Korean J. Chem. Eng., 32(1), 132-140 (2015)
DOI: 10.1007/s11814-014-0192-2

pISSN: 0256-1115
eISSN: 1975-7220

Process optimization and characterization of carvedilol solid dispersion with hydroxypropyl-β-cyclodextrin and tartaric acid

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(*Received 8 January 2014 • accepted 9 July 2014*)

Abstract−The present investigation concerns the experimental design in preparing a solid dispersion of ionized carvedilol with hydroxypropyl-β-cyclodextrin (HPβCD), tartaric acid (TA) by adopting 'kneading technique'. Simplex lattice design has been chosen to develop model equations that correlate the process variables such as HPβCD (mg), TA (mg), and kneading time (min) with the response variables, such as solubility (mg/mL) and drug release (%) from the solid dispersion. Software-generated ANOVA results confirmed the sufficiency of model equations. Results predicted by model equations are in good agreement with that of experimental results. Optimized formulation with variables 'CV: HPβCD: TA-kneading time' (200 mg: 689.6 mg: 227.6 mg-45 min) showed complete drug release (~99%) within 15 min and enhanced solubility of 1.89 mg/mL. The instrumental analysis (DSC, XRD& FTIR) of the optimized solid dispersion suggests a transformation of crystallinity of drug to amorphous form, due to its complexation with HPβCD. Hence, this combination of drug and carriers suggests an improvement of carvedilol bioavailability.

Keywords: Simplex Lattice Design, Ionized Carvedilol-hydroxypropyl-β-cyclodextrin-tartaric Acid Complex, Dissolution Rate, Solubility

INTRODUCTION

With progressive research for the formulation development of a newer drug delivery system, it has become apparent to assess the effects of factors (independent variables) on the responses (dependent variables). Statistical process control and experimental design are two very powerful tools for improving and optimizing a process. Applying this technique to product development improves the yield, reduces variability, and reduces development time as well as the overall cost. It is necessary first to identify the controlling factors and desired responses [1]. Present investigation deals with the experimental design to find the best conditions for enhancing aqueous solubility of drug.

Throughput screening of a new drug moiety incurs huge investment, out of which many are discontinued because of poor bioavailability. One of the primary reasons for poor bioavailability is low aqueous solubility of drugs, which are categorized under Biopharmaceutical Classification System (BCS) class II [2]. Formulation scientists have been practicing many methods to enhance the solubility of sparingly soluble drugs by adopting many methods, such as pro-drugs [3], salt formation [4], and formulation methods, such as particle size reduction [5], co-crystal formation [6], inclusion complexes using cyclodextrins [7] lipid formulations [8], and solid form changes, such as nanocrystals [9] and amorphous dispersions of API and polymers [10]. Of this, solid dispersion technique is most extensively used [11].

In present work, we chose carvedilol as model drug. Carvedilol is a nonselective beta, α_1-adreno receptor antagonist and vasodilator. It has 25-30% of oral bioavailability because of low aqueous solubility. Improving its aqueous solubility/dissolution by a suitable method may overcome the bioavailability problem. There are a few methods used to prepare a solid dispersion, out of which 'kneading' is the simplest one. The present study involves ionization of drug and its complexation with cyclodextrin in presence of hydroxyl acids. Ionization process is used to increase the apparent intrinsic solubility of drug in test medium. Hydroxyl acids (citric acid and tartaric acid) are changing the pH of microenvironment; this facilitates drug solubility and dissolution rate, even at the high pH level, and enhances the complexation efficiency of cyclodextrins [12].

CDs have the ability to enhance solubility, chemical stability and bioavailability of poorly water soluble drugs [13]. Low complexation efficiency is major problem associated with cyclodextrins; so a large amount of CDs is required to solubilize a small amount of lipophilic drug. Nowadays, derivatives of cyclodextrins are found most effective [14]. Hydroxypropyl-β-cyclodextrin (HPβCD), which is a hydroxyl alkyl derivative of βCD, was developed and widely studied in the field of drug encapsulation because of its inclusion ability along with high water solubility [15]. To enhance solubility of drug, a method needs to be developed with an aim to produce solid dispersion with a minimum amount of the carrier.

To analyze and optimize the process parameters it is necessary to understand their effects on the response variables. With the least number of experiments model equations are developed by the response surface methodology (RSM), which is an experimental design used for optimization. There are various designs such as central composite design; Box-Behnken design and Simplex design [16]. Generally, simplex designs are used to study the effects of mixture components on response variables. Two components and one im-

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Table 1. Parameters levels, design matrix and measured responses

Run order	Formulation parameters			% Yield	Drug content (mg)	Responses	
	A (mg)	B (mg)	C (min)			Sol pH 7.4	Release at 5 min
1	600	250	45	94.56±1.96	97.42±1.04	1.3±0.21	84.08±2.14
2	633.4	233.35	47.5	95.21±1.82	98.45±0.68	1.59±0.14	88.5±1.86
3	733.4	208.35	47.5	97.28±2.27	96.89±2.10	1.54±0.09	87.9±2.54
4	800	200	45	95.12±1.78	98.54±1.50	1.08±0.11	77.4±1.87
5	600	250	45	96.36±2.06	101.12±1.12	1.25±0.12	83.36±3.12
6	600	200	60	95.49±2.45	97.50±2.05	1.12±0.07	79.04±1.78
7	700	225	45	96.33±1.62	96.45±1.13	1.89±0.1	94.1±2.45
8	633.4	208.35	55.01	98.01±0.98	97.84±2.17	1.35±0.08	84.1±2.36
9	600	225	52.5	97.58±1.27	98.54±1.41	1.25±0.06	83.28±1.72
10	700	200	52.5	95.60±1.51	97.73±1.40	1.21±0.12	82.18±2.47
11	666.6	216.65	49.99	97.39±2.24	98.75±2.17	1.58±0.21	87.89±1.87
12	800	200	45	96.78±2.12	98.69±1.19	1.1±0.05	77.8±1.45
13	700	225	45	96.41±1.47	97.12±2.28	1.86±0.15	94.7±2.14
14	600	200	60	97.53±0.78	98.23±1.31	1.15±0.03	79.5±1.53

Parameters	Units	Notations	Limits	
			0	1
HPBCD	mg	A	600	800
TA	mg	B	200	250
Kneading time	min	C	45	60

portant process variable are chosen as variables in the present investigation.

