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Mixed Order Drug Release Kinetics Induced by L-HPC LH-11: A New Frontier In Improved Dissolution Behavior of Solid Dispersion Tablets of a BCS Class 2 Drug.

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ABSTRACT

The role of widely used disintegrant, L-HPC LH-11, in modulating the dissolution behavior of poorly water-soluble BCS Class 2 drug remains to be explored. The objective of the present study is to promote fast disintegration, rapid and complete release of Carvedilol from tablets by including low substituted hydroxypropyl cellulose. To improve aqueous solubility, the technique of solid dispersion in ternary hydrophilic carrier system of PEG 6000-Hydroxypropylmethyl cellulose (HPMC)-Tween-80 was utilised. Drug in amorphous or microcrystalline state led to solubility enhancement as elucidated by FTIR, DSC, XRD and SEM studies of solid dispersions. Period-specific analysis of drug release kinetics from solid dispersion tablets containing L-HPC exhibited mixed-order kinetics characterized by shift in kinetics from first order to Hixson-Crowell within 20 mins. Tablet disintegration by L-HPC generated finely divided drug particles of higher solubility. Differences observed in the dissolution behavior between CONTROL and batches containing L-HPC were statistically significant($p < 0.05$). It can be concluded that L-HPC, a well-known disintegrant can exert strong positive influence on dissolution-related parameters of solid dispersion tablets of BCS Class 2 drugs. Thus, L-HPC LH-11 can act as a dual-functional excipient in tablet manufacture minimizing the commercial production cost.

Keywords : BCS Class 2, HPMC, L-HPC LH 11, Solid Dispersion tablet, Dissolution efficiency, Mean Dissolution Time

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INTRODUCTION

Dissolution analysis of dosage forms is one of the most significant tests and powerful tools in product development and manufacturing, enables assessment of the effects of biopharmaceutical properties and formulation principles on the release properties of the drug as also in ensuring product quality. This is more true for poorly water-soluble drugs belonging to Class 2 of Biopharmaceutics Classification System (BCS) where the process of dissolution is rate–limiting to the process of absorption in vivo. Dissolution profile as well as release kinetics for such class of drugs should be definite and reproducible[1]. Strategies for solubility improvement render poorly water-soluble compounds suitable to be potential biowaiver candidates, as recommended by FDA (Food and Drug Administration) in 2000. Moreover, successful approach helps in designing more dose-efficient formulations which will reach the patients at an affordable price with greater therapeutic efficacy [2]. The concept of solid dispersion introduced by Sekiguchi and Obi in 1961 has been established as a successful solubilisation technology for BCS Class 2 drugs [3]. Different mechanisms have been postulated for observed solubility enhancement leading to improved in vivo performance with solid dispersions. These include particle size reduction, transformation to amorphous/microcrystalline state, improved wetting by hydrophilic carrier substances as evidenced by decrease in contact angle and interfacial tension etc.[4]. Ultimate consequence of any of the above-mentioned phenomena is the formation of a supersaturated drug solution in contact with the aqueous milieu of the gastrointestinal tract leading to fast and complete dissolution [5].

Carvedilol, a novel third generation β-blocker has provided 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 [6]. 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. The solubility profile of Carvedilol in different media and its dissolution parameters in water are presented in Table 1.

Table 1: Physicochemical properties of Carvedilol

CARVEDILOL

Chemical Formula:(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 [7-8]		
In Water (µg/ml) at 25° C	**In Phosphate buffer, pH 6.8(µg/ml) at 25°C**	**In gastric buffer, pH 1.2(µg/ml) at 25° C**
0.583	92.13	38.4

REPORTED DISSOLUTION PARAMETERS OF CARVEDILOL IN DISTILLED WATER [9]			
Q_{15mins} (%)	**$T_{50\%}$ (mins)**	**DE_{120} (%)**	**MDT (mins)**
1.93	>120MINS	3.95	56.23

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. To achieve dose uniformity, patient-compliance, ease of administration and improved drug release, solid dispersion of Carvedilol in carriers like PVP K30, porous silica, mannitol, lactose, urea, PEG 4000 and Gelucire 50/13 have been prepared [9-12]. Alternatively, melt-in-mouth tablets and mouth dissolving tablets of Carvedilol have also been designed [13-14]. Solid dispersions of furosemide and ibuprofen have been formulated into tablets by direct compression or wet granulation using 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[15-19].

In tablet technology, small proportions (2.5–5%) of hydrophilic low-substituted hydroxypropylcelluloses (L-HPCs) like L-HPC 11, L-HPC 21, have been used along with other excipients as

microcrystalline cellulose (MCC) and mannitol to promote disintegration via swelling without gelling [20-23]. L-HPC is reported to exert a very positive effect on famotidine tablets containing mannitol where it significantly decreased their wetting time, oral disintegration time and achieved complete drug release within 2 mins. However, no previous investigation has reported the role of L-HPC in modulating drug release pattern from tablet dosage form. The possibility of L-HPC being used as a dual-functional excipient has not been explored.

