RESEARCH ARTICLE

# Formulation and evaluation of mouth dissolving tablets containing carvedilol solid dispersion

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## ABSTRACT

The objective of the present investigation was to prepare mouth dissolving tablets (MDT's) of carvedilol, for achieving quick onset of action in congestive heart failure and hypertension. Solid dispersion of carvedilol with polyethylene glycol 6000 was prepared to ensure its solubility in buccal cavity and hence its absorption through pregastric region. Results of *in vitro* release study of optimized formulation revealed that more than 85% of drug was dissolved within 15 min in phosphate buffer pH 6.8 used as a dissolution medium. Hence, absorption of carvedilol through pregastric region could be expected. This would avoid its first-pass metabolism which is the major cause of its low bioavailability. Despite expertise in preparation of solid dispersion, they are not extensively used commercially because of instability of proper physical form of solid dispersion during processing or storage. Among various types of solid dispersions, crystalline solid solutions are physically stable form due to entrapment of amorphous drug in crystalline carrier matrix. In the present study, microwave-generated solid dispersion was prepared. The results of differential scanning calorimetry, Fourier-transform infrared, and dissolution studies revealed stability of drug in solid dispersion form. MDTs of solid dispersion of carvedilol were prepared and optimized by $3^2$ factorial design.

**Keywords:** Biopharmaceutic classification system Class II, factorial design, molecular dispersion, polyethylene glycol 6000, solubility enhancement

## Introduction

Carvedilol is Biopharmaceutic Classification System Class II drug that poses problems of bioavailability and bioequivalence owing to its low water solubility and extensive first-pass metabolism. Carvedilol is a non-selective β-adrenergic blocking agent used in the treatment of hypertension and congestive heart failure. Quick onset of action of carvedilol is a clinical demand in such cases. Mucoadhesive nanocapsules were developed for carvedilol to improve its permeation through sublingual mucosa to bypass its first-pass metabolism.[1-4]

Carvedilol is reported to be well absorbed through oral and pregastric region. Low molecular weight of carvedilol (406.47 Da) and its log P (3.8) further make it suitable candidate for various buccal and orodispersible dosage forms.[5,6] For a formulator, development of mouth dissolving tablet (MDT) is a cost-effective choice than the novel products with therapeutic advantages.[7,8] Improvement in dissolution characteristics of poorly soluble carvedilol was essential before its formulation development.[9] Amorphous solid dispersion is one of the promising approaches to increase the rate of dissolution of poorly soluble drugs like carvedilol. The major drawback of amorphous solid dispersion is that they revert back to crystalline form during processing or on storage.[10,11] This problem of recrystallization could be overcome through rational selection of manufacturing process and excipients.[12]

In the present study, solid dispersion of carvedilol was prepared by microwave processing using polyethylene glycol 6000 (PEG 6000) as a hydrophilic carrier matrix. The stability of physical form of solid dispersion was confirmed by Fourier-transform infrared (FTIR),

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differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) conducting stability studies. MDTs of solid dispersion of carvedilol were prepared and optimized by adopting factorial design.

## Materials

Carvedilol was obtained as gift sample from Indoco remedies, Mumbai, and crospovidone was obtained as gift sample from BASF, Mumbai. PEG 6000, Avicel PH102, mannitol, xylitol, and other chemicals used were of analytical grade or pharmaceutical grade.

## Methods

### Preparation of solid dispersion

Solid dispersion of carvedilol was prepared by kneading method.[13] Appropriately weighed quantities of drug with hydrophilic polymer PEG 6000 in the ratio of 1:3, 1:6, and 1:9 (standard deviation [SD] 1, SD2, and SD3, respectively) were kneaded with 10–15 ml of water for 25–30 min, to produce a homogeneous dispersion. It was dried in microwave (MW) oven at power level 2 (210 W) for 15–20 min until dryness. The dispersions after drying were pulverized and sifted through a #44 sieve to obtain a uniform particle size and stored in desiccators at room temperature until further use.

The stability study was performed for SD1, SD2, and SD3 at 40°C ± 2°C and 75% RH ± 5% RH up to 3 months. The samples were characterized using FT-IR, X-ray powder diffraction (XRPD), and DSC techniques to reveal the change if any in the amorphous form of a drug during 3 months storage.