The objective of the present work is to optimize a method for preparing the solid dispersion of carvedilol-HPβCD by Simplex lattice design, to check permeation of CV in a solid dispersion, and to carry out instrumental analysis of the product to check the interaction of drug with cyclodextrin.

EXPERIMENTAL

1. Materials

Carvedilol (CV) was provided by SUN Pharmaceutical Ltd., India as a gift sample; Hydroxypropyl-β-cyclodextrin (HPβCD) was provided by Roqutte Pharma, India as a gift sample. Tartaric acid (TA), and all other reagents and solvents used are of analytical grade.

2. Simplex Lattice Design

Simplex lattice design was used to optimize the factor levels to achieve the desired response. In this design, three factors were evaluated by changing their levels simultaneously. To gain indepth information of the experimental region and to evaluate the curvature, this study was conducted in a total of 14 experimental runs in accordance with three pure components (corners of the triangle) and three two-component blends (mid-points of the edges). In addition to these six mixtures, the software specified the three-component 'centroid' blend (one-third of each) and three check-blends, bringing the total of unique combinations to ten, of which four combinations were suggested to be replicated to provide a measure of pure error for estimating potential lack of fit. Interaction effects among the factors resolved by the design allow a mid-level value as a combination of factors [17]. Simplex design is generally used to study the effects of mixture components on response variables; in the present study, two factors were the composition of chemicals (HPBCD and TA) and the third one was a process variable (kneading period). The quadratic second-order model was fitted to the following equation, Eq. (1).

$$Y=\beta 1A+\beta 2B+\beta 3C+\beta 12AB+\beta 13AC+\beta 23BC \quad (1)$$

where, Y is the measured response (dependent variable) associated with each factor-level combination; responses (R1 and R2) expressed in terms of solubility (mg/mL) and drug release (%) in 5 min; β_1, β_2, β_3, β_{12}, β_{13} and β_{23} are the regression coefficients. Independent variables studied were A, B, and C are HPβCD (mg), tartaric acid (mg) and kneading time (min) respectively. In Table 1, levels of independent variables and design matrix and responses are shown. Responses were experimental data obtained following the design matrix. The design matrix was developed by Design Expert Software trial Version 7.0.0 (STAT-EASE Inc., Minneapolis, USA).

3. Preparation of Ionized Carvedilol - HPβCD-TA Ternary Complex

To check the effect of ionization on solubility, an accurately weighed amount of (200 mg) of CV was taken in a mortar-pestle, and excess amount of acetic acid was added to it. The mixture was ground thoroughly and kneaded up to 45 min. The paste was dried at room temperature overnight and then solid mass was dried at 88 °C under vacuum up to 72 h [12]. The dried mass was pulverized and sieved through a 120 mesh sieve. It was then stored in desiccators at 25 °C until further use. The dry powder containing ionized drug (200 mg) was used to prepare solid dispersions with a specified amount of HPβCD-TA as per the experimental design showed in Table 1. This mixture was moistened with a small volume of ethanol-water solu-

tion (15 : 85 v/v) [18]. The mixture was ground thoroughly in a mortar-pestle, and kneaded to a pasty mass by the addition of solvent drop wise up to the time as mention in Table 1. The paste was dried at room temperature overnight. The dried mass was pulverized and sieved through a 120 mesh sieve. It was then stored in desiccators at 25 °C for further use.

4. Determination of Yield (%) and Drug Content (%)

Prepared solid dispersion (drug-carrier complex) was collected and weighed accurately and the yield (%) of solid dispersion was calculated by the following, Eq. (2).

$$\text{Yield (\%)} = \frac{\text{weight of soliddispersion}}{\text{Total weight of carrierand drug}} \times 100 \quad (2)$$

A sample of 10 mg of CV solid dispersion was weighed and dissolved in 5 ml of methanol and diluted up to 95 ml with double distilled water in a volumetric flask and then necessary dilution was made. The content of drug was determined by UV Spectrophotometric method.

5. Determination of Saturation Solubility

To determine saturation solubility, an excess amount of sample was added to 10 mL of phosphate buffer (pH 7.4). The volumetric flasks fitted with glass stoppers were placed in a water bath at a constant temperature of 37±0.5 °C and shaken for 24 h to attain equilibrium. Next, the content of the vessel was centrifuged. The supernatant solutions were filtered through a Whatman filter paper (pore size 11 μm) and then suitably diluted. Absorbance was recorded at 241 nm by UV-spectrophotometer (Analab UV-180, India). Each test was repeated three times.

6. *In Vitro* Dissolution Studies

Dissolution studies of prepared samples were performed using a USP type II (TDT 06P Electro lab, India) dissolution test apparatus. Accurately weighed pure drug and SD (20 mg equivalent amount of CV) was placed in a dissolution paddle containing 900 mL of phosphate buffer (pH 7.4), which was fixed at 37±0.5 °C and stirring speed of 50 rpm. Samples were collected periodically from dissolution medium, and same quantity of fresh medium was replaced after each withdrawal. Each withdrawal sample was filtered through Whatman filter paper (pore size 11 μm), and its concentration was determined by UV Spectrophotometric method. Each test was repeated three times.

The response variable's data (solubility and dissolution) were subjected to statistical analysis and significant models along with response surfaces were obtained. The models were validated by checkpoint formulations and % error was calculated.

7. *Ex Vivo* Absorption Study in a Goat-intestine Segment

Ex vivo absorption study was carried out to compare the permeation rate of CV-solid dispersion with that of pure drug. This study was performed following the method of Karasov and Diamond [19]. Small intestine of already slaughtered male goat was collected from the local market. An intestinal segment (6 cm length, 0.75 cm inner diameter of lumen) was cut and washed thoroughly with warm Krebs-Ringer phosphate buffer (KRPB) solution [20]. After tying up one end of this segment, the inner cavity of sac/lumen was filled with a solution of phosphate buffer (pH 7.4) containing solid dispersion (20 mg equivalent amount of CV). The other end was closed. The two ends of the sac were then fixed between the two ends of a "disintegration tester" and immersed in 900 mL solution (PB pH 7.4, 37±0.5 °C, 75 rpm) kept in the basket. Drug was permeated through the mucosal layer from mucosal compartment to the outside medium (serosal compartment). Samples were withdrawn from serosal compartment at preselected time intervals of 15 min and fresh medium was replaced after each withdrawal. Withdrawn samples were analyzed by UV spectrophotometer at 241 nm. After several hours (5 h for pure CV and 2.5 h for optimized formulation) the segment was removed from the medium and the liquid remaining in the intestinal sac was collected from one end of the segment. The whole intestinal segment was triturated with the help of mortar and pestle and then homogenized in phosphate buffer pH 7.4. Thus, drug that remained in the liquid of intestinal sac and mucosal layer was determined to check the mass balance of CV. The whole experiment was repeated in triplicate (n=3) using the fresh medium as well as fresh intestinal segment each time.

