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Research Article

Fabrication of a Disintegration-Accelerated Matrix Tablet of Carvedilol

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ABSTRACT
Poor aqueous solubility and low oral bioavailability of Carvedilol, a novel third generation anti-hypertensive drug necessitates exploration of formulation strategies to achieve quick onset of action and prolonged drug release from a dosage form. In the present study, disintegration-accelerated solid dispersion-based matrix tablet of Carvedilol has been designed with L-HPC LH-11, mannitol and Avicel PH-102. Addition of higher percentage of L-HPC (3.5% w/w) in the tablet formulation, TSD-L' resulted in maximum rate of simulated saliva uptake of 0.568 ± 0.02 mg/sec and minimum disintegration time of 7mins 10.29 ± 14.45 secs in phosphate buffer (pH-6.8). Fibrous nature of L-HPC leads to enhanced saliva uptake by wicking action into the porous network of tablet resulting in high swell volume without gelling. Creation of hydrophilic network promoted the disintegrant activity. However, no improvement in dissolution efficiency and mean dissolution time for TSD-L' could be observed in comparison to the batch, TSD-L. Fitting of drug release data to the kinetic models showed that the formulation batches obeyed Higuchi kinetics i.e. diffusion of drug occurred from hydrophilic swellable matrix.

Keywords: Hydrophilic swellable matrix, Carvedilol, L-HPC.

Introduction

Carvedilol, a novel third generation β-blocker has given a new "look" in the management of cardiovascular diseases associated with other serious co-morbidities, because of its multifarious activities and fewer side effects compared to traditional β-blockers. It is very suitable for management of hypertension in asthmatic and diabetic patients [1]. It has free-radical scavenging properties and maintains normal ratio of high-density lipoproteins to low density lipoproteins (HDL/LDL). It also provides protection of the heart and blood vessels against secondary damage due to hypertension itself, as well as other related causes, such as ischemia, pressure overload, and atherosclerosis [2]. However, it fails to produce desired therapeutic effect upon oral administration because of its poor aqueous solubility and dissolution-rate limited absorption from gastro-intestinal tract. Solubility profile of Carvedilol in different media and its dissolution parameters in water are presented in **Table 1.** Moreover, it possesses poor flowability, compressibility and compactibility [3].

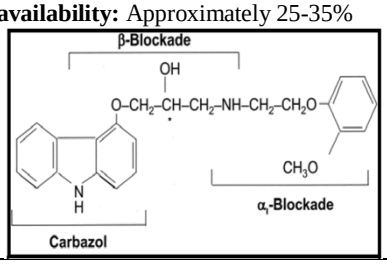
Clinical benefits of Carvedilol over other antihypertensive drugs necessitate fabrication of formulation strategies for ensuring better solubility, dissolution profile and hence bioavailability from oral dosage form. Solid dispersion technique has proved highly successful for enhancing aqueous solubility of drugs [8]. In the technique, drug is dispersed in solid state in hydrophilic carriers e.g. Polyethylene glycols of varying molecular weights, and improved solubility is attributed to reduction in particle size, increase in wettability, decrease in contact angle and interfacial tension, reduction in crystallinity etc [9]. To achieve dose uniformity, patient-compliance, ease of administration and improved drug release, solid dispersions of drugs viz. Carvedilol, furosemide have been compressed into tablets by addition of various excipients like mannitol, dicalcium phosphate, microcrystalline cellulose etc. and low concentrations of Ac-di-sol, Crospovidone etc to promote faster disintegration of the tablets, prior to dissolution [10, 11, 12].

