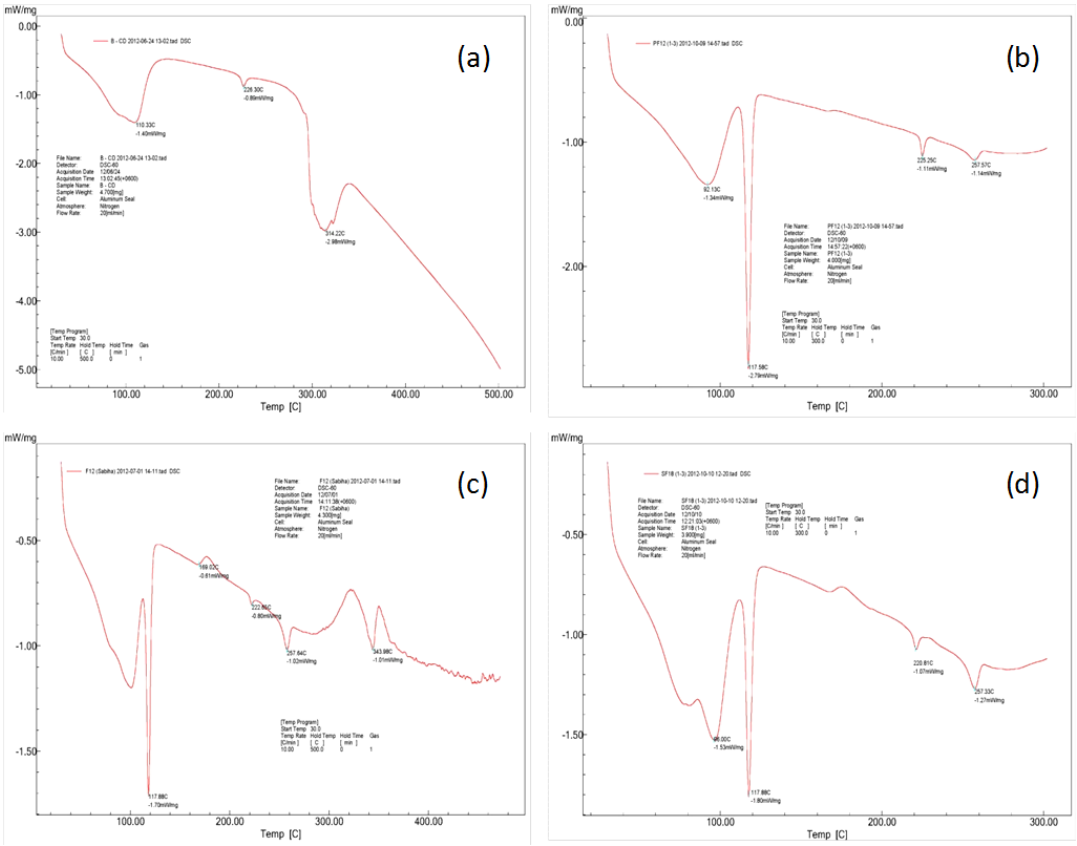

Fig. 5: DSC curve of a) β-cyclodextrin, b) physical mixture PM3, c) inclusion complex IC3 and d) stability sample SIC3.