8. Solid-state Characterizations of Optimized Solid Dispersion by Instrumental Analysis (FTIR, XRD, DSC)

These analyses give support to detect any type of interaction between drug and carriers.

Fourier transform infrared (FTIR) spectroscopy of solid dispersions samples was performed using Shimadzu Co., Kyoto, Japan combined with Quick Snap sampling modules by the KBr disc method over wave number range of 4,000-400 cm^{-1}. Pure polymer, drug (CV), and drug/polymer physical mixtures were run as controls. 10 mg of sample was taken for this study.

XRD study was conducted on the samples (pure drug, pure carrier substances and selected formulation) to check its crystalline characteristics using a Rigaku Miniflex diffractometer (Rigaku Co., Ltd., Japan) with a Kb filter, Cu radiation, a voltage of 30 kV and a 15 mA current. Each sample (25 mg) in the X-ray holder was continuously spun and scanned at a rate of 1°/min over a 2 θ range of 10-70°, and the results were processed by a pre-loaded computer program.

DSC measurements were performed on samples by using a differential scanning calorimeter (Pyris diamond TG/DTA; P, Perkins Elmer Instruments) with a thermal analyzer. Under nitrogen flow of 150 mL/min, approximately 5.83 mg of CV, carrier substances and SDs with respective carriers were placed in a sealed aluminum pan, and heated at a scanning rate of 10 °C/min over the temperature range of 30° to 300 °C.

RESULTS AND DISCUSSION

1. Development of Mathematical Models

From the trial batch investigation, we observed that solid dispersion with the following combinations (ionized CV : HPβCD : TA - 200 : 600 : 150) shows better solubility and dissolution rate. Thus, we considered further to optimize the processing variables in the application of multivariate analysis. The solid dispersions were prepared using kneading method according to the design matrix as shown in Table 1. The amount of HPβCD (mg), tartaric acid (mg) and kneading time (min) were selected as independent variables; solubility (mg/mL) and drug release (%) in 5 min were selected as dependent variables. Response data (Table 1) were fitted in experimental design and analyzed by DOE software, design expert v7.

Table 2. ANOVA results (based on coded values) for the linear regression models

Solubility in pH 7.4			Release at 5 min		
Factor	b-Coefficient	p-Value	Factor	b-Coefficient	p-Value
A	1.09	<0.0001	A	77.76	<0.0001
B	1.27	<0.0001	B	83.62	<0.0001
C	1.14	<0.0001	C	79.34	<0.0001
AB	2.83	<0.0001	AB	54.58	<0.0001
AC	0.52	0.0018	AC	15.35	0.0002
BC	0.29	0.0343	BC	5.96	0.0365
Other statistics			Other statistics		
R^2=0.9931; Adjusted R^2=0.9887			R^2=0.9926; Adjusted R^2=0.9880		
Predicted R^2=0.9636			Predicted R^2=0.9809		
Adequate precision=42.276			Adequate precision=41.93		

*Lack-of-fit is non significant [for solubility, p (0.2868)>0.05) and for release, p (0.118)>0.05]

The software-generated ANOVA and models were analyzed, and finally with the elimination of insignificant terms mathematical model equations were obtained.

2. Analysis of ANOVA for Solubility in pH 7.4 (SolpH 7.4) and Release in 5 min (pH 7.4)

The ANOVA result of solubility (Table 2) shows the interaction effects of HPβCD and TA (A*B), TA and kneading time (B*C) and HPβCD and kneading time (A*C). In this case, linear mixture components, AB, AC and BC are significant model terms. The Pred R-Squared of 0.9636 is in reasonable agreement with the Adj R-Squared of 0.9887. Adeq Precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. Here, the ratio of 42.276 indicates an adequate signal.

The ANOVA result of drug release (%) (Table 2) shows the interaction effects of HPβCD and TA (A*B), TA and kneading time (B*C) and HPβCD and kneading time (A*C). ANOVA reveals linear mixture components, AB, AC, BC are significant model terms. The Pred R-Squared of 0.9809 is in reasonable agreement with the Adj R-Squared of 0.9880. Adeq Precision 41.930 indicates an adequate signal.

With the consideration of the absolute magnitude of regression coefficients of A, B and C these are almost higher in $rel_{5\,min}$ than $sol_{pH\,7.4}$, and these have similar ranking effects in both $sol_{pH\,7.4}$ and $rel_{5\,min}$.

The final mathematical models for the aqueous solubility and $rel_{5\,min}$ of Carvedilol are specified below, and this can be used for the prediction of solubility and $rel_{5\,min}$ of Carvedilol within design space,

1. Equation obtained in terms of actual factors.

$$sol_{pH\,7.4}=1.09*A+1.27*B+1.14*C+2.83*A*B+0.52*A*C+0.288*B*C \quad (3)$$

2. Equation obtained in terms of actual factors.

$$rel_{5\,min}=77.76*A+83.62*B+79.34*C+54.58*A*B+15.35*A*C+5.96*B*C \quad (4)$$

The above equations suggest that the factor B has a more significant effect on solubility and release in 5 min followed by factor C and A.