In tablet technology, low-substituted hydroxyl propyl celluloses (L-HPCs) like L-HPC 11, L-HPC 21, in small proportions (2.5–5%) have been used as disintegrant in traditional formulae in combination with other excipients as microcrystalline cellulose (MCC) and mannitol [13, 14, 15]. Fibrous nature of L-HPC leads to enhanced liquid uptake by drawing liquid into the porous network of tablet resulting in substantial volume expansion or swelling without gelling. Creation of hydrophilic network is thus facilitated which promotes the disintegrant activity [16]. In such circumstances, the pore structure plays a significant role and any hydrophobicity of tablet ingredients will hinder the process of tablet rupture and disintegration. For this type of system, it is important to maintain the porous structure having a low interfacial tension toward aqueous fluids, which can be achieved by improving the wettability of the drug by formulating as solid dispersion, using small percentage of surfactant like Tween-80. Disintegration and subsequent fast dissolution of a tablet manufactured by direct compression depends on the single or combined action of optimum amount of disintegrant, water-soluble and water-insoluble excipients. L-HPC is reported to exert a very positive effect on famotidine tablets containing mannitol where it significantly decreased their wetting time and oral disintegration time. Synergistic effect of water-soluble mannitol and L-HPC increased the degree of cracking and bursting of tablets ensuring complete drug release within 2 mins. This occurs since wetting is closely related to the inner structure of the tablets and the hydrophilicity of excipients. [13]. Moreover, mannitol induces tablet swelling [17]. Disintegration action of microcrystalline cellulose (Avicel PH-102) can be attributed to penetration of water by capillary action into the hydrophilic tablet matrix.

Due to the presence of high percentage of hydrophilic polymer in the solid dispersion, along with surfactant, the tablet will be wetted quickly, which will further absorb water by wicking because of microcrystalline cellulose and L-HPC, swell and disintegrate due to additional effects of mannitol and finally release solubilized drug from the matrix in a prolonged fashion owing to the various insoluble, hydrophilic components in the formulation [18,19]. Therefore, maximum therapeutic effectiveness for orally administered poorly water-soluble drug can be achieved if dissolution efficiency of the drug can be enhanced and release can be prolonged simultaneously by designing an insoluble hydrophilic disintegration-accelerated swellable matrix system.

The aim of the present investigation is to prepare solid dispersion of Carvedilol in a hydrophilic carrier system by melting-solvent evaporation technique and fabricate tablets thereof, using right combination of various excipients to achieve matrix type model formulations possessing good disintegration property, high solubility and rapid dissolution.

Table 1 Structure and Physicochemical Properties of Carvedilol

CARVEDILOL
Chemical Structutre: (2RS)-1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino] propan-2-ol **Molecular Weight:** 406.5 **Molecular Formula:** $C_{24}H_{26}N_2O_4$ **Melting Point:** 114 - 115° C **Oral Bioavailability:** Approximately 25-35% 

Reported Solubility Values Of Carvedilol In Three Different Media[4]-[6]

In Water (µg/ml) at 25° C	In Phosphate buffer, pH 6.8(µg/ml) at 25°C	In Gastric buffer, pH 1.3(µg/ml) at 25° C
0.583	92.13	38.4

Reported Dissolution Parameters Of Carvedilol In Distilled Water[7]

Q_{15mins} (%)	$T_{50\%}$ (mins)	DE_{120} (%)	MDT (mins)
1.93	>120MINS	3.95	56.23

MATERIALS AND METHODS

Carvedilol was gift sample from Zydus Pharmaceuticals, India, L-hydroxypropyl cellulose LH-11 (L-HPC) and hydroxylpropylmethyl cellulose (HPMC) were provided as gift samples from Colorcon, India. All other chemicals of analytical grade were purchased from Merck India Ltd. and fresh distilled water was used throughout the study.

Preparation and Characterisation of Carvedilol solid dispersions (CAR-SD)

The quaternary solid dispersion (Drug: PEG 6000: HPMC: T-80 = 1: 8.675: 0.075: 0.25) was prepared by melting-solvent evaporation technique [20]. The ratios are expressed as weight/weight.

For drug content determination, solid dispersion equivalent to 1mg of Carvedilol was accurately weighed, dissolved in 5ml of dichloromethane: methanol (8:2) as solvent [21] and shaken for 1h. For equilibrium solubility studies, solid dispersion equivalent to 1 mg of pure drug was added to 75 ml of water in a conical flask and shaken overnight at 37±0.5°C. For both the investigations, the solution was filtered through 0.45µ filter, filtrate suitably diluted and analyzed for drug content spectrophotometrically at 285nm against solvent as blank and at 240nm for solubility determination.

