Research Journal of Pharmaceutical, Biological and Chemical Sciences

Influence of Excipient Combination on Release Kinetics from Solid Dispersion Tablets of a Model BCS Class II Drug

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ABSTRACT

Superdisintegrant absorbs water by wicking or capillary action undergoes swelling, induces hydrodynamic pressure in the tablet core causing rupture and disintegration to finer particles of higher specific surface area available for interaction with dissolution medium. Disintegrant efficiency and its performance in dissolution improvement is markedly influenced by the hydrophilicity of the filler excipient. In the present experimental work, soluble diluent, lactose(L) and hygroscopic, insoluble diluent, di-calcium phosphate dihydrate(D), were combined with superdisintegrant, Ac-di-sol to produce tablets of Danazol solid dispersion(DZ-SDT) and evaluated for determination of their water absorption percentage, disintegration time and release kinetics. High hydrophilicity and fibrous nature of Ac-di-sol resulted in water absorption percentages of 60% and 52% into the tablet structure for the batches DZ-SDT(L)-2 and DZ-SDT(D)-2 respectively. Use of di-calcium phosphate dihydrate as filler in tablet containing 8% w/w of Ac-di-sol as superdisintegrant produced matrix tablet with a capacity to absorb sufficient water, undergo quite rapid disintegration, achieve release of 60% of drug within 8 mins and 6-fold lowering in Mean Dissolution Time. Therefore, proper combination of filler and superdisintegrant is crucial to achieve desired disintegration characteristics and release profile of drug from solid dispersion tablets of a BCS Class II drug.
Keywords: Superdisintegrant, filler hydrophilicity, water absorption percentage, release kinetics

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INTRODUCTION

Selection of excipients in tablet manufacture plays a crucial role and it depends on factors like, physicochemical characteristics of drug or Active Pharmaceutical Ingredient, type of tablet, manufacturing process and desired release profile. In spite of extensive research in the area of controlled release oral drug delivery systems, scientists are still interested in fabrication of conventional tablets dosage forms, intended to be swallowed whole, that will disintegrate quickly, and release their medicaments rapidly in the gastrointestinal tract so as to be absorbed and elicit therapeutic response. To achieve better bioavailability of a BCS Class II drug, where gastrointestinal absorption is dissolution-rate limited, relatively rapid disintegration is one of the pre-requisite steps, prior to dissolution.

Solubility of the API as well as excipients can affect the rate and mechanism of tablet disintegration. Poor aqueous solubility of API may hinder drug release from tablet, even if it disintegrates. Therefore, formulation of solid dispersion of drug in hydrophilic carrier like polyethylene glycol 6000 may be a preliminary step before fabrication of a tablet. Various mechanisms postulated for observed solubility enhancement of API in solid dispersion include reduction in particle size, increase in wettability, decrease in contact angle and interfacial tension, reduction in crystallinity etc. [1-2]. Water-soluble excipients have a propensity to dissolve the tablets whereas insoluble materials generally tend to disintegrate tablets in presence of appropriate concentration of a suitable disintegrant. In tablet manufacture, drug-excipient interaction may affect the process of dissolution e.g. phenyl-propanolamine HCl–Ac-di-sol exhibited incomplete release, while the release from the corresponding control tablet (without any disintegrant) and a tablet with pre-gelatinized starch as the disintegrant showed almost complete release [3].

Superdisintegrant is a class of excipient which absorbs water by wicking or capillary action, swells to a large extent, induces hydrodynamic pressure in the tablet core thereby promoting disintegration [4]. They can also accelerate drug release from tablets due to production of finer particles exposing greater surface area for interaction with dissolution medium. Disintegrant action and efficiency may be influenced by the hydrophilicity of filler as in the case of cross-linked polyvinyl alcohol [5-6]. Lactose-based tablets containing 3% (w/w) Ac-di-sol disintegrated via surface erosion, and the formulation containing di-calcium phosphate anhydrous (13.7% w/w) manufactured by high shear wet granulation exhibited desired disintegration and release characteristics. There are reports in the literature of lactose or di-calcium phosphate dihydrate, being used as filler in tablet formulation using Ac-di-sol as superdisintegrant [7-9].Cross-linking in the structure of hydrophilic Ac-di-sol imparts water-insolubility and swell-ability by wicking without gelling, enabling it to act as a superdisintegrant. Moreover, Ac-di-sol is reported to aid in compressibility [10]. Tablet manufacture by direct compression necessitates incorporation of highly compactable microcrystalline cellulose, capable to undergo plastic deformation, in order to balance the brittle fracture induced by addition of di-calcium phosphate. Microcrystalline cellulose can also be used with lactose in the process of direct compression.