3. Validation of Developed Models

Simplex lattice equations from multiple regression analysis were validated by choosing randomly five check point formulations pre-

Table 3. Validation of check point formulations

S. No.	Experimental composition			Response variable	Experimental value	Predicted value	Percentage error
	A (mg)	B (mg)	C (min)				
CPF 1	744.6	200.5	49	Solubility in pH 7.4	1.19	1.23	3.2
				Release at 5 min	79.64	81.62	2.4
CPF 2	659.3	228.7	46.95	Solubility in pH 7.4	1.68	1.72	2.3
				Release at 5 min	88.96	91.64	2.9
CPF 3	637.1	216.9	52.14	Solubility in pH 7.4	1.42	1.45	2.0
				Release at 5 min	85.39	86.24	0.98
CPF 4	689.36	213.1	49.36	Solubility in pH 7.4	1.50	1.57	4.4
				Release at 5 min	85.12	88.61	3.9
CPF 5	602.9	221.1	53.5	Solubility in pH 7.4	1.22	1.28	4.6
				Release at 5 min	80.09	83	3.5

CPF is check point formulation

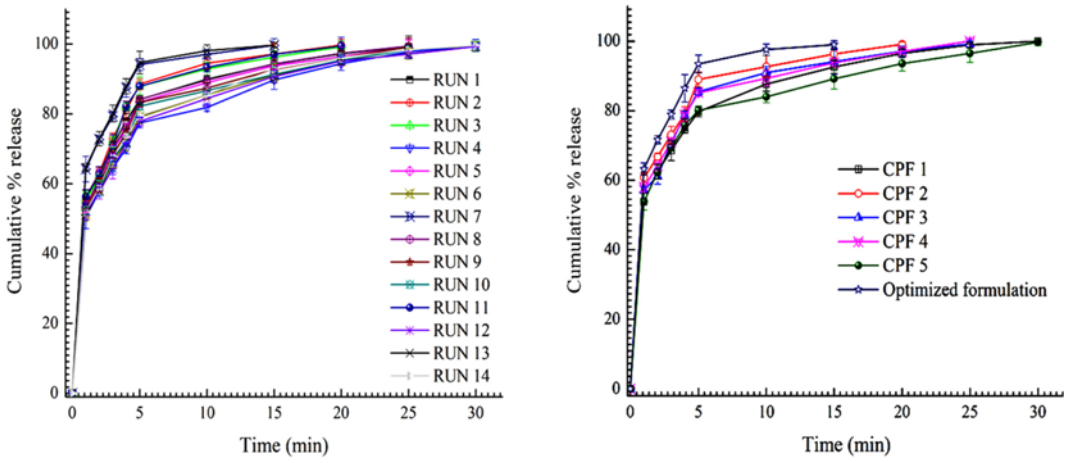

Fig. 1. Dissolution profiles of carvedilol inclusion complex prepared as per the experimental design.

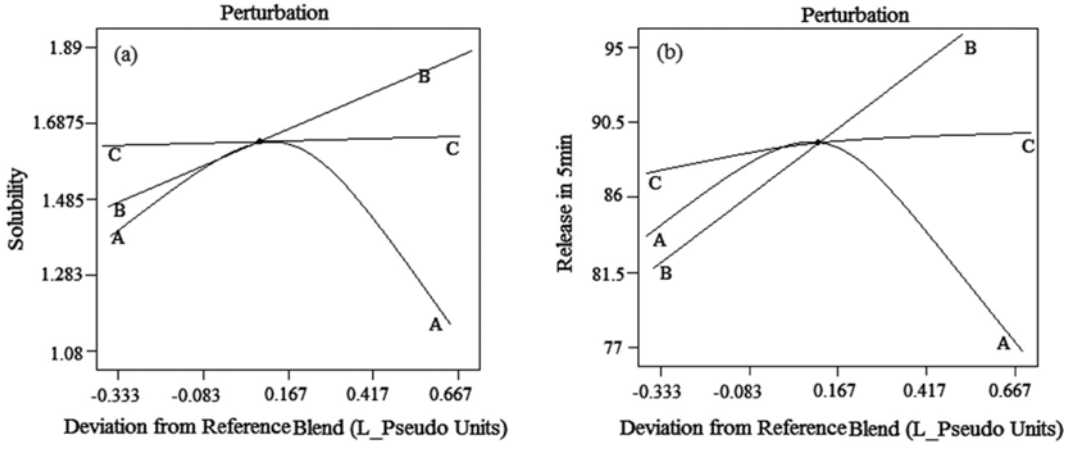

Fig. 2. Perturbation plot showing the effect of all factors on (a) solubility and (b) release in 5 min.

pared with the same conditions within the experimental ranges. For each response, the average of three experimental data is presented as the actual result. The percentage error/deviation between an actual result of these checkpoint formulations and respective predicted values are presented in Table 3. Release profiles of various solid dispersions as per design matrix and check point formulations are depicted in Fig. 1.

Low percentage error between the actual and the predicted values was observed, indicating that the developed models could yield a precise result.

4. Effect of Process Parameters on the Responses

A perturbation plot (Fig. 2) depicts the effect of all the factors at the center point in the design space. The result indicates that the solubility and dissolution of carvedilol increase with increase in concentration of HPβCD until reaching its center value. The solubility then starts to decrease as HPβCD concentration increases beyond the center limit, and this can be attributed to the formation of insoluble complex at higher HPβCD concentration; kneading did not show any effect on solubility and dissolution rate. In case of TA, it showed a linear increment in both the responses.

The solubility and dissolution of carvedilol solid dispersion was investigated in pH 7.4 phosphate buffer. Figs. 3 and 4 illustrate the effect of process parameters on solubility and dissolution rate; the report clearly shows that TA had a prominent effect on the solubility and dissolution rate of drug than HPβCD and kneading time, because TA creates an acidic environment around the drug molecule, which facilitates better solubility of drug even at a high pH (7.4) and enhances the complexation efficiency of cyclodextrin [21]. Increasing the kneading did not show any effect on solubility and dissolution rate.

Increasing the concentration of cyclodextrin, drug solubility was enhanced up to a certain extent; after that it deviated negatively. Since high concentration of cyclodextrin increased viscosity, it caused a low rate of dissolution and solubility of drug in the intra-particles zone [22].

5. Optimization by Desirability Function

An optimized solid dispersion was made by choosing the maximum response, which was based on the constraints of the physiochemical parameters.