In the past, several studies have been carried out on design and development of fast disintegrating/dissolving tablets but very few have focused on interpretation of release kinetics attributed to disintegration-activated drug release. Drug release from fast-release tablets prepared from solid dispersions, solid dispersion matrix tablets, fast-dissolving intraoral drug delivery systems and conventional fast-dissolving tablets have been found to follow first-order kinetics [24-26]. However, it seems more likely that drug release from fast disintegrating/dissolving solid dispersion tablets may occur initially in a monoexponential fashion leading to dissolution of finely divided particles of improved solubility as induced by the presence of hydrophilic swellable L-HPC LH-11 and other excipients.

In the present investigation, attempts have been made to elucidate drug release kinetics of Carvedilol tablets fabricated from solid dispersions in ternary hydrophilic carrier system of PEG 6000-Hydroxypropylmethyl cellulose (HPMC)-Tween-80, and employing right combination of mannitol, Avicel PH102 and L-HPC. Novel period-specific drug release kinetic analysis was performed with an aim to postulate the role of L-HPC LH-11 in modulating dissolution behavior of Carvedilol solid dispersion tablets and to establish it as a dual-functional excipient in tablet manufacture.

MATERIAL 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 characterization of Carvedilol solid dispersions (CAR-SD)

The quaternary solid dispersion (Drug: PEG 6000: HPMC: Tween-80 = 1: 8.675: 0.075: 0.25) was prepared by melting-solvent evaporation technique[27]. 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 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 estimation of drug content and solubility enhancement at 285nm and 240nm respectively.

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 given 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.

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Table 2: Composition of various batches of Carvedilol Solid Dispersion Tablets (TSD) by direct compression

NOMENCLATURE	CONTROL	TSD-L	TSD-L1	TSD-L2	TSD-L3	TSD-L4
INGREDIENTS	% w/w for each 180mg tablet					
CAR-SD	48.75	48.75	48.75	48.75	48.75	48.75
MANNITOL	19.75	19.75	19.75	19.75	19.75	19.75
AVICEL PH-102	11.5	11.5	11.5	11.5	11.5	11.5
L-HPC LH-11	---	1.5	2.0	2.5	3.0	3.5
DICALCIUM PHOSPHATE, DIHYDRATE	20.0	18.5	18.0	17.5	17.0	16.5
TALC	Quantity Sufficient					
MAGNESIUM STEARATE	Quantity Sufficient					

Characterisation 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 individually with potassium bromide (KBr) and compressed to yield KBr discs. 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 nitrogen atmosphere at a flow rate of 20 mL min^{-1} 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 having 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. Scanning electron microscopy (Jeol; Model-JSM360, UK) of pure drug, PEG 6000 and the solid dispersion was carried at an acceleration voltage of 17 kV at X950 magnification with samples being mounted onto the stubs using double-sided adhesive tape, coated with a thin layer of palladium.

Characterisation methods for Solid Dispersion Tablets (TSD) of Carvedilol

Wetting time

A twice-folded tissue paper (10.75mm×12 mm) was placed in a 6.5 cm diameter culture dish containing definite volume of gastric buffer (pH 1.2) (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 wetting time [24]. The experiments were repeated thrice.

In vitro disintegration time

Disintegration time for the tablets was determined using USP disintegration apparatus in gastric buffer (pH 1.2, 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, LABINDIA Model No. DS-8000). One tablet from each batch was placed in 900 ml of gastric buffer(pH 1.2) maintained at 37 ± 0.5°C and stirred at 50 rpm. Aliquot of 10ml was withdrawn at different time intervals and replenished immediately with same volume of pre-warmed medium. The absorbance values for the aliquot filtrate at 240nm were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2=0.995). All tests were done in triplicate and mean was taken to calculate cumulative release profile.

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Comparison of in vitro dissolution data

For comparison of dissolution profiles, several model-dependent or model-independent approaches can be adopted. The data obtained from each experiment were subjected to statistical analysis using one-way analysis of variance(ANOVA) followed by Newman–Keuls multiple comparisons test. $p < 0.05$ was considered to be indicative of significance.

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) were fitted to different kinetic models (first order and Hixson- 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 [28].

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

where j is the sample number, n is the number of dissolution sampling points, $t_j^{\wedge}$ 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 and determine the effect of L-HPC on drug release. DE was calculated as follows[28].

$$(\%\ \mathrm{DE}) = \frac{\int_0^t Y \, dt}{Y_{100} t} \times 100 \quad \ldots (2)$$

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.

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.

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 in Table 3 showed that the solid dispersion approach employing ternary carrier system of PEG 6000-HPMC-Tween 80 produced 2-fold improvement in drug solubility with solubility value of 2.408±0.017µg/ml at 37°C. Pure Carvedilol spectrum in 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 [29]. The disappearance of all the characteristic peaks of pure crystalline drug in the CAR-SD indicates that the drug particles might have been masked by the high proportion of polymer molecules. A new absorption peak at 1,108 or 1111.24 cm^{-1} indicated formation of secondary hydrogen bond between drug and carrier leading to higher solubility of drug from solid dispersion. No evidence of chemical interaction could be observed between the components.