Instrumental methods of analysis of CAR-SD

Fourier-transform infrared (FT-IR) spectra were obtained by using an FT-IR spectrometer (BRUKER-Alpha, USA). Previously ground samples of pure drug, pure carriers and solid dispersion (CAR-SD) were mixed thoroughly with potassium bromide (KBr), an infrared transparent matrix, to prepare the KBr discs by compressing the powders in a hydraulic press. The scans were obtained in the range of 4,000 to 500 cm^{-1}.The DSC thermograms [Perkin Elmer (Singapore); Model–Pyris Diamond TG/DTA] were recorded with 2–5 mg samples of pure Carvedilol, Polyethylene glycol (PEG) 6000 and solid dispersion (CAR-SD) after heating in hermetically sealed aluminum pans under a nitrogen atmosphere at a flow rate of 20 mL min^{-1} as purging gas with a scanning rate of 10°C min^{-1} from 20 to 350°C. X-ray powder diffraction studies (Rigaku, Model-Ultima III, Japan) of Carvedilol, PEG 6000 and CAR-SD were performed with Ni-filtered Cu Kα radiation with 40 kV of tube voltage and 30 mA of tube current and scanned over the 2θ range of 5–70°. Overlaying of the thermograms and diffractograms was done with OriginPro 8. Samples of pure drug, PEG 6000 and the solid dispersion were mounted onto the stubs using double-sided adhesive tape, coated with a thin layer of palladium and scanning electron microscopy (Jeol; Model-JSM360, UK) was carried at an acceleration voltage of 17 kV. The selected magnification was x 950.

Preparation of Solid Dispersion Tablets

Prior to compression, the compatibility study was carried out by physically mixing CAR-SD and the tablet excipients. Powder flow behavior was characterized by angle of repose, Compressibility index and Hausner ratio. Excipients were dried and sieved through mesh no. 60. Solid dispersion tablet batches were prepared by mixing the various ingredients in the percentages **shown in Table 2** by direct compression with 10-station Minipress single punch tablet machine **(**Karnavati Engg. Pvt. Ltd., India) to produce round, flat-faced tablets.

Tablets were designed to weigh around 180 mg ± 5% and contain 12.5mg of Carvedilol. The tablet shape, size, thickness and hardness were held constant for all the batches.

Wetting or Wicking time

A twice-folded tissue paper (10.75×12 mm) was placed in a 6.5 cm diameter culture dish containing definite volume of simulated saliva (phosphate buffer, pH6.8) (2drops of water soluble dye eosin added). A tablet was carefully placed on the surface of tissue paper and the time required for dye solution to reach the upper surface of the

tablet was noted as the wicking time [22]. The experiments were repeated thrice.

Table 2 Composition of Various Batches of Carvedilol Solid Dispersion Tablets (TSD) by Direct Compression

Nomenclature	CONTROL-TSD	TSD-L	TSD-L'
Ingredients	**% w/w for each 180mg Tablet**		
CAR-SD	48.75		
Mannitol	19.75		
AVICEL PH-102	11.5		
L-HPC LH-11	--	2.5	3.5
Dicalcium Phosphate, Dihydrate	20	17.5	16.5
Talc	Quantity Sufficient		
Magnesium Stearate	Quantity Sufficient		

Rate of saliva uptake

Experimental set-up was same as that in the estimation of wetting time. In this test, weight of the tablet was taken prior to wetting and post-wetting. End-point of the study was the wetting of the tissue paper at the bottom due to penetration of simulated saliva added drop-wise on the top surface and time taken was noted down. The experiments were repeated thrice. Rate of saliva uptake, SU (mg/sec) was determined using the equation:

$$\text{Rate of saliva uptake} = \frac{(W_b - W_a)}{\text{Time}} \quad \ldots (1)$$

In vitro disintegration time

Disintegration time for the tablets was determined using USP disintegration apparatus with simulated saliva (phosphate buffer, pH 6.8, 900 ml at 37°C) as the disintegrating medium.