Upon analyzing various response variables and comprehensive evaluation of the feasibility of search and exhaustive grid search, the formulation composition of carvedilol=200 mg; HPβCD=689.6 mg; TA=227.6 mg; kneading time=45 min (Table 4) was found to fulfill the requisites of an optimum formulation. The optimized for-

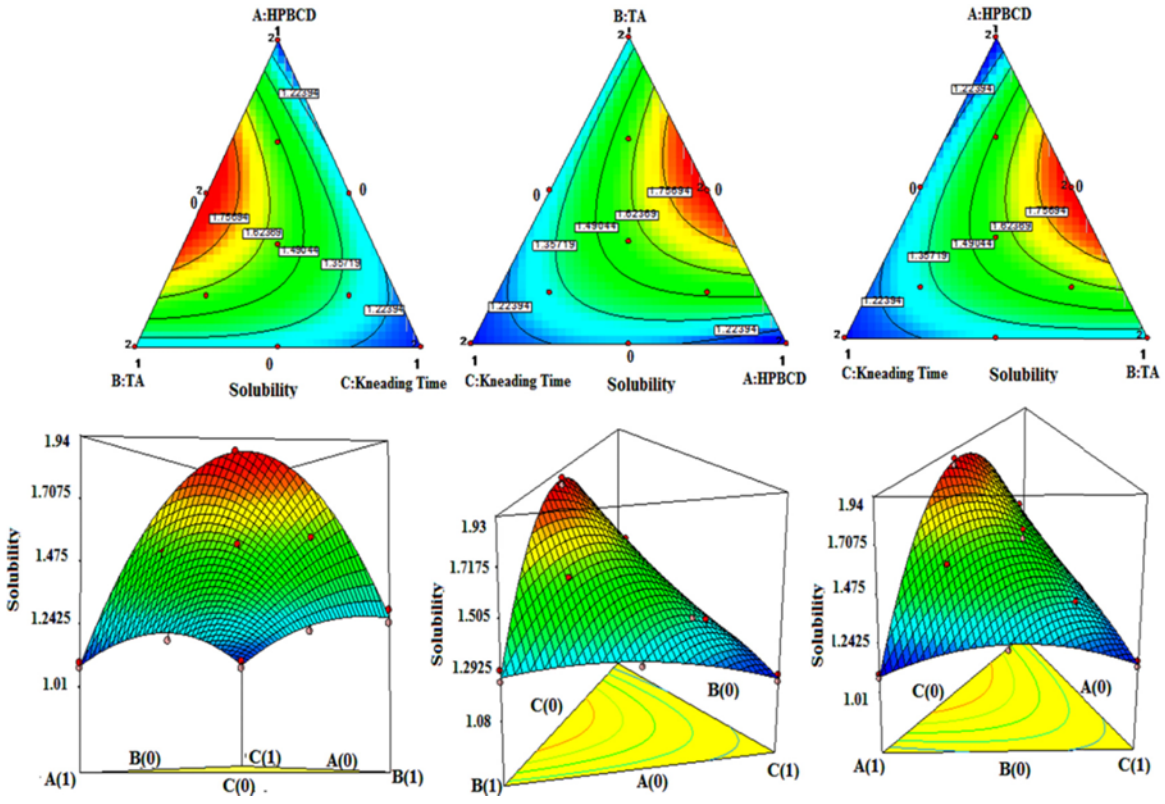

Fig. 3. Contour plot and simplex lattices plot showing effect of (a) HPβCD, (b) TA and (c) Kneading time on solubility in pH 7.4 of Carvedilol inclusion complex (R1).

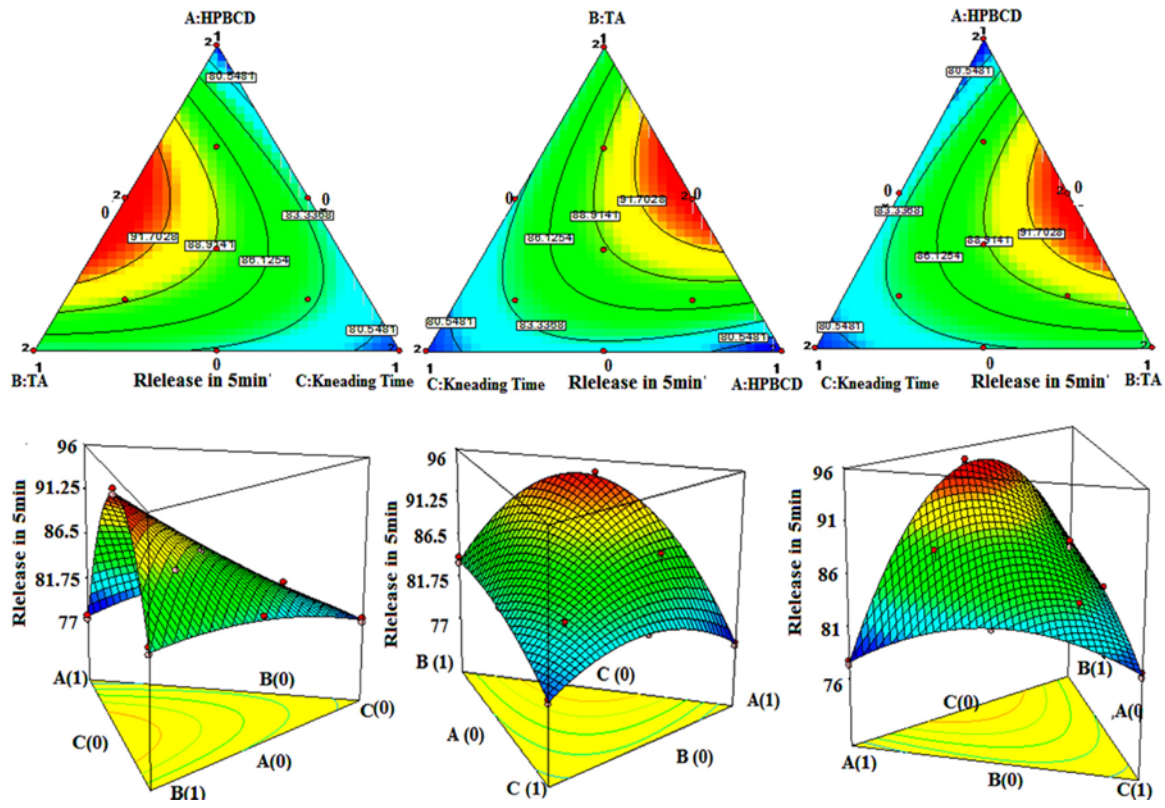

Fig. 4. Contour plot and simplex lattices plot showing effect of (a) HPβCD, (b) TA and (c) Kneading time on $rel_{5\,min}$ (%) of Carvedilol inclusion complex (R2).