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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±0.205	116.81	148.77
CAR-SD	2.408±0.017	62.98	128.97

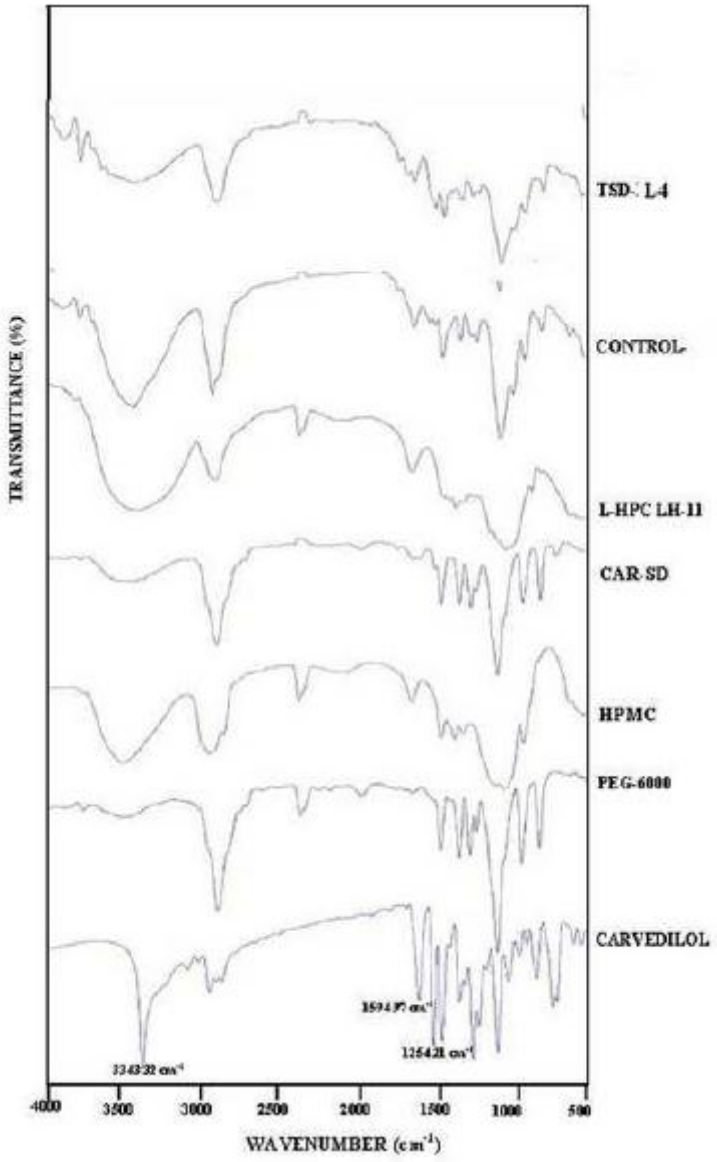

Figure 1: Overlaid FTIR spectra of pure components, CAR-SD and pre-compression powder mixture.

The DSC curve of pure Carvedilol exhibited a single endothermic peak with melting observed at 116.81°C and possessing heat of fusion (ΔH_f) value of 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 presented in Figure 2a showed absolute disappearance of drug peak but a slight shift in the position of the peak of PEG 6000 towards the left. This observation suggests that the drug particles have lost their crystallinity completely and have become soluble in molten PEG forming a monotectic system. The diffraction spectrum of pure Carvedilol given in Figure 2b revealed the crystalline nature of the drug showing numerous peaks at 2θ values 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. Peak intensity was considerably reduced in the solid dispersion. Thus, it can be concluded that bulk of the drug might have lost its

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crystalline structure and have been transformed into higher energy amorphous or microcrystalline form in SD. Since the positions of the peaks of PEG-6000 are visible in SD, any possibility of chemical interaction between the constituents or formation of a new compound is totally ruled out. Photomicrographs of the pure drug showed them as blunt crystals as observed from Figure 2c. In the solid dispersion, drug and carrier regions could not be identified separately. Therefore, the findings from DSC and XRD studies about the microcrystalline or amorphous nature of the solid dispersions is corroborated by the micrographs.