In vitro dissolution study

In vitro drug dissolution of all tablet batches was carried out using USP-type II dissolution apparatus (paddle type) (8-station dissolution test apparatus, Model No. DS-8000). The dissolution medium [900 ml gastric buffer (pH 1.3)] was placed into the dissolution flask maintained at 37 ± 0.5°C& and rpm of 50 [23]. One tablet from each batch was placed in the dissolution apparatus. Dissolution studies were carried out for 180mins. Aliquot of 10ml was taken at different time intervals & the dissolution medium in the vessel was replenished with the same volume of fresh medium. Aliquot was filtered and analysed spectrophotometrically at 240 nm. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2=0.9878). All tests were done in triplicate and marketed formulation was studied for comparison.

Comparison of in vitro Dissolution Data

For comparison of dissolution profiles, several model-dependent or model-independent approaches can be adopted. The data were compared using Student's *t*- test of the two samples assuming equal variances to evaluate the differences between groups. The significance level (α= 0.05) was based on the 95% probability value ($p < 0.05$).

Model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency) or mean dissolution time. The mean in vitro drug release data (n=3) from 0% to 85% release were fitted to different kinetic models (first order, Higuchi and Hixon- Crowell). The value of the coefficient of determination (R^2) was selected as the criterion to identify the best-fit model of drug release from the tablets. The Mean Dissolution Time (MDT) for each batch has been determined with the help of the following equation [24].

$$\text{Mean Dissolution Time (MDT)} = \frac{\sum_{j=1}^{n} \hat{t}_j \, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad \ldots (2)$$

where j is the sample number, n is the number of dissolution sampling points, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} [calculated as $(t_j+t_{j-1})/2$] and ΔM_j is the additional percentage of drug released in the time interval between t_{j-1} and t_j.

The Dissolution Efficiency (DE, %) was used to evaluate the dissolution performance of the batches in comparison to the marketed formulation. DE was calculated as follows [24].

$$\text{Dissolution Efficiency} = \frac{\int_0^t Y \, dt}{Y_{100}\, t} \times 100 \ldots\ldots (3)$$

where y is the percentage of drug dissolved at time t.
DE was determined for the entire time period of release study for each batch.

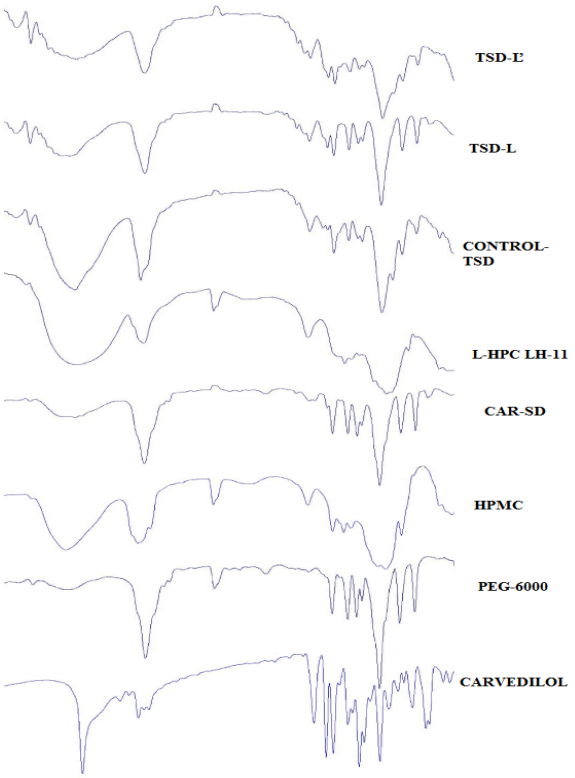


Figure 1 Overlaid FTIR Spectra of Pure Components, CAR-SD and Pre-compression powder mixture

Other release parameters used to characterise and compare dissolution profiles for tablet batches include cumulative percent released at x mins [Q_{xmins}(%)] and time taken for a fixed percentage of drug to be released [$T_{y\%}$ (mins)]. The results are displayed in **Table 3**.