Table 4. The criterion for numerical optimization

Parameter	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
HPβCD	Is in range	0	1	1	1	3
TA	Is in range	0	1	1	1	3
Kneading time	Is in range	0	1	1	1	3
R1-Sol (mg/mL)	Maximize	1.08	1.89	1	1	3
R2-Rel at 5 (min)	Maximize	77.4	94.7	1	1	3

Batch optimized formulation

Number	A-HPβCD (mg)	B-TA (mg)	C-Kneading time (min)	R1-Sol (mg/mL)	R2-Rels at 5 (min)	Desirability
1	689.6	227.6	45	1.89	94.49	0.994

Table 5. Study of mass balance of pure carvedilol and optimized formulation in *ex vivo* absorption experiment

Formulation	% of Drug in pH 7.4				
	Serosal compartment	Mucosal compartment	Intestinal membrane	Total recovery of CV	Permeation coefficient ($\mu g/cm^2/h$)
Pure Carvedilol	72.45±1.46	21.47±	5.78±0.67	99.7	194.08
Optimized formulation	86.57±1.82	11.23±	1.71±0.73	99.51	460.78

mulation has an aqueous solubility of 1.89 mg/mL and release at 5 min of 94.49%, which was very high when compared with pure drug solubility (0.0301 mg/mL) and in vitro release % at 5 min (3.29%).

6. *Ex Vivo* Absorption Study in a Goat-intestine Segment

The extent of *in vivo* absorption can be predicted on the basis of permeability and solubility of drug [23]. Intestine of a slaughtered animal was used to perform *ex-vivo* absorption study, which is less expensive, fast and is not subjected to permission from Animals Ethical Committee. It was observed that 86.57% drug from a solid dispersion was permeated into the serosal compartment through the intestinal membrane in 2.50 h study; some amount of CV remained in the liquid of mucosal compartment (11-12%) and lesser amount was absorbed within the intestinal mucosal membrane (1.71%). Results of the optimized formulation and pure drug are shown in Fig. 4. In mass balance calculation, ~99% of CV was found accountable (Table 5). We observed that 72.45% of pure drug permeated into the serosal compartment, 21.47% remained within the intestinal mucosal compartment, and 5.78% remained within a mucosal membrane. In mass balance calculation, 99-100% of CV was found accountable; permeability coefficient of drug in a solid dispersion and pure drug is presented in Table 5. Results of optimized formulation and pure drug are shown in Fig. 5; it indicated that carvedilol in solid dispersion form showed more permeability than that of pure drug.

7. FTIR Spectroscopic Analysis

The solid-state interaction between the carrier and drug can be explained by FTIR spectroscopy. The pure carvedilol, carriers and their solid dispersion are characterized in Fig. 6.

The FTIR spectrum (Fig. 6(a)) of CV exhibits characteristic peaks at 3,344 cm^{-1} corresponding to the N-H stretching vibration of the secondary amine, three intense absorption bands 2,922, and 2,835.3 cm^{-1} corresponding to C-H aliphatic stretching, and 1,101 cm^{-1} corresponding to C-O stretching. In addition other sharp bands appear at 1,500-1,400 cm^{-1} (C-C aromatic stretching) and 1,255 cm^{-1} (C-N

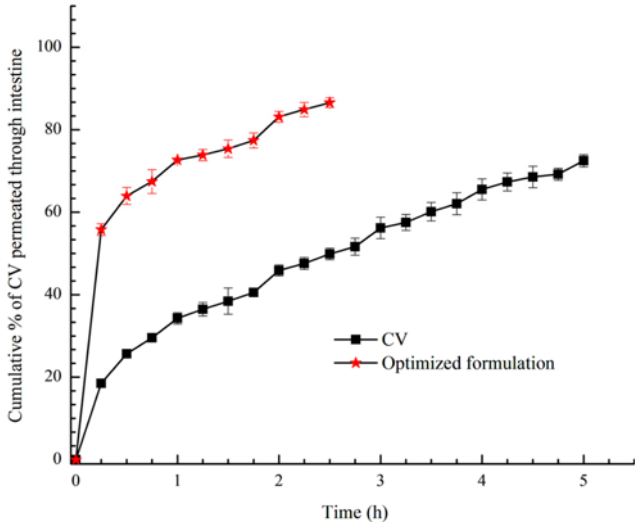

Fig. 5. Permeation study of carvedilol and optimized formulation in pH 7.4.

stretching) [24]. In Fig. 6(b) the ionized CV spectrum shows the same type of characteristic peak; it indicates no changes occurred with carvedilol after ionization.

The FTIR spectrum of TA (Fig. 6(c)) clearly exhibits bands around 3,399 cm^{-1}, 3,330 cm^{-1}, 1,713 cm^{-1} and 937 cm^{-1}, corresponding to the O-H stretching, C=O stretching due to carboxylic acid group and O-H bending, respectively.

The spectrum of HPβCD (Fig. 6(d)) shows prominent absorption bands at 3,385 cm^{-1} (O-H stretching vibrations), 2,929 cm^{-1} (C-H stretching vibrations), 1,641 cm^{-1} (C-C stretching vibration - aromatic ring) and 1,159, 1,032 cm^{-1} (C-H, C-O stretching vibration) [25].