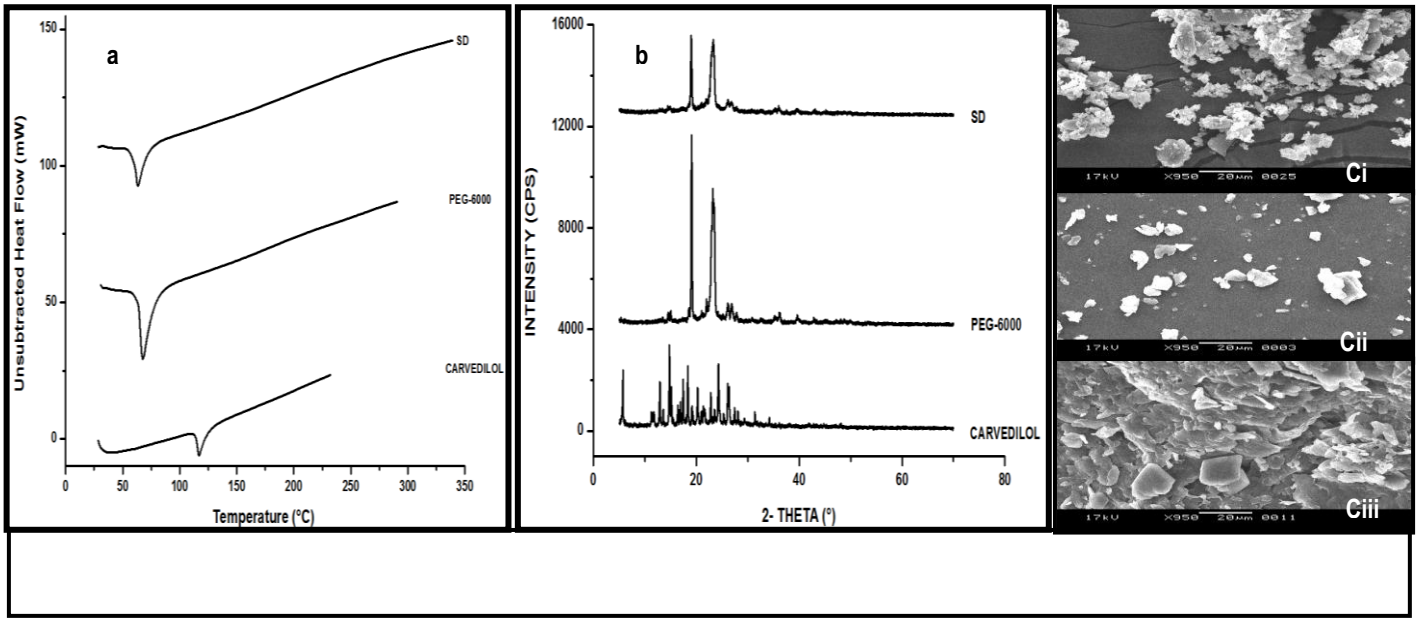

Figure 2: (a) Overlaid DSC Thermograms; (b) Overlaid diffractograms from XRPD Studies; (c) SEM Micrographs of (i) Carvedilol, (ii) PEG-6000, (iii) CAR-SD.

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 from 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. 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 (TSD)

All the tablet batches fulfilled the IP specifications for weight variation (Indian Pharmacopoeia)[30]. 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. Friability is an indicator of the tablet's physical strength. All the formulae complied with the compendia standards as no more than 1% loss in tablets' weights was observed after the test. No tablet was chipped, cracked, split or broken.

Wetting time and Disintegration time

The effect of addition of L-HPC on the wetting time and disintegration time of formulation batches is evident from Figure 3**.** All the prepared tablet batches subjected to wetting test in gastric buffer were wetted in less than 1 min, except CONTROL and TSD-L. The wetting time was least for TSD-L4 at 03.29±1.981secs.The differences in values of wetting time between CONTROL and all other batches was found to be statistically significant ($p < 0.5$) from Table 4. TSD-L4 also possessed minimum disintegration time of 5 mins 58.02 secs±10.43 secs. The disintegration time for other batches in gastric buffer(pH 1.2) varied from 10 mins 5.23 secs±9.28 secs for CONTROL to 6 mins 43.79secs±12.59secs for TSD-L3. Differences observed in Table 4 carried statistical significance specially with reference to TSD-L4 and all other batches ($p < 0.5$). L-HPC is known to undergo exothermic interaction with water, possesses low crystallinity index values between 0.62-0.86, may

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form intermolecular hydrogen bonds, thereby attracting water molecules and undergoes plastic deformation during compression. Therefore, sequential and statistically significant reduction in wetting and disintegration times from TSD-L to TSD-L4 can be attributed to the synergistic action of mannitol and increasing proportions of L-HPC LH-11 in the formulae as also the critical ratio of L-HPC and Avicel PH 102 [19-20].