Table 3 Characterization of Carvedilol and its solid dispersion (CAR-SD)

	Solubility in water at 37°C for 24 hours (µg/ml)	Data from Differential Scanning Calorimetric Study	
		Melting Point (°C)	Heat of Fusion; ΔH_f (J/g)
Carvedilol	1.318	116.81	148.77
CAR-SD	2.408	62.98	128.97

RESULTS AND DISCUSSION

Characterization of Pure Carvedilol in CAR-SD:

The drug content of the solid dispersions varied between 97.1% to 98.7% of the theoretical value. Solubility enhancement data showed that SD was effective in improving the solubility of poorly water-soluble drug, Carvedilol by almost 2-fold **Table 3**. Pure Carvedilol spectrum **Figure 1** exhibited characteristic peaks at 3343.32 cm^{-1} (O-H and N–H stretching vibration bends merging together), 3061.3 cm^{-1}, 2993.26 cm^{-1}, 2922.31cm^{-1}, 2879.81 cm^{-1} and 2842.5 cm^{-1} (C-H stretching vibration), 1594.97 cm^{-1} (N–H bending), 1254.21 cm^{-1} (O-H and N–H stretching vibrations) and 1503.2cm^{-1} (–C-C– multiple bonds), matching with the literature values [25]. The disappearance of all the characteristic peaks of pure drug as crystalline powder in the CAR-SD indicates that the drug particles might have been masked by the high proportion of polymer molecules. An absorption peak at 1,108 or 1111.24cm^{-1} indicated formation of secondary hydrogen bond which was absent in pure drug. No evidence of chemical interaction could be observed between the components. The formation of hydrogen bond between drug and polymer confers higher solubility of drug in the solid dispersion compared to pure drug. The DSC curve of pure Carvedilol exhibited a single endothermic peak corresponding to the melting of drug. Onset of melting was observed at 116.81°C, the corresponding heat of fusion (ΔH_f) was 148.77 J/g where as pure PEG 6000 showed a melting endotherm at 67.51°C and the corresponding heat of fusion (ΔH_f) was 180 J/g. DSC scans of the SD showed absolute disappearance of drug peak but prominent peak of PEG 6000 with slight shifting in melting point towards lower temperature **Figure 2A.** Complete disappearance of drug endotherm in solid dispersion suggests that the drug is either completely soluble in molten PEG or no crystallinity is left in the drug when formulated as solid dispersions. Presence of PEG peak in the formulations indicated the formation of monotectic system where melting point of carrier remains nearly unchanged in presence of drug. The diffraction spectrum of pure Carvedilol showed that the drug was crystalline as demonstrated by numerous peaks observed at 2θ of 5.74°, 12.9°, 14.76°, 17.42°, 18.34°, 20.24°, 24.32°and 26.38° (finger print region) with peak intensities (counts per sec, CPS) of 2404, 1950, 3383, 2038, 2575, 1704, 2625 and 1746 respectively. Characteristic peaks of Carvedilol were present in much reduced intensity in the solid dispersion **Figure 2B**.