### FT-IR spectroscopy

FT-IR spectra of pure drug and solid dispersions (SD1, SD2, and SD3) before and after stability studies were recorded on JASCO FT-IR spectrophotometer (FT-IR 8400S, Shimadzu) using KBr powder technique. The instrument operated under dry air purge and the spectra were collected at scanning speed 2 mm/s with a resolution of 4 $cm^{-1}$ over the region of 4000–400 $cm^{-1}$. The spectra were evaluated for the presence of principle peaks of drug. The FT-IR spectra of carvedilol and its solid dispersions before and after 3 months stability study are shown in Figure 1.

### DSC

The DSC study was performed for pure carvedilol and its solid dispersions before and after stability testing period to confirm the physical form of the solid dispersion. The DSC patterns were recorded on a Mettler Toledo (Star$^e$ SW 920). Each sample (2–4 mg) was heated in crimped aluminum pans at a scanning rate of 10°C/min in an atmosphere of nitrogen using the range of 40–160°C. The DSC thermograms are shown in Figure 2.

### XRPD

X-ray diffraction pattern for solid dispersions (SD1, SD2, and SD3) was compared with that of pure carvedilol. The XRD patterns were recorded automatically using rate meter with a time constant of 2 × 102 pulse/s and scanning speed of 20 (2θ min). X-ray diffractograms of solid dispersion before and after 3 months are shown in Figures 3 and 4, respectively.

### Development of MDT's and preparation of preliminary batches of MDT's for selection of superdisintegrant

A comparative study was carried out for selection of superdisintegrants from crospovidone (Kollidon$^R$ CL-F), sodium starch glycolate, and croscarmellose sodium. MDTs of solid dispersions of carvedilol of composition SD1 were prepared using as per the composition reported in Table 1. All the tablets were compressed at constant compression pressure. MDTs were evaluated for disintegration time (DT). The results are shown in Table 1.

### Optimization of MDT by full factorial design

A full $3^2$ factorial design was chosen for the optimization of formulation.[14] Amount of PEG 6000 (X1) in solid dispersion and amount of superdisintegrant (X2), i.e., crospovidone were selected as independent factors [Table 2], whereas DT and percent drug release at 15 min were selected as responses. Nine formulations were prepared as per the composition reported in Table 3 and evaluated for DT and the drug release study [Table 4]. The MDTs of carvedilol were prepared by direct compression method using 6 mm flat punch on Karnawati Mini press II MT Rimek 12 station compression machine. The results were analyzed by applying ANOVA using design expert version 8.0.5.

To investigate the factors systematically, a factorial design was employed. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \quad (1)$$

Where

- Y: Percent drug released in 15 min ($Y_1$) and DT in s ($Y_2$)
- $\beta_0$: Arithmetic mean response of the nine runs
- $\beta_1$: Estimated coefficient for the factor $X_1$
- $\beta_2$: Estimated coefficient for the factor $X_2$
- $\beta_{12}$: Interaction shows how the response changes when 2 factors simultaneously changed
- $\beta_{11}$ and $\beta_{22}$: Are included to investigate nonlinearity.

A stability study of optimized batch (M3) of MDTs was carried out at 40°C ± 2°C and 75% ± 5% RH for 90 days.[15] Results of stability data for optimized (M3) formulation are shown in Table 5.

## Results and Discussion

### Preparation and stability of solid dispersions

FTIR studies indicated the formation of hydrogen bond between the –NH group of carvedilol and –OH group PEG 6000. The FTIR spectra of