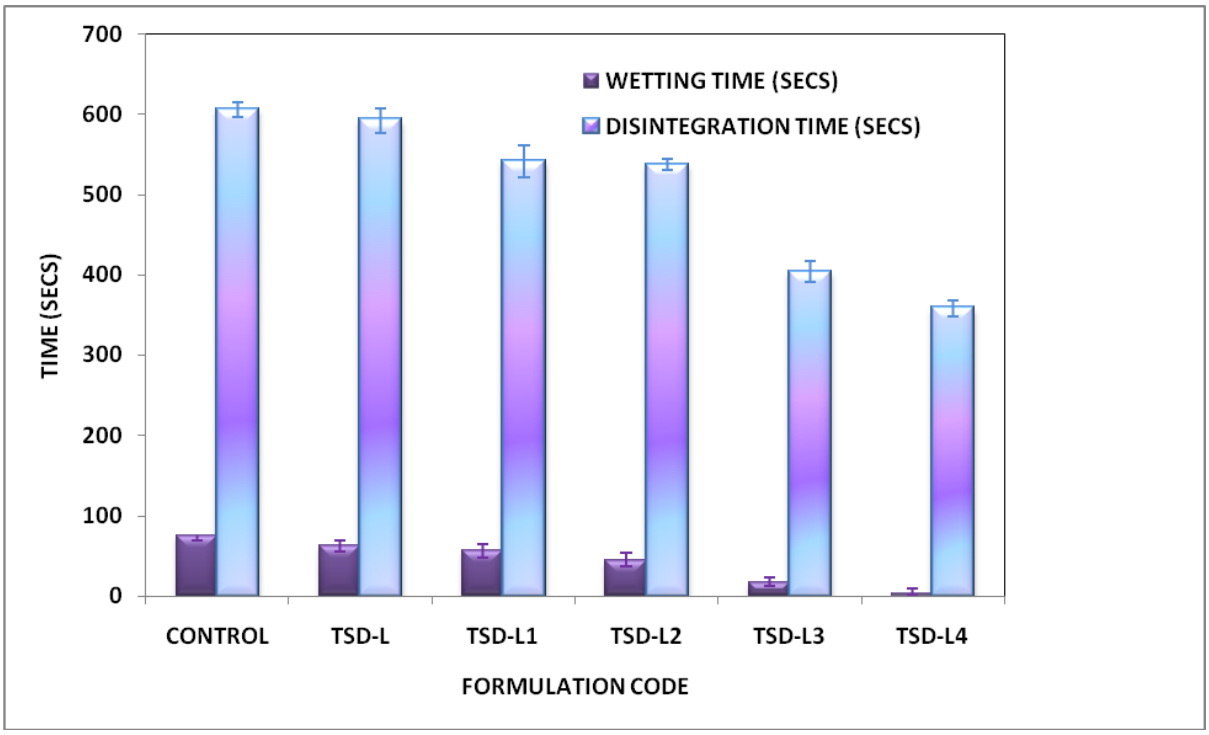

Figure 3: Bar graph representation of Wetting time and Disintegration time of different batches of Carvedilol Solid Dispersion Tablets in gastric buffer(pH 1.2).

Table 4: In vitro characterization of Carvedilol-TSD batches (Values are mean ± Standard Deviation; n=3)

PARAMETERS	FORMULATION CODE					
	CONTROL	TSD-L	TSD-L1	TSD-L2	TSD-L3	TSD-L4
WETTING TIME* (min:sec)	01:15.39 ±07.009	1:02.61 ±06.82	56.97 ±10.06	00:43.89 ±6.341	0:17.21 ±05.63	00:03.29 ±1.981
DISINTEGRATION TIME (min:sec)**	10:05.23 ±9.28	9:52.59 ±15.33	9:01.40 ±19.79	08:56.91 ±6.82	6:43.79 ±12.59	05:58.02 ±10.43
DE (%)***	34.92±1.16	46.52±2.75	49.8±1.73	53.47±2.05	53.91±1.55	54.2±2.29
MDT (mins)***	56.84±2.23	25.11±1.01	22.2±2.61	19.8±2.86	19.1±1.31	18.3±2.19
$Q_{15(mins)}$ (%)#	21.71±1.83	34.29±1.54	35.76±2.33	36.68±1.93	39.17±2.01	39.57±1.67
$Q_{30(mins)}$ (%)#	69.6±1.47	73.2±3.02	74.84±2.90	74.87±2.61	79.56±1.03	79.96±2.26
$T_{50\%}$ (mins)##	33±0.25	19.8±0.15	19.1±0.49	19.0±0.36	18.6±0.09	18.4±0.71
$T_{75\%}$ (mins)##	75±0.43	30.8±0.43	30.2±0.27	30.1±0.68	27.3±1.01	27.1±0.95

** No significant differences between CONTROL and TSD L($p > 0.05$) and significant differences between CONTROL and other formulations (TSDL1–TSDL4) ($p < 0.05$).*

*** Significant differences between CONTROL and all other formulations (TSDL–TSDL4) ($p < 0.05$). Significant differences among TSDL2, TSDL3 and TSDL4 ($p < 0.05$). No significant differences between TSD L and TSD L1($p > 0.05$).*

**** Significant differences between CONTROL and all other formulations (TSDL–TSDL4) ($p < 0.05$). Significant differences between TSDL and TSDL1, TSDL1 andTSDL2-TSDL4 ($p < 0.05$). No significant differences among TSD L2, TSDL3 and TSD L4 ($p > 0.05$).*

 # Significant differences between CONTROL and all other formulations (TSDL–TSDL4) ($p < 0.05$). Significant differences between TSDL-TSDL2 and TSDL3 and TSDL4 ($p < 0.05$). No significant differences between TSDL3 and TSD L4 ($p > 0.05$).

Significant differences between CONTROL and all other batches ($p < 0.05$). No significant differences among all other batches ($p > 0.05$).