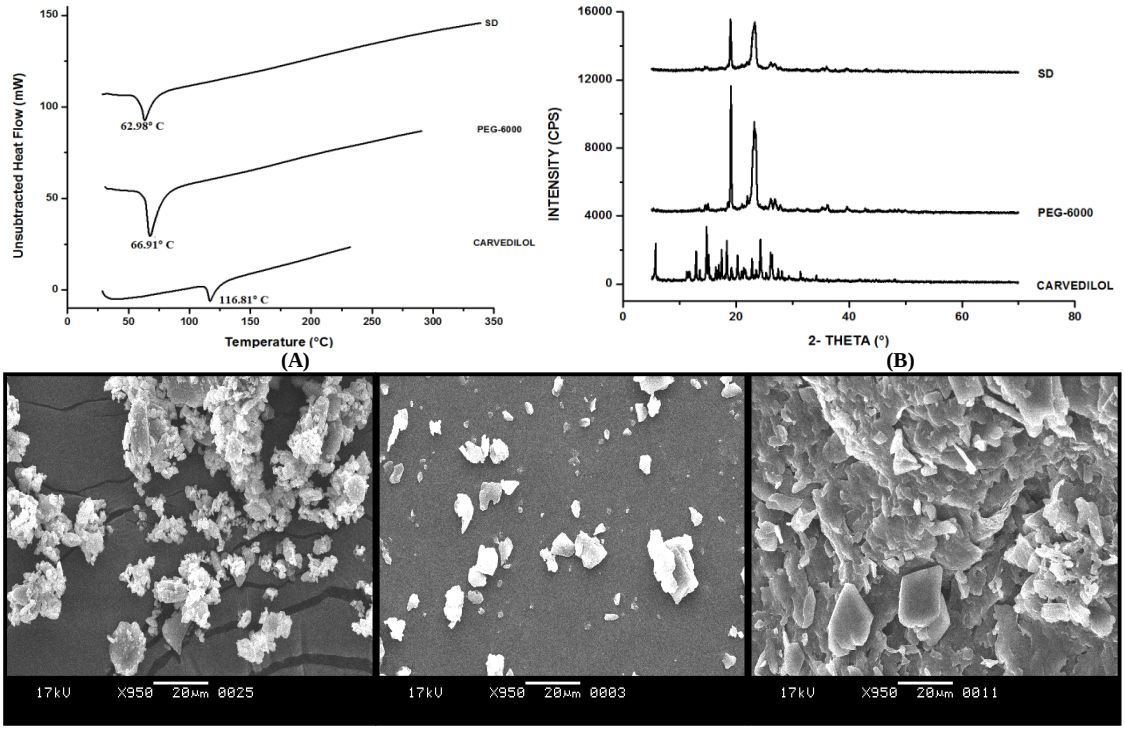


Figure 2 (A) Overlaid DSC Thermograms; (B) Overlaid diffractograms from XRPD Studies; (C) SEM Micrographs of (i) Carvedilol, (ii) PEG-6000, (iii) CAR-SD

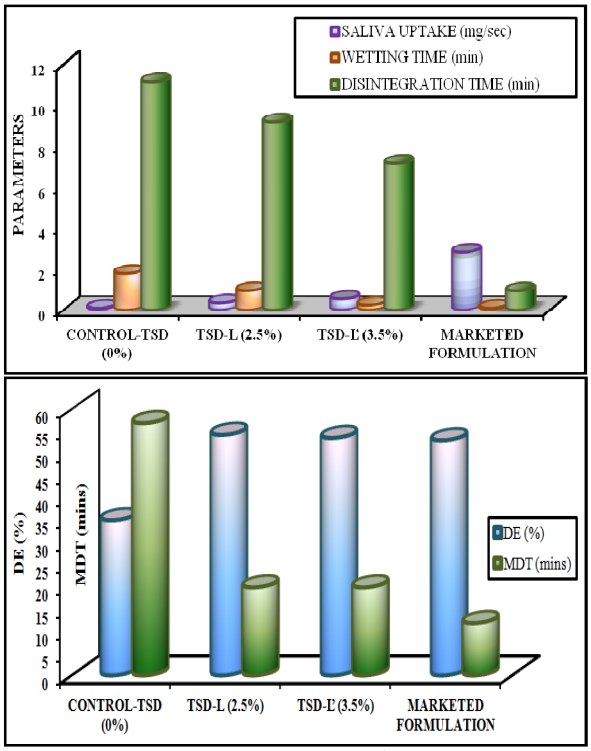


Figure 3 Comparative Bar Graphs of Disintegration and Dissolution Parameters of Carvedilol-TSDs with respect to the Marketed Formulation

Thus, it can be concluded that the drug might have lost its crystalline structure and have been transformed into amorphous or microcrystalline state in SD. Since the positions of PEG-6000 peaks have not changed in the formulation and in fact are superimposable, any possibility of chemical interaction or compound formation is totally ruled out between the components of solid dispersions. Photomicrographs of the pure drug showed them as blunt crystals. In the solid dispersion, particles appeared as irregularly shaped agglomerates with no clear demarcation between particles of drug, PEG 6000 or HPMC being visible. Therefore, the finding from DSC and XRD studies about the microcrystalline or amorphous nature of the solid dispersions is established also from SEM studies.