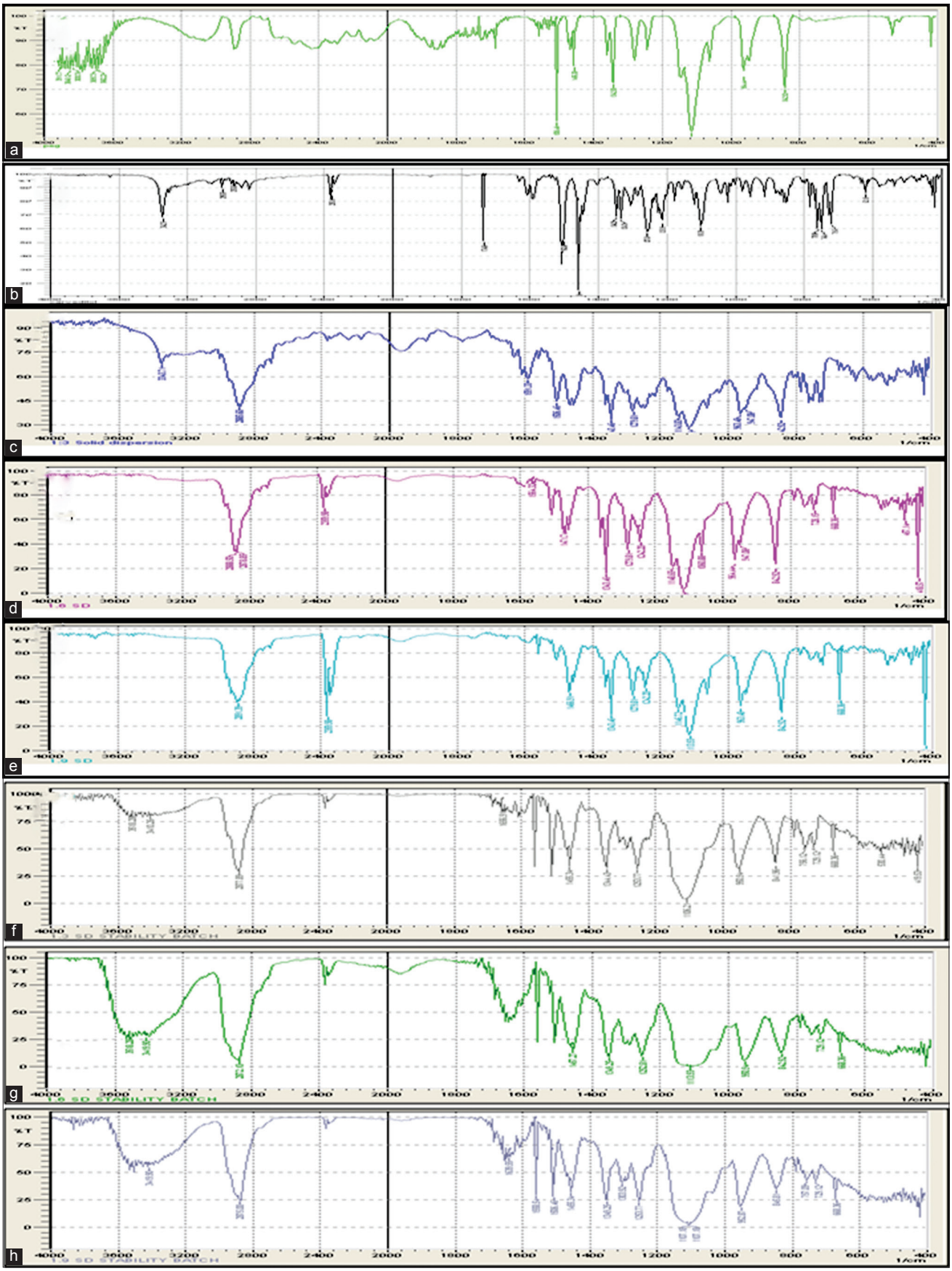


**Figure 1:** Fourier-transform infrared spectra of (a) carvedilol, (b) polyethylene glycol 6000, (c) standard deviation (SD) 1, and (d) SD2 and (e) SD3 of freshly prepared samples (f) SD1, (g) SD2, and (h) SD3 after 3 months stability studies

**Table 1:** Compositions of preliminary batches of MDTs for the selection of superdisintegrants

| Ingredient (mg/tablet[α]) batch code | SD of carvedilol (equivalent to 12.5 mg drug) | Avicel PH 102 | SSG[β] | CCS[c] | CP[d] | Xylitol | Mannitol | Mg. stearate | DT (s) |
|---|---|---|---|---|---|---|---|---|---|
| P1 | 50 | 118 | 10 | - | - | 10 | 10 | 2 | 65±4.0 |
| P2 | 50 | 118 | - | 10 | - | 10 | 10 | 2 | 49±2.0 |
| P3 | 50 | 118 | - | - | 10 | 10 | 10 | 2 | 30±2.0 |