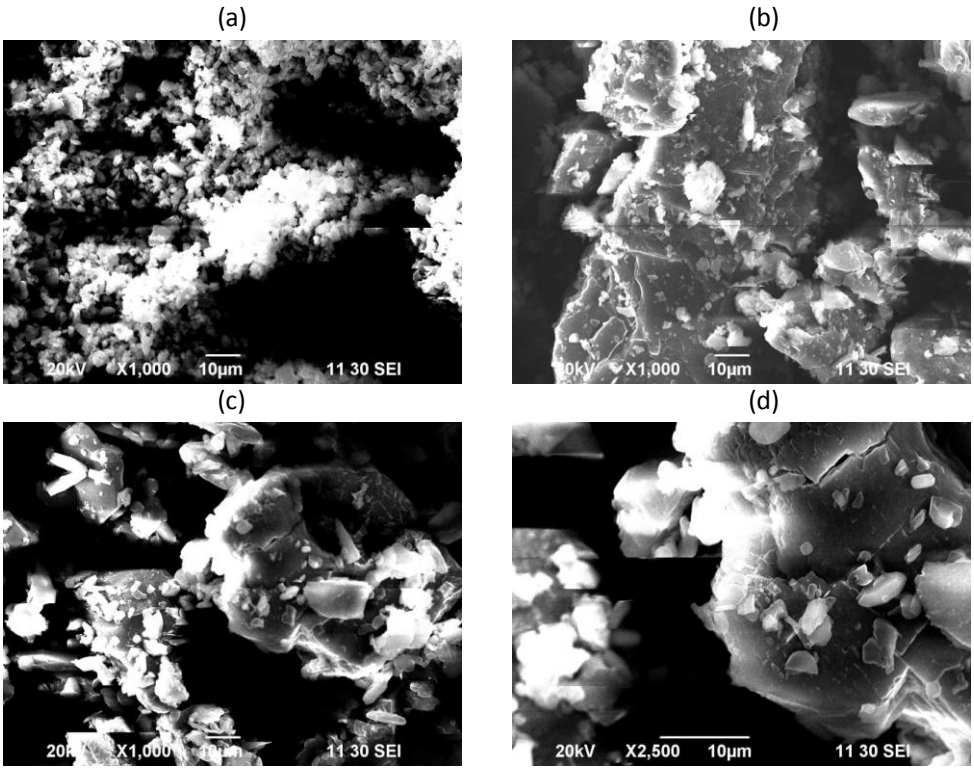

Fig. 6: SEM images of a) carvedilol at ×1000 magnification, b) β-cyclodextrin at ×1000 magnification, and inclusion complex IC3 at- c) ×1000 magnification and d) ×2500 magnification.

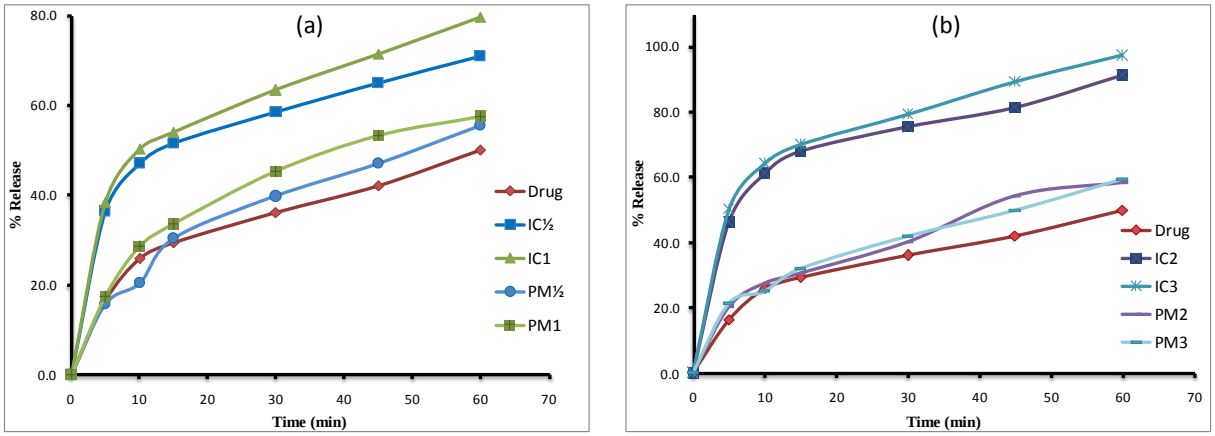

Fig. 7: In vitro release study of carvedilol from inclusion complexes and physical mixtures.

In vitro dissolution study of inclusion complexes showed significant improvement in dissolution and solubility profile of carvedilol (Fig. 7). Untreated drug dissolved to only 49.92% after an hour of dissolution while the solid complexes were able to release 70.80% to 97.25% of incorporated drug within same time. The complexes not only liberate an increased amount of drug throughout the dissolution period, but the dissolution rate increased markedly by inclusion technique. The rate and extent of dissolution enhanced with the increase of carrier content in the dispersion. 58.36%, 63.25%, 75.36% and 79.36% of incorporated drug was discharged from inclusion complexes IC½, IC1, IC2 and IC3 respectively in 30 minutes of dissolution. Thus, the rate of release increased as a function of carrier content in the solid complexes, and the improvement further continued to the end of dissolution. Similar trend of improvement of drug release was obtained in case of physical mixtures of all ratios. PMs were found to release 55.37% to 59.50% of incorporated drug. But the ICs were able to liberate the drug at a greater rate when compared to raw drug and physical mixtures.

To characterize the release profile of carvedilol from the solid complexes, mean dissolution time (MDT), fractional dissolution time values ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$), percent dissolved drug in 60 minutes (DP_{60}), and percent dissolution efficiency (% DE) were calculated and presented in Table 2.

Table 2: MDT values and fractional dissolution times ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) in minute and % $DE_{(10\ min)}$ and % dissolved drug in 60 minutes (DP_{60}) of prepared ICs.