Effect of L-HPC on dissolution process related parameters

The dissolution efficiency (DE) of TSD-L4 (3.5% L-HPC) was found to be maximum at 54.2 ±2.29 % which decreased to 34.92 ±1.16% for CONTROL(L-HPC absent). The MDT value of TSD-L4 was 3-fold less than that of CONTROL which was statistically significant ($p < 0.05$). Differences in the values of DE and MDT as observed in Table 4 for the batches TSD-L2, TSD-L3 and TSD-L4 were statistically insignificant ($p > 0.05$). The

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batches TSD-L2 and TSD-L3 possessed MDT values of 19.8±2.86 mins and 19.1±1.31mins respectively. Alteration in DE and MDT with change in composition is depicted in Figure 4. Lower value of MDT and greater value of DE is desirable from tablets with rapid dissolution profile. The desirable objectives have been achieved with the use of L-HPC. Closer inspection of the values for $T_{75\%}$ and $T_{50\%}$ showed the results for CONTROL to be higher and significantly different from batches containing L-HPC) ($p < 0.05$). Comparing the data for cumulative percent of drug released at 15 mins (Q_{15}) and 30 mins (Q_{30}) revealed overall better performance for all batches except CONTROL, which is statistically quite significant for the batches containing higher percentages of L-HPC) ($p < 0.05$). Batches TSD-L3 and TSD-L4 did not differ in these parameter values) ($p > 0.05$). Strong effect of L-HPC on dissolution process related parameters is thus clearly evident. Therefore, in addition to acting as a disintegrant, L-HPC also shows promise in improving the dissolution profile of a poorly water-soluble drug, more so, at higher percentages (3% and 3.5%). L-HPC can thus be exploited as a dual-functional excipient, playing crucial roles in both the processes of disintegration and dissolution of a solid dosage form.

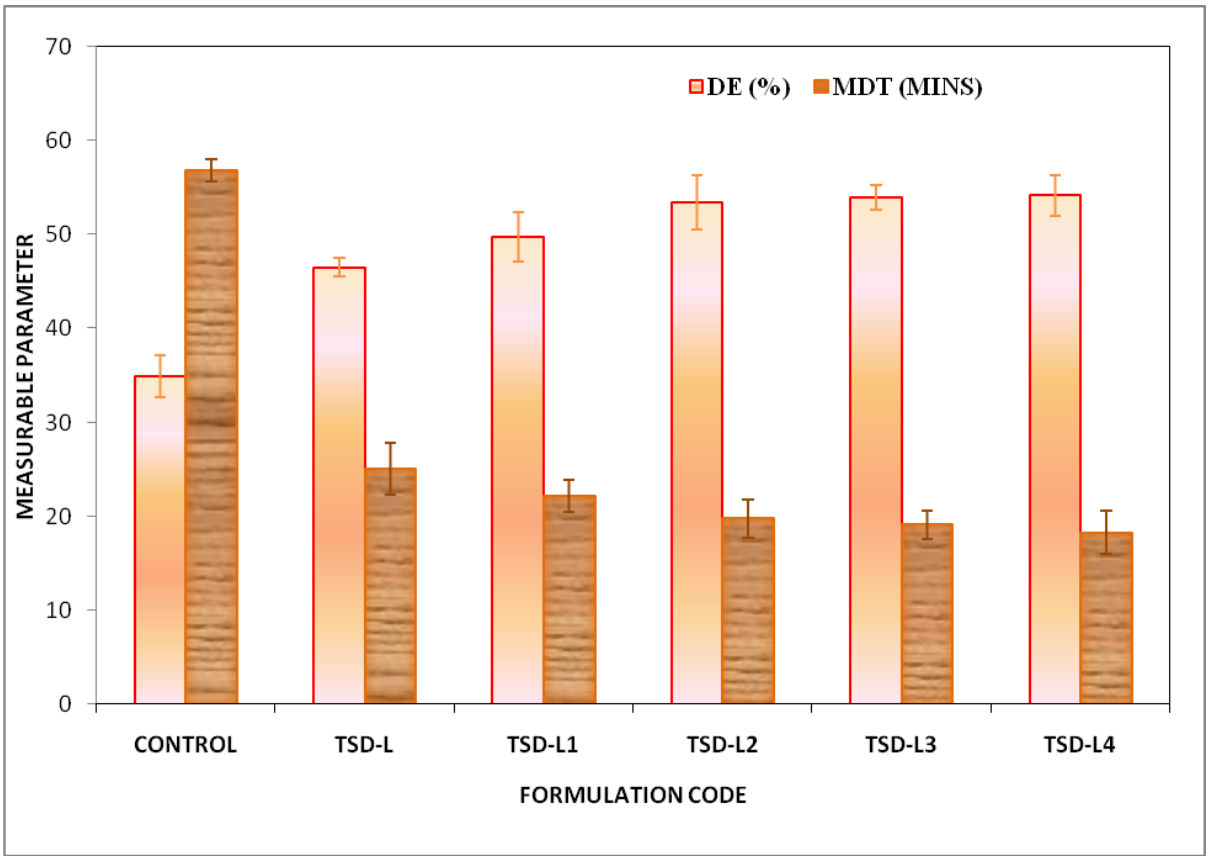

Figure 4: Bar graph representation of Dissolution Efficiency and Mean Dissolution Time of different batches of Carvedilol Solid Dispersion Tablets in gastric buffer(pH 1.2).