Pre-compression powder behavior

In the FTIR spectra of powder mixtures prior to compression, the characteristic peaks of PEG 6000, mannitol, HPMC and L-HPC could be located **Figure 1**. No signal due to drug was seen probably due to dilution effect by high percentage of carrier and excipients in the mixture. Pre-compression powder possessed fair to passable flow property since the angle of repose was found to lie between 19.9-26.8^{o}, Compressibility index varied between 18.5 and 22.8% and Hausner ratio in the range of 1.0 to 1.2.

Evaluation of Carvedilol Solid Dispersion Tablets (SDTs)

All the tablet batches fulfilled the IP specifications for weight variation [23]. Content uniformity was found to be good where the percentage of drug content exceeded 97%. The hardness values for the tablets were in the range of 3-3.5kg/cm^2 tablet. Friability is an indicator of the tablet's physical strength. All the formulae complied with the compendia standards as none of them had percentage loss in tablets' weights that exceeded 1%, and no tablet was chipped, cracked, split or broken.

Table 4 In vitro Characterization of Carvedilol-TSDs. (Values are mean ± Standard Deviation; n=3)

Parameters	Formulation Code			
	CONTROL-TSD	TSD-L	TSD-L'	MARKETED FORMULATION
Wetting Time (min:sec)	1:48.42±08.96	0:58.98±07.98	0:15.90±06.22	0:06.58±01.34
Rate of Simulated Saliva Uptake (mg/sec)	0.1095±0.11	0.3677±0.07	0.568±0.02	2.839±0.09
Disintegration Time (min:sec)	11:09.01±14	9:10.10±26.73	7:10.29±14.45	0:58.32±09.96
DE (%)	34.92	54.2	53.47	52.93
MDT (mins)	56.84	19.8	19.8	11.74
$Q_{15(mins)}$ (%)	21.71	36.7	36.3	66
$Q_{60(mins)}$ (%)	69.6	100% (47mins)	100% (48mins)	100% (25.2mins)
$T_{50\%}$ (mins)	33	18.8	18.8	11
$T_{75\%}$ (mins)	75	30.5	30.5	17
R^2_{Hig}	0.976	0.980	0.980	0.987
k_{Hig}	9.78	19.67	19.4	27.82

Wicking time, Rate of saliva uptake and Disintegration time

Figure 3 show in details the main effects of addition of L-HPC on the tablets' wetting time, rate of saliva uptake and disintegration time, in comparison to marketed formulation. All the prepared tablet batches subjected to wicking test in simulated saliva were wetted within an acceptable time of less than 1 min, except Control-TSD, the minimum being observed for TSD-L' where the wicking time was 15.90 secs ± 6.22. It was also observed that the batch TSD-L' which had the least wetting time also had the highest rate of saliva uptake of 0.568 mg/sec ± 0.02 and minimum disintegration time of 7mins 10.29secs ± 14.45 showing a strong correlation between disintegration time and wetting time **Table 4**. L-HPC is known to undergo exothermic interaction with water, possesses low crystallinity index values between 0.62-0.86, may form intermolecular hydrogen bonds, thereby attracting water molecules and undergoes plastic deformation during compression [14]. All these characteristics promote rapid disintegration of L-HPC-based tablets i.e. batches TSD-L and TSD-L' compared to the batch Control-TSD where it is

not present. Observed performance of the two batches is further possible since the ratio of L-HPC and Avicel PH 102 has been maintained at 2:8 as suggested in the literature [17]. Moreover, L-HPC is reported to produce significant lowering in disintegration time when mannitol is present as a diluent in the formulation [13].