Name	MDT (min)	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$	$\%DE_{10\ min}$	DP_{60}
Carvedilol	97.03	11.50	61.83	193.48	8.18	49.92
IC½	47.95	0.97	15.22	98.27	18.11	70.80
IC1	31.22	0.95	11.71	64.31	19.12	79.54
IC2	17.61	0.33	5.42	36.04	23.11	91.36
IC3	13.71	0.27	4.28	28.08	25.13	97.25

Table 3: Release kinetics of carvedilol from inclusion complexes.

Formulation	Zero Order		First Order		Highuchi		Korsmeyer		Hixon-Crowell	
	K_o	R^2	K_1	R^2	K_h	R^2	*n*	R^2	K_{hc}	R^2
Drug	0.685	0.840	-0.004	0.910	6.152	0.980	0.412	0.974	0.038	0.478
IC½	0.868	0.669	-0.007	0.836	8.358	0.897	0.252	0.982	0.040	0.376
IC1	0.997	0.715	-0.009	0.905	9.426	0.923	0.276	0.986	0.042	0.395
IC2	1.100	0.653	-0.014	0.914	10.640	0.885	0.248	0.963	0.043	0.371
IC3	1.192	0.673	-0.022	0.947	11.450	0.899	0.250	0.986	0.044	0.376

Mean dissolution time is an indication to predict the dissolution rate from dispersion systems. Higher the MDT, lower the drug releasing ability of dosage forms. Untreated drug was found to have MDT value of 97.03 minutes, whereas the inclusion complexes had MDT ranging from 13.71 minutes to 47.95 minutes. Similarly fractional dissolution values $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ were remarkably lower than the raw drug. Time to release 25% of incorporated drug ($T_{25\%}$) of untreated carvedilol was 11.50 minutes, while, it was below 1 minute for all the complexes that indicated to the efficiency of inclusion system. Percent dissolved drug in 60 minutes (DP_{60}) also showed similar results that the inclusion systems were able to release far greater amount of drug.

Dissolution efficiency (DE) is a tool to measure the extent of dissolution at a certain time point. It is calculated by comparing the total area under the dissolution curve of a certain time with the area of complete dissolution. Therefore, greater the percentage of DE, higher the rate of drug release. Within 10 minutes of dissolution, the untreated drug dissolved only 8.18% while, the solid complexes were found to have percent dissolution efficiencies of 18.11% to 25.13% and it was increasing according to the carrier content in the dispersions. To categorize the release pattern, kinetic modeling of release data was performed by plotting the release data with different mathematical equations. From different models, release pattern of inclusion complexes best fit with first order and Korsmeyer model according to higher regression coefficients (R^2 values ranging from 0.836 – 0.947 for first order and 0.963 – 0.986 for Korsmeyer model). It is because the complexes released drug at a progressive manner. Release exponent '*n*' of Korsmeyer pappas is accepted as an indication to the release mechanism from the complexes. All the preparations were found to have *n* value below 0.276 which is denotes to diffusion as the predominant mechanism for drug release because, release exponent *n* value below 0.45 is an indication to fickian diffusion to be the governing mechanism of drug release from the complexes (Razzak *et al.*, 2008).

DISCUSSION

Crystalline carrier β-cyclodextrin rendered the drug more compacted, granular and free flowing. Presence of greater amount of carriers in complexes made them more flowable as suggested by Carr's index (CI) and Hausner ratio (HR) in Table 1. Blend uniformity and suitability of manufacturing technique were indicated by drug content study and percent yield calculation.

FT-IR spectra of carvedilol showed characteristic peaks at different positions and some combined peaks. Such integration of peaks might be due to the possibility of intermolecular hydrogen bond formation between adjunct carvedilol molecules. Similar peak positions were described by Pokharkar *et al*. (2009). IR spectra of ICs showed much similarity with that of carvedilol. Presence of all other major peaks and absence of additional peaks in spectra of both complexes indicated that there were very little or no interaction between carvedilol and β-cyclodextrin (Fig. 1c and d). Spectra of physical mixtures were almost superimposition of characteristic peaks of carvedilol and β-cyclodextrin. Even stability samples of ICs showed no significant differences from initial spectra and no other additional peaks that clearly indicated absence of any interaction between carvedilol and carrier (Fig. 2g & h).

X-ray diffractogram of carvedilol showed numerous and distinct peaks that demonstrated the crystallinity of untreated drug. Whereas, diffraction figure of IC showed presences of similar peaks at identical positions. Thus it indicated to the presence of crystalline drug in the inclusion complex. Similar existence of crystalline drug in solid cyclodextrin complexes made of kneading method was also reported in literature (Pokharkar *et al*., 2009).