[a]Total weight of tablet is 200 mg, [b]sodium starch glycolate, [c]croscarmellose sodium, [d]crospovidone. DT: Disintegration time, SD: Standard deviation

**Table 2:** Levels of X1 and X2 and their coded values

| Levels | Coded factors | Factors | |
|---|---|---|---|
| | | $X_1$ amount of drug: Amount of PEG in SD | $X_2$ amount of crospovidone in mg |
| Low | - | 1:3 | 10 |
| Medium | 0 | 1:6 | 15 |
| High | + | 1:9 | 20 |

PEG: Polyethylene glycol, SD: Standard deviation

**Table 3:** Compositions of factorial batches of MDT's

| Ingredient (mg/tablet) batch code (coded levels of $X_1$ and $X_2$) | SD of carvedilol (equivalent to 12.5 mg drug) $X_1$ | Avicel PH 102 | Crospovidone $X_2$ | Xylitol | Mannitol | Mg. stearate | Weight of the tablet in mg |
|---|---|---|---|---|---|---|---|
| M1 (−1,−1) | 50 | 118 | 10 | 10 | 10 | 2 | 200 |
| M2 (−1,0) | 50 | 113 | 15 | 10 | 10 | 2 | 200 |
| M3 (−1,+1) | 50 | 108 | 20 | 10 | 10 | 2 | 200 |
| M4 (0,−1) | 87.5 | 80.5 | 10 | 10 | 10 | 2 | 200 |
| M5 (0,0) | 87.5 | 75.5 | 15 | 10 | 10 | 2 | 200 |
| M6 (0,+1) | 87.5 | 70.5 | 20 | 10 | 10 | 2 | 200 |
| M7 (+1,−1) | 125 | 43 | 10 | 10 | 10 | 2 | 200 |
| M8 (+1,0) | 125 | 38 | 15 | 10 | 10 | 2 | 200 |
| M9 (+1,+1) | 125 | 33 | 20 | 10 | 10 | 2 | 200 |

SD: Standard deviation

**Table 4:** Results of evaluation of factorial batches

| Response | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 |
|---|---|---|---|---|---|---|---|---|---|
| Drug released at 15 min | 62.46±0.68 | 74.43±0.69 | 86.63±0.73 | 46.12±0.69 | 51.14±0.71 | 59.32±0.69 | 49.09±0.69 | 53.39±0.68 | 56.58±0.69 |
| DT (s) | 42±3 | 38±2 | 32±1 | 97±3 | 89±2 | 86±3 | 120±4 | 113±2 | 109±2 |

*All values indicate mean±SD ($n$=3). DT: Disintegration time

**Table 5:** Results of stability studies of optimized formulation

| Test period | DT (s) | % Drug dissolved in 15 min |
|---|---|---|
| Initial 1 month | 28±3 | 90.52±0.61 |
| 2 months | 29±5 | 90.49±0.52 |
| 3 months | 29±7 | 89.24±0.57 |

DT: Disintegration time

crystalline carvedilol showed characteristic peak at 3346.61 $cm^{-1}$ (-NH starching) The disappearance of this peak in kneaded solid dispersions (SD2 and SD3 in particular) was strong evidence of hydrogen bonding between the drug and polymer through the secondary amine group of carvedilol [Figure 1].[7,16] The DSC thermograms of SD1, SD2, and SD3 clearly indicated amorphization and/or miscibility of the drug in carrier matrix. The DSC curve of pure carvedilol exhibited a single endothermic peak at 118°C corresponding to the melting of the drug. The absence of a carvedilol melting peak in SD suggested that either carvedilol was completely soluble in the liquid phase of the polymer