Concerning mechanism of drug release from the solid dispersion based tablets, the dissolution data were subjected to first-order and Hixson-Crowell kinetic models and r2 values are given in Table 5. Although, CONTROL batch obeyed first-order kinetics, the r^2 value (0.872) was too low for consideration. The remaining batches were found to follow first order kinetics with r^2 varying from 0.887 to 0.961. Fitting of the release data for the different batches (including CONTROL), to Hixson-Crowell model showed the r^2 values lying between 0.864 and 0.915.

Similarity in the dissolution behavior of L-HPC containing batches and marked difference from the CONTROL batch, low r^2 value for CONTROL, TSD-L2 and TSD-L4 and closeness in r^2 values for two models prompted to attempt period-specific kinetic analysis. This analysis would validate our postulate of drug release following mixed-order kinetics. The entire study period (τ) for all the formulations (except the CONTROL) was divided into two segments : (a). from initial sampling point till 20 mins (τ_1) and (b) from t=20 to end (τ_2). Cut-off point at t=20 was chosen because beyond this point , all the batches (except CONTROL) showed an erratic behavior with respect to first-order kinetics and a definite pattern on the basis of Hixson-Crowell kinetics. This

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approach led to the observation of shift or switch-over in kinetics from first-order to Hixson-Crowell in τ_2. In τ_1, an improvement in the r^2 value for first-order kinetics was obtained in all the cases with values ranging between 0.965-0.974. For the same segment, the formulations TSD-L1, TSD-L2 and TSD-L4 showed same r^2 value for Hixson-Crowell kinetics. However, for all the formulations in τ_2, Hixson kinetics predominates, with r^2 lying between 0.971 and 0.987. With the CONTROL batch, the same pattern was observed only after 90 mins. Therefore, for the solid dispersion tablets containing varying percentages of L-HPC, initial drug release was highly concentration-dependent releasing drug particles of improved solubility. Presence of L-HPC facilitated uptake of aqueous buffer, faster wetting and rupture of tablets into granules and mono-disperse particles compared to CONTROL, leading to compliance with Hixson-Crowell kinetic model for later part of the profile beyond 20 mins. Although TSD-L3 and TSD-L4 showed comparable values for different dissolution related parameters, highest percentage of L-HPC (3.5%) in TSD-L4 promoted 97.25±3.37% of drug release in 40 mins in contrast to 93.71±2.94% in 40 mins from TSD-L3 as observed from Figure 5.