In vitro dissolution studies

TSD-L and TSD-L' achieved 100% drug release within 47 mins and 48 mins respectively. Though the values are poor compared to the marketed formulation, they are 1.5 times better with respect to Control-TSD. Comparison of $t_{50\%}$ and $t_{75\%}$ values for the drug to be released from the three batches showed that the compositions can be arranged as follows: Marketed formulation < TSD-L' = TSD-L< Control-TSD (**Table 4)**. The value of %DE for pure drug in Control-TSD (34.92%) was enhanced in both the batches almost to the same percentage (54%), which is comparable with the marketed formulation. The MDT of Control-TSD in gastric buffer is 56.24 min which is reduced to 19.8mins for the other two batches, the value being higher than the marketed formulation. Bar graph **Figure 3** represents the relationship between %DE and MDT for all the formulations with marketed product. **Figure 4** shows the comparative mean dissolution profiles of Carvedilol from tablets containing solid dispersions using mannitol as an excipient and also incorporating L-HPC. Q_{15} and Q_{60} values (percent drug dissolved within 15 and 60 mins) are reported in **Table 4**. All these studies indicate that the dissolution efficiency of the batches containing L-HPC is similar to the marketed product and the difference in the profiles between TSD-L and TSD-L' is found to be statistically insignificant at a significance level of p-value ≤ 0.05. Fitting of release data to the three kinetic models mentioned above showed that all the three batches obeyed Higuchi kinetics, i.e. drug diffusion occurred through the matrix tablets formed by mannitol and L-HPC and the corresponding rate constant values, K_{Hig} are also provided in the **Table 4**. Therefore, addition of higher percentage of L-HPC may have produced lower disintegration time but no further benefit in the dissolution parameters. Moreover, high value of dissolution efficiency indicates that once the drug is released from the matrix after disintegration, it dissolves rapidly which may predict quick onset of action in vivo.

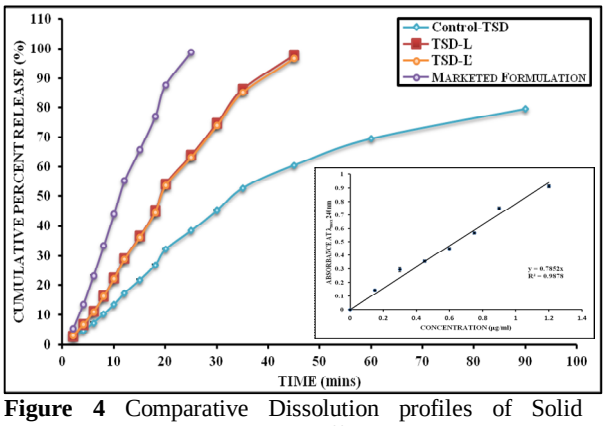


Figure 4 Comparative Dissolution profiles of Solid Dispersion Tablets in Gastric Buffer (pH-1.3). Inset shows the calibration curve of pure Carvedilol in the medium at 240 nm. (Values are mean ± Standard Deviation; n=3)

CONCLUSION

Formulation of Carvedilol solid dispersion in the carrier system of PEG 6000, HPMC and Tween 80 has successfully improved the aqueous solubility of the drug giving impetus to the fabrication of a disintegration-accelerated matrix type of tablet by inclusion of 19.75% w/w mannitol and two different percentages of disintegrant, L-HPC LH-11. Maintaining the optimum ratio of L-HPC and Avicel PH-102 in the formulation achieved the desired wetting and disintegration parameters for the tablet batches. Although L-HPC promoted disintegration and dissolution, addition of higher percentage did not produce statistically significant differences in the release profile. Thus, fabrication of disintegration-accelerated solid dispersion-based matrix tablet of Carvedilol may lead to rapid onset of action due to rapid disintegration and dissolution. Hydrophilic matrix formation with prolonged drug release may help in more effective management of hypertension, requiring less frequent administration.

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