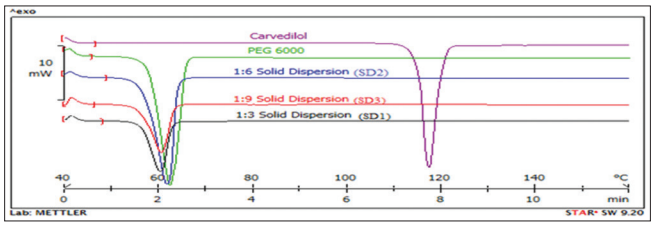


**Figure 2:** Overlay of differential scanning calorimetry thermograms of carvedilol, polyethylene glycol 6000, standard deviation (SD) 1, SD2, and SD3

or the absence of a crystalline form of carvedilol [Figure 2]. In either case, the carvedilol was molecularly dispersed in PEG 6000. Thus, improved drug dissolution observed in further study might be due to amorphization or due to wetting.

XRPD analysis was used to judge any changes in crystallinity of the drug during processing or storage. The diffraction spectrum of

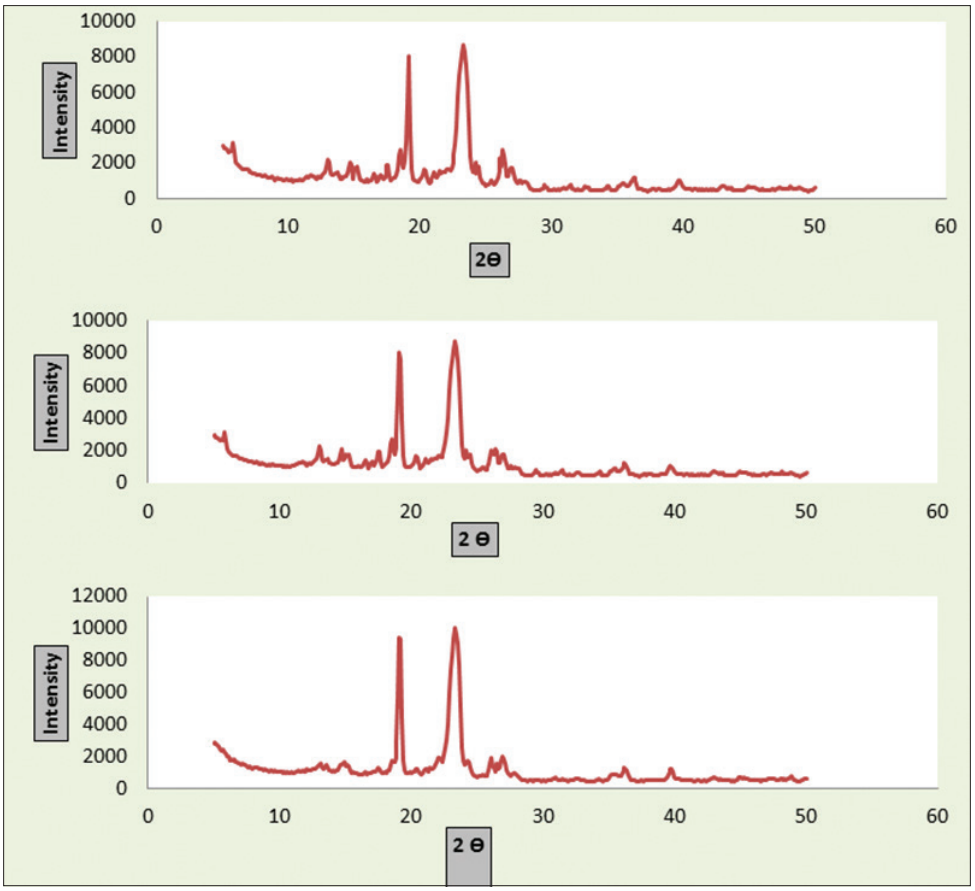


**Figure 3:** X-ray diffractogram of standard deviation (SD) 1, SD2, and SD3 after 3 months stability testing

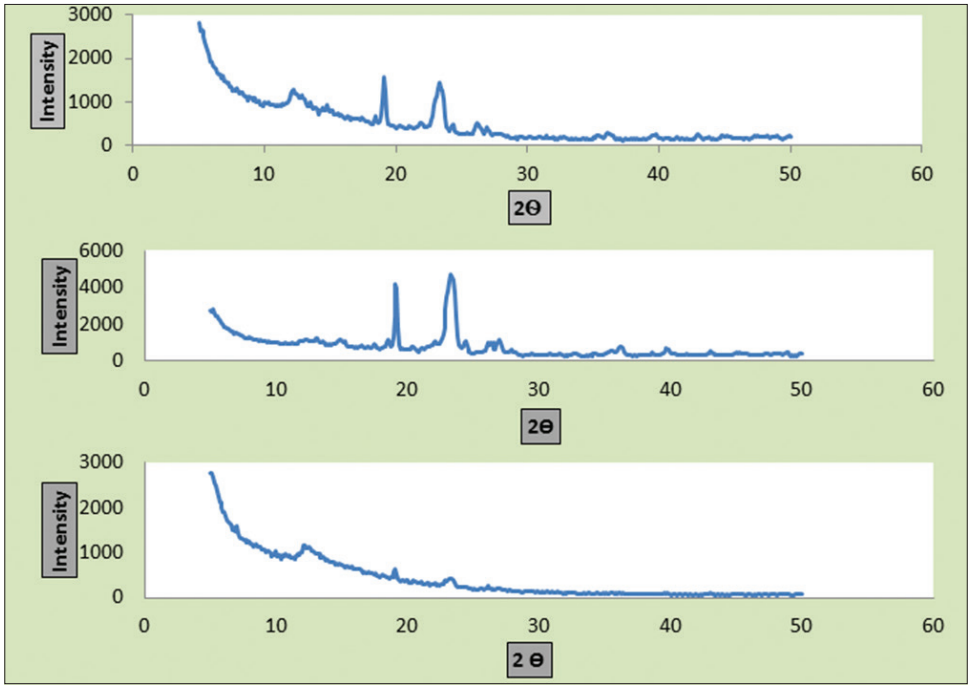


**Figure 4:** Contour plot showing effect of variables on disintegration time

pure carvedilol showed characteristics peaks at 2θ angles of 14.8°, 24.3°, 24.4°, and 26.2° indicating that the drug was in crystalline nature. The X-ray diffractograms of solid dispersions of carvedilol with PEG 6000 showed disappearance of peak. This indicated that