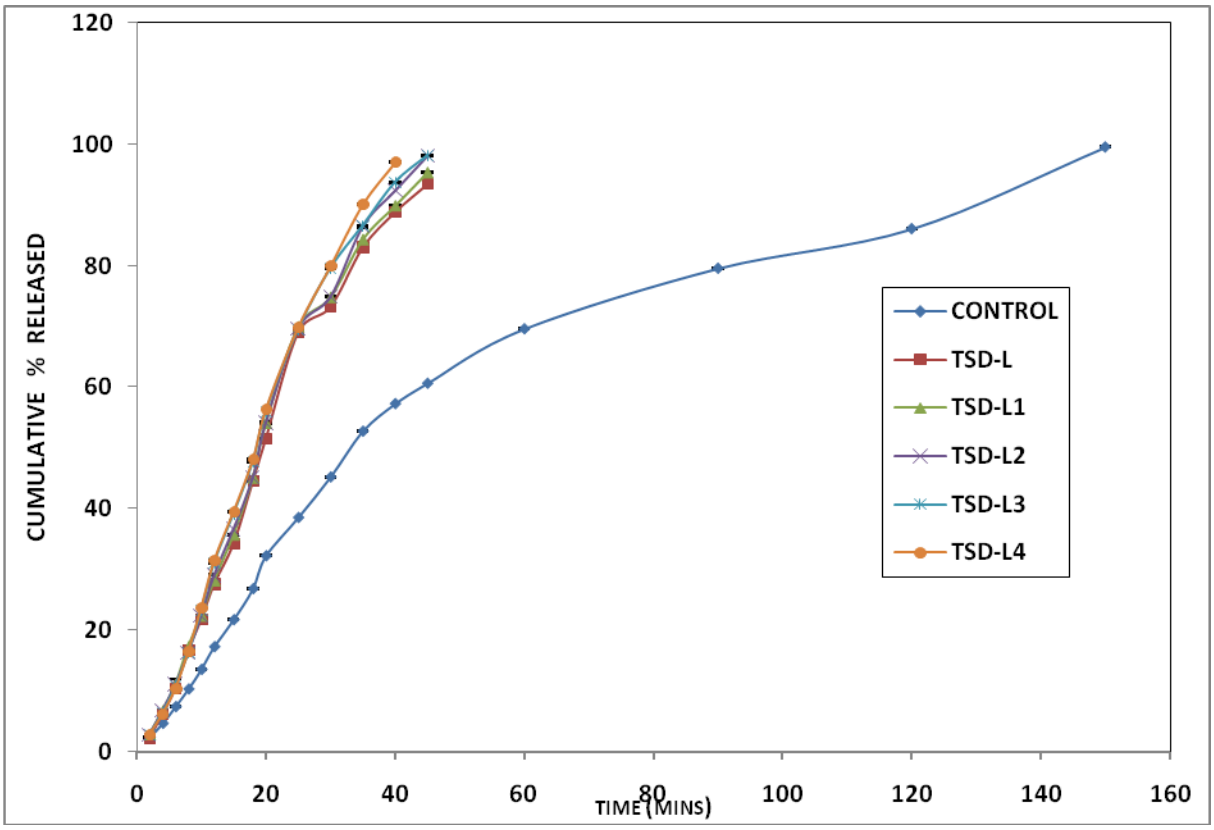

Figure 5: Comparative dissolution profiles of various batches of Solid Dispersion Tablets of Carvedilol in gastric buffer (pH 1.2) (Values are mean ± Standard Deviation; n=3).

No previous study on the use of L-HPC in tablet formula explored its role in promoting rapid and complete drug release. Moreover, mixed-order kinetics of dissolution has not been observed before for fast-release tablets of BCS Class 2 drugs. Rapid release of drug from tablets can be guaranteed only by rapid disintegration into fine particles. Formulation of solid dispersion by employing a mixture of hydrophilic substances as carrier enhances the solubility of Carvedilol to a considerable extent owing to the existence of drug particles in microcrystalline or amorphous state. Further, tabletting of solid dispersions by direct compression using mannitol as excipient, adding an optimum percentage of L-HPC LH-11 and employing critical ratio of L-HPC and Avicel PH 102 may provide the desired release profile of mono-disperse particles of an otherwise poorly water-soluble drug [31-32]. Thus, it can be concluded that to ensure quick wetting, fast disintegration, achieve improved and rapid drug release of a BCS class 2 drug from tablets, it is best to formulate it into solid dispersion and then compress the resulting dispersion directly into tablets by including a dual-functional excipient like L-HPC LH-11 in the formula.

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Table 5: Period-specific drug release kinetic analysis of Carvedilol Solid Dispersion Tablets in gastric buffer(pH 1.2)

Batch	First-order kinetics			Hixson-Crowell kinetics		
	τ	τ_1	τ_2	τ	τ_1	τ_2
CONTROL	y=-0.012x+2.1 r^2= 0.872	y= -0.008x+2.004 [a] r^2= 0.986	y= -0.028x +4.02 [b] r^2= 0.877	y= -0.023x+2.313 r^2= 0.697	y= -0.032x+2.482 [a] r^2= 0.754	y= -0.005x+0.836 [b] r^2= 0.968
TSD-L	y= -0.026x+2.142 r^2= 0.961	y= -0.016x+2.045 r^2= 0.974	y= -0.034x+2.419 r^2= 0.970	y= -0.071x+2.682 r^2= 0.864	y = -0.123x+3.205 r^2= 0.957	y= -0.025x+1.076 r^2= 0.978
TSD-L1	y= -0.028x+2.165 r^2= 0.945	y= -0.017x+2.047 r^2= 0.965	Y= -0.042+2.602 r^2= 0.962	y= -0.085x+2.807 r^2= 0.915	y= -0.121x+3.14 r^2= 0.966	y= -0.022x+1.066 r^2= 0.984
TSD-L2	y=-0.034x +2.248 r^2= 0.887	y=-0.017x +2.048 r^2= 0.968	y= -0.061x +3.145 r^2= 0.941	y= -0.071x+2.637 r^2= 0.876	y= -0.121x+3.145 r^2= 0.968	y= -0.024x+1.134 r^2= 0.975
TSD-L3	y = -0.026x+2.121 r^2= 0.967	y= -0.018x+2.055 r^2= 0.972	y= -0.061x+3.12.2014 r^2= 0.95	y= -0.071x+2.623 r^2= 0.862	y=-0.127x+3.175 r^2= 0.967	y= -0.023x+1.071 r^2= 0.971
TSD-L4	y= -0.035x+2.22 r^2= 0.903	y= -0.019x+2.059 r^2= 0.966	y= -0.066x+3.216 r^2= 0.948	y= -0.078x+2.706 r^2= 0.894	y= -0.128x+3.181 r^2= 0.966	y= -0.031x+1.273 r^2= 0.987

τ = entire sampling period; τ_1 = sampling period from initial time point to 20 mins; τ_2 = sampling period from t = 20 to terminal time point; [a] = initial sampling point to 90 mins; [b] = 90 mins to terminal time point

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CONCLUSION

Carvedilol, a classical example of a BCS Class 2 drug has been found to exist in microcrystalline state when dispersed in a hydrophilic carrier, composed of PEG 6000-HPMC-Tween-80, resulting in 2-fold improvement in aqueous solubility. It can be postulated that initial drug release from the tablets occurred in mono-exponential fashion after which it switched over to predominantly Hixson-Crowell kinetics characterized by dissolution of mono-disperse microcrystalline drug particles. Therefore, in addition to acting as disintegrant, presence of low percentage of L-HPC could successfully improve the dissolution behavior of solid dispersion tablets of Carvedilol leading to sequential first-order and Hixson-Crowell kinetics of drug release from the formulations.

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