The aim of the present investigation is to study the effect of hygroscopicity and solubility of filler used in combination with superdisintegrant on the water absorption percentage, disintegration time and release kinetics of a model BCS Class II drug, Danazol, from solid dispersion tablets manufactured by direct compression. In the experimental work, soluble diluent, lactose and hygroscopic, insoluble diluent, di-calcium phosphate dihydrate, were combined with superdisintegrant, Ac-di-sol to produce tablets of Danazol solid dispersion.

MATERIALS AND METHODS

Materials

Danazol was obtained as a gift sample from the Serum Institute of India Ltd. Ac-di-sol was provided as a generous gift sample from Matrix Laboratories, Hyderabad. All other chemicals of analytical grade were purchased from Merck India Ltd. Fresh distilled water was used throughout the study.

Experimental

Preparation and Characterization of Danazol Solid Dispersion (DZ-SD)

The solid dispersion (Drug: PEG 6000 = 1: 2) was prepared by melting-solvent evaporation technique [11].

The drug content of the solid dispersion was determined by dissolving an amount equivalent to 2 mg of DZ in chloroform and measuring the absorbance of the solution at 286 nm using the UV–Visible spectrophotometer (Shimadzu UV-1700, Pharm Spec) [12]. The percentage of drug present in a particular formulation was calculated from the calibration curve of Danazol in chloroform. For solubility determination, an amount of solid dispersion containing Danazol equivalent to 50 mg of was dispersed in 50 ml of distilled water, shaken at 37 ± 0.5°C for 24 hrs. The suspension was filtered through a 0.45µm membrane filter and the filtrate was analyzed spectrophotometrically at 284 nm.

In vitro dissolution study

In vitro drug dissolution of DZ - SD 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 water containing 0.02% wt./vol. Tween 80)] in the dissolution flask was stirred at 75 rpm and maintained at 37 ± 0.5°C. Solid dispersion containing drug equivalent to 30mg. was addedto the medium [13]. Aliquots of 10 ml were taken at 30min-intervals for 300mins. At each sampling point, the dissolution medium in the vessel was replenished with the same volume of fresh medium. Aliquot was filtered and analyzed spectrophotometrically at 284 nm. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2 = 0.988). All the tests were done in triplicate.

Analysis of in vitro Dissolution Data

The mean in vitro drug release data (n = 3) were fitted to two kinetic models (first order and Hixon-Crowell) to identify the kinetics of drug dissolution pattern in solid dispersions by comparison of the relative magnitudes of the coefficient of determination (r^2) for each model. The Mean Dissolution Time (MDT) for pure drug and its solid dispersion has been determined with the help of the following equation (Eqn. 1) [14].

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

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 dissolved in the time interval between t_{j-1} and t_j.

The Dissolution Efficiency (DE, %) was used to evaluate the dissolution performance of the SD in comparison to pure drug. DE was calculated as follows (Eqn. 2) [15].

$$\text{Percent Dissolution Efficiancy (\% DE)} = \frac{\int_0^t Y \, dt}{Y_{100} \, t} \times 100 \qquad \ldots\ldots(2)$$

Where y is the percentage of drug dissolved at time t. DE was determined for the entire time period of dissolution study.

Other release parameters used to characterize and compare dissolution profiles include dissolved percentage (DP) at 60 and 240 minutes and time taken for a fixed percentage of drug to be released [$t_{y\%}$ (mins)]. The results are displayed in **Table 1.**

Table 1: Characterisation of Danazol Solid Dispersion (DZ-SD) (Drug : PEG 6000 =1:2) by melting-solvent evaporation method (Values in the parentheses indicate mean ± standard deviation; n=3).

Parameters	DZ	DZ - SD
Equilibrium Solubility (µg/ml) in distilled water at 25^{0}C (24 h)	24.17 ± 4.68	87.44 ± 12.01
DATA FROM DSC STUDY		
Melting point (^{0}C)	222.19	67.81
Δ H_f (J/g)	221.62	175.07
DISSOLUTION STUDY PARAMETERS FOR DRUG AND BINARY SYSTEM		
DP$_{60mins}$	9.56 ± 0.2374	36.19 ± 0.1624
DP$_{240mins}$	18.21 ± 0.2865	61.5 ± 0.1324
t$_{50\%}$ (mins.)	>300	158
DE (%)	13.32	47.47
MDT (mins.)	108.39	98.58
Kinetics	First Order (r^2 = 0.997)	Hixon – Crowell (r^2 = 0.967)

Statistical Analysis

The data were compared using a Student's *t* test of the two samples assuming equal variances to evaluate the differences. The significance level ($\alpha = 0.05$) was based on the 95% probability value ($p < 0.05$).