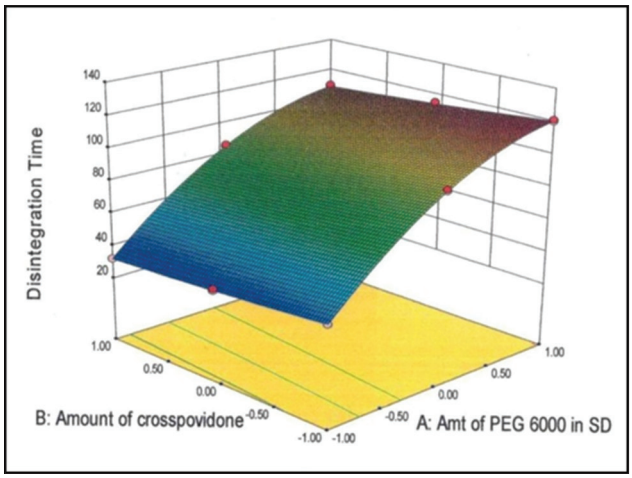


**Figure 5:** X-ray diffractogram of freshly prepared standard deviation (SD) 1, SD2, and SD3

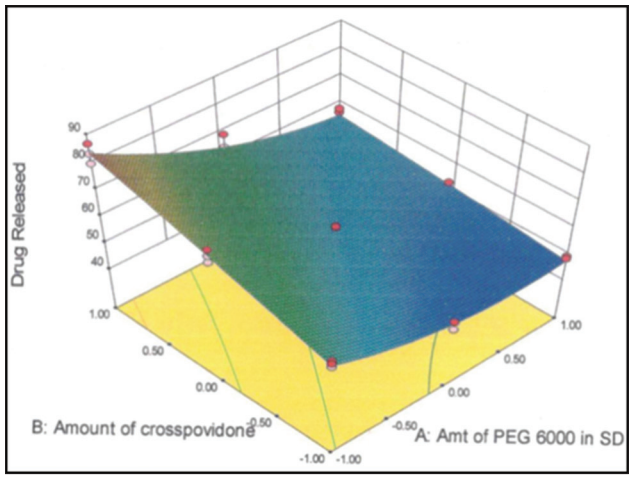


**Figure 6:** Contour plot showing effect of variables on drug release at $t_{15}$

the drug is in amorphous nature in solid dispersion [Figure 5]. It is to be worth noted that the peak intensities of pure PEG 6000 were retained in solid dispersions. The proportion of PEG 6000 was higher than carvedilol that prevented its recrystallization as supported by the XRPD diffractograms [Figures 3 and 5]. It was observed that the characteristic PXRD peaks of carvedilol were absent in the diffractograms of the solid dispersions even after 3 months. Although there is an improvement in the dissolution of poorly soluble drugs in their solid dispersion form, their commercialization is limited because of instability of amorphous form of the drug in it.[17] In the present study, the results of FTIR, DSC, and PXRD analysis of solid dispersions exhibited that carvedilol was molecularly dispersed in PEG 6000 and remained so even after 3 months.

## Development of MDTs and selection of superdisintegrant

To develop a MDT, excipients with good compactability were selected. Avicel PH 102 was selected as directly compressible excipient. It is also reported to aid in the disintegration of tablet. Mannitol was added to generate a cooling sensation and for good mouthfeel. Xylitol was added as sweetener. Magnesium stearate was added for its lubrication properties and to enhance tablet appearance. From the data given in Table 1, it was clear that formulation containing crospovidone as a superdisintegrant (P3) exhibited rapid disintegration. The basic purpose of designing MDT is to hasten disintegration of tablet in buccal cavity. In the present study, the DT of formulation P3 was found to be least. This might be because of wicking mechanism of crospovidone that generated hydrostatic pressures necessary to provide rapid disintegration of tablet. Thus, it was found that composition of formulation P3 was best suited than P1 and P2 and selected for further studies.

## Optimization of formulation of MDTs

Compressibility index of powder blend of factorial batches prepared as per the composition mentioned in Table 3 was found to be in the range between 12.23% and 19.57%. The percentage drug released at 15 min and DT for the 9 batches (M1-M9) showed a wide variation from 45.19% to 91.05% and from 32 to 120 s, respectively [Table 4]. The data clearly indicated that the percentage drug release and DT were strongly depended on the levels of selected independent variables.

The polynomial equation showing the effect of independent variables on DT was as follows:

$$\text{D.T.}\ (Y_1) = 90.07 + 38.89X_1 - 5.28X_2 - 0.25X_1X_2 - 14X_1^2 + 0.72X_2^2 \quad (2)$$

As amount of PEG 6000 in solid dispersion increased, DT as indicated by the positive coefficient of X1 increased. As the amount of crospovidone increased, the DT decreased as indicated by negative coefficient of X2. The interaction between the factors X1 and X2 was found to negate the effect of each other. Contour plot is shown in Figure 4.

The polynomial equation showing the effect of independent variables on percent drug release at 15 min was as follows:

$$\%\ \text{Release}\ (Y_2) = 56.82 - 10.26X_1 + 7.72X_2 - 3.65X_1X_2 + 5.33X_1^2 - 0.33X_2^2 \quad (3)$$

As amount of PEG 6000 in solid dispersion increased, percent drug release at 15 min decreased as indicated by the negative coefficient of X1. As the amount of crospovidone increased percent drug release at 15 min increased as indicated by positive coefficient of X2. The interaction between the factors X1 and X2 was found to negate the effect of each other. Contour plot is shown in Figure 6.

## Conclusion

In the present study, suitability of PEG 6000 for the preparation of stable amorphous solid dispersion of carvedilol was investigated. The *in vitro* dissolution studies of optimized formulation showed more than 85% drug dissolution in 15 min. Incorporation of the solid

dispersion of carvedilol in MDT exhibited good stability and drug dissolution characteristics. The effect of the formulation variables on the critical attributes of carvedilol MDTs was verified using $3^2$ full factorial designs. Thus, optimized MDT of carvedilol is expected to exhibit improved bioavailability, due to fast dissolution and avoidance of first-pass metabolism by allowing the maximum absorption of drug through oral cavity.

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