In a physical mixture (Fig. 6(e)) (CV: HPβCD: TA), functional groups of CV were dominantly exposed, though its intensity was

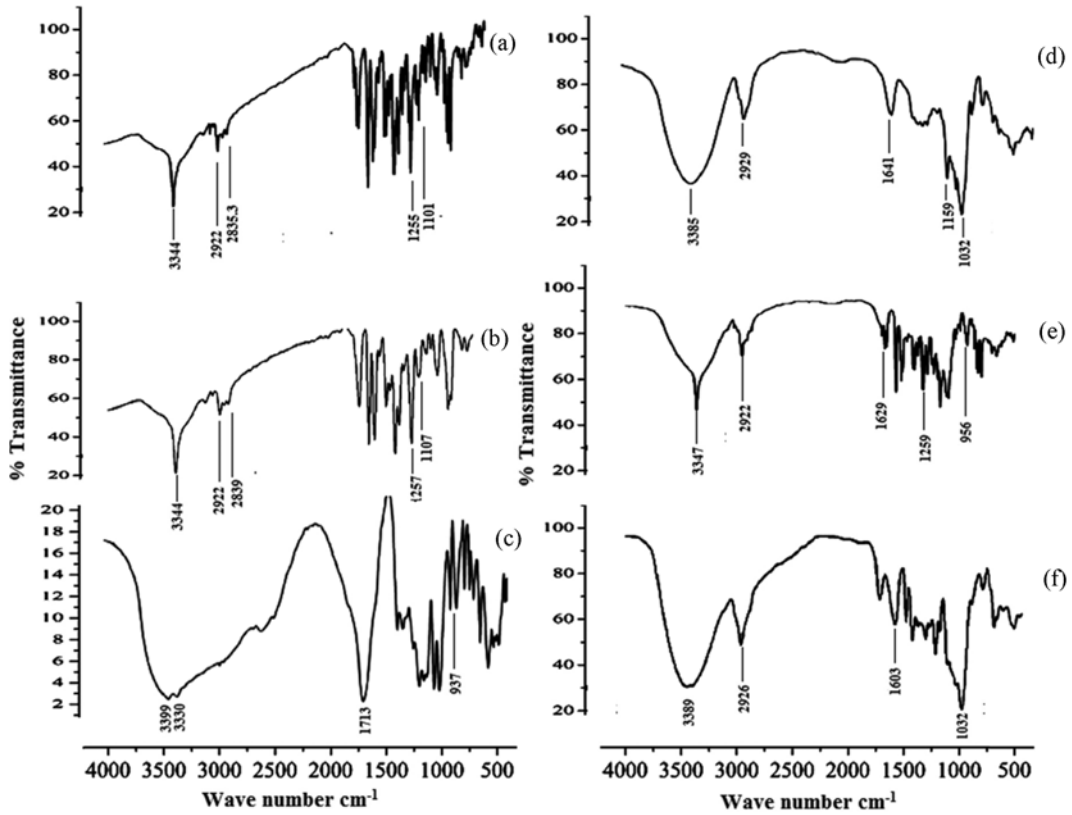

Fig. 6. FTIR of (a) Carvedilol; (b) Ionized carvedilol; (c) TA; (d) HPβCD; (e) ionized CV : HPβCD : TA.

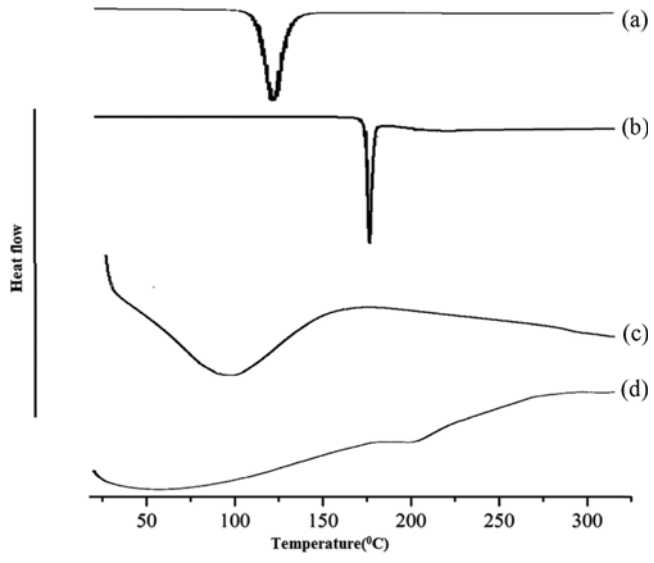

Fig. 7. DSC of (a) Carvedilol; (b) TA; (c) HPβCD; (d) ionized CV : HPβCD : TA.

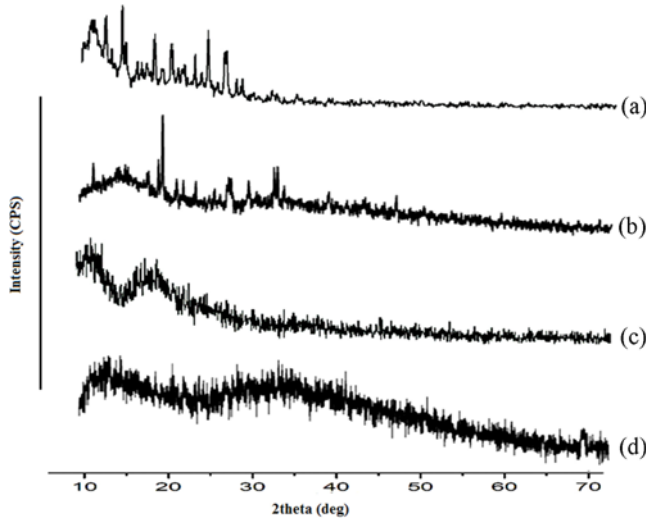

Fig. 8. X-ray diffraction of (a) Carvedilol; (b) TA; (c) HPβCD; (d) ionized CV : HPβCD : TA.

reduced. In case of SD, the peak corresponding to O-H and N-H stretching vibrations, which were broader at 3,344 cm^{-1} (Fig. 6(f)), indicated the complexation of drug by hydrogen bonding with the carrier.

8. X-ray Diffraction Analysis

The XRD patterns of the drug (CV), different carriers (HPβCD, and TA) and their SD are shown in Fig. 7. CV exhibits sharp peaks owing its crystallinity with diffraction peaks at 2 θ of 12.8°, 15.62°, 17.46°, 18.56°, 20.1°, 24.3° and 26.2° (Fig. 7(a)), which is a match with the reported graph [26]. Carriers TA exhibit crystalline characteristic peaks (Fig. 7(b)) in their XRD chart, respectively [27], HPβCD, exhibits amorphous characteristic peak (Fig. 7(c)) [25]. In case of CV: HP-βCD: TA solid dispersion system all characteristic peaks corresponding to CV disappeared (Fig. 7(d)), indicat-

ing that CV was complexed with carrier to some extent.