DSC thermogram of carvedilol showed its sharp melting peak at 117.66 °C. This characteristic peak was present in each thermogram of physical mixture, ICs and stability samples. It revealed that the drug remained in crystalline structure in the inclusion complexes and no significant interactions took place in the preparations though there was a little shift of the peak positions of the carrier. The FT-IR spectra and X-ray powder diffractogram of drug and inclusion complexes also stated the same. Similarly, the complexes were found stable after 3 months' accelerated stability study as no alteration was observed in the thermograms.

In vitro drug release study revealed carrier dependant release behavior of carvedilol from the ICs. Higher the carrier contents in the complexes, greater the release rate and extent was observed. Physical mixtures were also able to improve the

dissolution criteria of carvedilol, but not up to the level as did the ICs. It was probably due to the formation of water soluble complexes and molecular dispersion attained in case of ICs. Greater content of carrier in higher ratios provided the chance of forming more complexes and hence, dissolution behavior was improved. For the same reason, dissolution rate was improved significantly at a progressive manner with the increase of carrier content as suggested by lower MDT (min), $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ values and higher $\%DE_{10\ min}$ values. Furthermore, kinetic modeling confirmed the predominant mechanism of drug release from the complexes was diffusion.

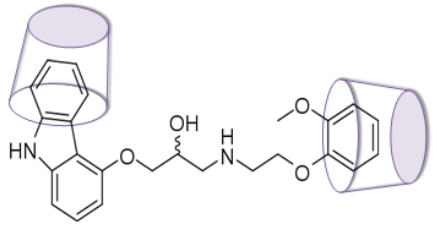

Fig. 8: Proposed structure of β-cyclodextrin-carvedilol inclusion complex.

To interpret the mechanism of higher drug release from the inclusion complexes, we need to understand the complexation technique first. Due the atomic arrangement of β-cyclodextrin, it forms a truncated cone like shape by seven glucopyranose units with a lipophilic central cavity of about 6.0–6.5 Å and a hydrophilic outer surface. Inclusion complexes are formed by usually non-covalent interaction between a drug and host cyclodextrin molecule where it can encapsulate hydrophobic part of the drug entity into its lipidic inner cavity. The resulting complex conceals most of the hydrophobic functionality in the core cavity of the cyclodextrin, while the hydrophilic groups on the outer surface remain open to the environment that finally consequences in formation of a water soluble cyclodextrin-drug complex (Devi *et al*., 2010). As the inclusion complexes were formed by weak forces like electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, release of conformational strain, and charge transfer (Palem *et al*., 2010), the complex can dissociate instantaneously to release the entrapped drug. A structure of β-cyclodextrin-carvedilol inclusion complex has been proposed in Fig. 8. Therefore, drug and cyclodextrin complexation is a reversible process which continuously dissociates and forms instantly in aqueous solutions (Devi *et al*., 2010). These composites are also able to form in-situ inclusion complexes in dissolution medium that can enhance drug dissolution even when there is no complexation in the solid state (Rasheed *et al*., 2008). Complexation with cyclodextrins can alter the physicochemical properties of a drug drastically by locking the drug in the host cavity and modifying different characteristics including appearance, crystalline structure, solubility, permeability etc. The reduction of drug crystallinity on complexation or solid dispersion with cyclodextrins also contributes to increase in apparent drug solubility and dissolution rate (Londhe and Nagarsenker, 1999). Solubility of drug from the inclusion complexes can be further improved by dilution and in some cases by competitive displacement with endogenous lipophiles after administration (Devi *et al*., 2010).

In this study, the drug remained in crystalline structure in inclusion complexes as suggested by differential scanning calorimetric study and X-ray diffraction analysis. Besides, FT-IR studies also indicated to little or no interaction between the drug and cyclodextrin molecules. Thus the study reports concluded to some IC complex formation by kneading method and also, greater amount of complex were formed in presence of ample carriers (in higher ratios) that finally revealed higher drug release. Other methods of IC formation can be followed to obtain greater inclusion complexes in order to improve the solubility and dissolution criteria of carvedilol further.

CONCLUSION

Inclusion complexes of carvedilol were found to improve the solubility and dissolution behavior markedly in comparison to untreated drug and physical mixtures. Kneading method was found suitable for IC preparation. The solid complexes were found to have compatible, stable and effective over time. Though β-cyclodextrin is the least soluble compound in cyclodextrins, still it improved the release behavior significantly. The complexes can be incorporated in tablet or capsule and in vivo study can be performed in order to observe their therapeutic efficacy.