9. Differential Scanning Calorimetric Analysis

The DSC curves in Fig. 8 reveal the solid-state interaction of CV with the carrier's HPbCD and TA. The thermogram of CV and TA exhibits sharp endothermic peak at 118 °C and 172 °C, respectively (Fig. 8(a), (b)), owing to its melting point, which complies with that of reported data [28]. The physicochemical properties such as melting, boiling or sublimation points generally shift to a different temperature or disappear within the temperature range when pure molecules interact with other substances.

In Fig. 8(c) HPbCD shows a very broad endothermic peak at 92 °C, which could be attributed to the release of water molecules from the hydrophilic cavity [25].

DSC thermograms of solid dispersion systems, (CV : HPβCD : TA) (Fig. 8(d)) reveal the disappearance of endothermic peak of CV. It might be due to its homogeneous dispersion within the carrier and amorphization, and it suggests the formation of an inclusion complex. Many investigators reported earlier on the disappearance of melting peak of crystalline drug in solid dispersion as evidenced in its thermogram.

CONCLUSION

We investigated the effects of process variables (i.e., an amount of HPβCD (A), TA (B), and kneading time (C)) on solubility and dissolution rate of carvedilol in pH 7.4 using simplex lattice design. Results of multiple regression analysis indicated that an intermediate level of A, high level of B and low level of C make an optimized solid dispersion product (CV-200, HPβCD-689.6, TA-227.6, kneading time - 45), which shows enhanced solubility and *in vitro* dissolution rate. Solubility enhancement factor of optimized formulation with respect to that of pure drug was found as 63 times higher. Optimized formulation was more permeable than that of pure drug through goat intestinal membrane.

ACKNOWLEDGEMENTS

The authors express gratitude to M/s. Sun Pharmaceutical Ltd., India and M/s. Roquette Pharmaceutical Ltd., Mumbai, India, for their generous gifts of carvedilol and cyclodextrins respectively. The authors are thankful to the Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India for providing the infra structural facilities.

NOMENCLATURE

CV : carvedilol
βCD : β-cyclodextrin
HPβCD : hydroxypropyl-β-cyclodextrin
PVP K-30 : polyvinyl pyrrolidone K-30
PLX-407 : poloxamer-407
TA : tartaric acid
CD : cyclodextrin
min : minutes
FTIR : fourier transform infrared
DSC : differential scanning calorimetric
XRD : powder X-ray diffraction
KBr : potassium bromide
cu : copper

REFERENCES

1. R. C. Nagarwal, A. Srinatha and J. K. Pandit, *AAPS PharmSciTech*., **10**, 977 (2009).
2. D. T. Friesen, M. Crew, W. J. Curatolo, J. A. S. Nightingale, R. Shanker and D. T. Smithey, *Mol. Pharm*., **5**, 1003 (2008).
3. V. J. Stella and K. W. N. Addae, *Adv. Drug Deliv. Rev.*, **59**, 677 (2007).
4. A. T. M. Serajuddin, *Adv. Drug Deliv. Rev.*, **59**, 603 (2007).
5. H. G. Brittain, *J. Pharm. Sci*., **91**, 1573 (2002).
6. M. Li, A. Davies, N. Malek, N. Qiao, W. Schlindwein and G. Trappitt, *Int. J. Pharm*., **419**, 1 (2011).
7. T. Loftsson, C. Amiel, P. Jansook, K. L. Larsen, M. Messner, M. D. Moya-Ortega, T. T. Nielsen, H. H. Sigurdsson and V. Wintgens, *J. Inclus. Phenom. Macro. Chem*., **69**, 377 (2011).
8. M. A. Rahman, R. Harwansh, A. Hussain, S. Hussain and M. A. Mirza, *Curr. Drug Deliv*., **8**, 330 (2011).
9. C. M. Keck, S. Gohla and R. H. Muller, *Eur. J. Pharm. Biopharm*., **78**, 1 (2011).
10. J. K. Lee, K. B. Kim and M. H. Lee, *Intermetallics*, **18**, 2019 (2010).
11. A. T. M. Serajuddin, *J. Pharm. Sci*., **10**, 1058 (1999).
12. T. Loftsson, M. Masson, N. Schipper and H. H. Sigurdsson, *Pharmazie*, **59**, 25 (2004).
13. M. P. Buera, P. A. P. Cevallos and B. E. Elizalde, *J. Food Eng*., **99**, 70 (2010).
14. D. Duchene and D. Wouessidjewe, *Drug Dev. Ind. Pharm*., **16**, 2487 (1990).
15. W. Misiuk and M. Zalewska, *Carbohydr. Polym*., **77**, 482 (2009).
16. G. A. Lewis, D. Mathieu and R. P. T. Luu, *Pharmaceutical experimental design*, CRC Press, New York.
17. James Goodnight., JMP 10 *Design of Experiments Guide*, SAS Publishing, Cary, 177 (2012).
18. V. Pokharkar, S. Dhar, A. Khanna, L. Mandpe and V. Venkatpurwar, *Acta Pharm*., **59**, 121 (2009).
19. W. H. Karasov and J. M. Diamond, *J. Comp. Physiol. [B]*, **152**, 105 (1983).
20. R. Bouer, L. Barthe, G. Houin, C. Philibert, C. Tournaire and J. Woodley, *Fundam Clin Pharmacol*., **13**, 494 (1999).
21. P. Mura, G. Bramanti, M. T. Faucci and A. Manderioli, *J. Incl. Phenom. Macroc. Chem*., **39**, 131 (2001).
22. J. J. T. Labanderia, M. T. E. Diaz, M. Kata and J. L. V. Jato, *Eur. J. Pharm. Sci*., **1**, 291 (1994).
23. M. J. Ginski, J. E. Polli and R. Taneja, *Int. J. Pharm*., **177**, 117 (1999).
24. A. Paradkar, A. A. Ambike, B. K. Jadhav and K. R. Mahadik, *Int. J. Pharm*., **271**, 281 (2004).
25. J. Wang, Y. Cao, B. Sun and C. Wang, *Food Chem*., **124**, 1069 (2011).
26. R. N. Shamma and M. Basha, *Powder Technol*., **237**, 406 (2013).
27. E. Pincu and V. Meltzer, *Cent. Eur. J. Chem*., **10**, 1584 (2012).
28. A. Paradkar, A. A. Ambike, K. R. Mahadik, L. P. Mandpe, M. N. Padamwar and V. B. Pokharkar, *Powder Technol*., **167**, 20 (2006).