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REFERENCES

Abdel-Razek TTM, Bennasir H, Sridhar S. Carvedilol – a novel "look" at β-blockers in management of cardiovascular disease. Int J Pharm Bio Sci, 2010; 1(2): 1-6.

Bhutani S, Hiremath SN, Swamy PV, Raju SA. Preparation and evaluation of inclusion complexes of carvedilol. J Sci Ind Res, 2007; 66: 830-834.

Del Valle EM. Cyclodextrins and their uses: A review. Process Biochem, 2004; 39: 1033-1046.

Devi NKD, Rani AP, Javed M, Kumar KS, Kaushik J, Sowjanya V. Cyclodextrins in pharmacy- an overview. Pharmacophore, 2010; 1 (3): 155-165.

Hussain MN, Masum MAA, Akhter A, Sharmin F, Reza MS. Formulation and evaluation of gastro retentive floating tablets of simvastatin using hydrophilic rate retardant. Bangladesh Pharm J, 2012; 15(2): 119-126.

Kramer BK, Ress KM, Erley CM, Risler T. Pharmacokinetic and blood pressure effects of carvedilol in patients with chronic renal failure. Eur J Clin Pharmacol, 1992; 43: 85-88.

Liu B, Li W, Zhao J, Liu Y, Zhu X, Liang G. Physicochemical characterisation of the supramolecular structure of luteolin/cyclodextrin inclusion complex. Food Chem, 2013; 141(2): 900-906.

Loh GOK, Tan YTF, Peh KK. Enhancement of norfloxacin solubility via inclusion complexation with β-cyclodextrin and its derivative hydroxypropyl-β-cyclodextrin. Asian J Pharm Sci, 2016 (Press).

Londhe V, Nagarsenker M. Comparision between hydroxypropyl-β-cyclodextrin and polyvinyl pyrrolidine as carriers for carbamazepine solid dispersions. Indian J Pharm Sci, 1999; 61: 237-240.

Masum MAA, Sharmin F, Islam SMA, Reza MS. Enhancement of solubility and dissolution characteristics of ibuprofen by solid dispersion technique. Dhaka Univ J Pharm Sci, 2012; 11(1): 1-6.

Palem CR, Chopparapu KSC, Subrahmanyam PVRS, Yamsani MR. Cyclodextrins and their derivatives in drug delivery: a review. Cur Trends Biotech Pharm, 2012; 6(3): 255-275.

Pokharkar V, Khanna A, Venkatpurwar V, Dhar S, Mandpe L. Ternary complexation of carvedilol, β -cyclodextrin and citric acid for mouth-dissolving tablet formulation. Acta Pharm, 2009; 59: 121-132.

Pooja S, Meenakshi B, Shruti S. Physicochemical characterization and dissolution enhancement of loratadine–hydroxypropyl-β-cyclodextrin binary systems. J Pharm Sci Res, 2011; 3(4): 1170-1175.

Rasheed A, Kumar ACK., Sravanthi VVNSS. Cyclodextrins as drug carrier molecule: a review. Sci Pharm, 2008; 76: 567-598.

Razzak MSMI, Khan F, Khan MZR, Fatema K, Islam MS, Reza MS. Effect of channeling agents on the release profile of theophylline from methocel K4M based matrix tablets. Dhaka Uni J Pharm Sci, 2008; 7(1): 27-32.

Shilpa C, Manish B, Ajinath S. Formulation and evaluation of bilayer floating tablet of carvedilol phosphate. J Drug Del Ther, 2012; 2(5): 9-19.

Srikanth MV, Babu GVMM, Rao NS, Sunil SA, Balaji S, Ramanamurthy KV. Dissolution rate enhancement of poorly soluble bicalutamide using β cyclodextrin inclusion complexation. Int J Pharm Pharm Sci, 2010; 2(1): 191-198.

Tapas A, Kawtikwar P, Sakarkar D. An improvement in physicochemical properties of carvedilol through spherically agglomerated inclusion complexes with PVP K30. Acta Polo Pharm Drug Res, 2012a; 69(2): 299-308.

Tapas A, Kawtikwar P, Sakarkar D. An improvement of micromeritic properties and dissolution behaviors of carvedilol spherical agglomerates crystallized in presence of inutec SP1. Turk J Pharm Sci, 2012b; 9 (1): 101-112.

USP 32-NF 27. The United States pharmacopeia – The National Formulary. Rockville, MD: The United States Pharmacopeial Convention, Inc; 2009.

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