Instrumental methods of analysis of DZ-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 carrier and solid dispersion (DZ-SD) were mixed thoroughly with potassium bromide, an infrared transparent matrix, to prepare the KBr discs by compressing the powders in a hydraulic press at a pressure of 1,000 psig. 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 for 2–5 mg samples of pure Danazol (DZ), Polyethylene glycol (PEG) 6000 and Solid Dispersion (DZ-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 Danazol, PEG 6000 and solid dispersion 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°.

Preparation and Evaluation of Solid Dispersion Tablets

Four batches of tablets were prepared using either lactose (L) or di-calcium phosphate dihydrate (D) as fillers (36% w/w); magnesium stearate and talc as lubricant. Superdisintegrant, Ac-Di- Sol was added to the formulae, DZ-SDT(L)-2 and DZ-SDT(D)-2 at 8 % w/w of tablet weight.(**Table 2**) Round, flat-faced tablets corresponding to 180 mg total weight with 30 mg of Danazol present as solid dispersion were prepared by direct compression using 8mm punch with 10-station Minipress single punch tablet machine **(**Karnavati Engg. Pvt. Ltd., India).

Table 2: Composition of various batches of Danazol Solid Dispersion Tablets (DZ-SDT) by direct compression.

Ingredients	Formulation code (% w/w)			
	DZ – SDT(L)-1	DZ – SDT(D)-1	DZ – SDT(L)-2	DZ - SDT(D)-2
Solid dispersion	45	45	45	45
Lactose(L)	36	-	36	-
Di-calcium phosphate dihydrate(D)	-	36	-	36
Microcrystalline cellulose	18.6	18.6	10.6	10.6
Ac-di-sol(ADS)	-	-	8	8
Magnesium stearate	0.3	0.3	0.3	0.3
Talc	0.1	0.1	0.1	0.1
Total weight(mg)	180	180	180	180

Tablets of all the batches weighed around 180 mg ± 5% and contained 27-28 mg of Danazol. The tablet shape, size, thickness and hardness were held constant for all the batches. Percentage loss in weight due to friability for the formulations was within the pharmacopoeial specifications. No tablet was chipped, cracked, split or broken.

Water absorption percentage

A piece of tissue paper folded twice was kept in a culture dish. A tablet was placed on the paper and water (maintained at $37^{o}C$) was added drop wise for a definite time interval. The water absorption(WAP) was calculated from the difference in weight of tablet following water uptake and initial weight of tablet and expressed as percentage using the following equation (Eqn. 3)[16]. The experiments were repeated thrice.

$$WAP = \frac{W_b - W_a}{Time} \times 100$$

(3)

In vitro disintegration time

Disintegration time for the tablets was determined using USP disintegration apparatus with water (900 ml at 37°C) as the disintegrating medium.

In vitro dissolution study

In vitro drug dissolution of the tablet batches were carried out as before by placing one tablet from each batch in the dissolution apparatus. Dissolution studies were carried out for 30 mins. Aliquots of 10 ml were taken at intervals of 2, 4, 6, 8, 10, 20, 25 and 30 mins, the dissolution medium in the vessel was replenished with the same volume of fresh medium. Aliquot was filtered and analyzed spectrophotometrically at 284 nm. All the tests were done in triplicate.

Analysis of in vitro Dissolution Data

The mean in vitro drug release data (n = 3) were fitted to different kinetic models (first order, Higuchi and Hixon-Crowell) and the best-fit model was selected on the basis of the value of the coefficient of determination (r^2) for each model. All the data were statistically analysed. Drug release profiles were also evaluated on the basis of Mean Dissolution Time (MDT), Dissolution Efficiency (DE, %) and $t_{y\%}$ as before. DE was determined for the entire time period of release study for each batch. The results in terms of MDT, DE, and release kinetics are presented in **Table 3**.

Table 3: Disintegration and dissolution test parameters for different batches of Danazol Solid Dispersion Tablets.
(Values in the parentheses indicate mean ± standard deviation; n=3).

Formulation code / Parameters		DZ – SDT (L) - 1	DZ – SDT (L) - 2	DZ – SDT (D) - 1	DZ – SDT (D) - 2
Water Absorption Percentage (WAP)		48.38 ± 0.0276	60.15 + 0.0234	40.85 ± 0.0276	52.83 ± 0.0273
DT (sec.)		524 ± 0.0547	311.66 + 0.0234	252 ± 0.0497	225 ± 0.0740
$t_{60\%}$(mins.)		> 30 mins.	> 30 mins.	> 30 mins.	8.2 mins.
DE (%)		21.41	22.92	22.76	39.45
MDT (mins.)		17.27	17.41	4.0	3.51
Kinetics (r^2)	1st order	0.998	0.993	0.971	0.989
	Hixon - Crowell	0.943	0.956	0.977	0.972
	Higuchi	0.998	0.986	0.964	0.993

RESULTS AND DISCUSSION

Characterization of Pure Danazol in DZ-SD

The drug content (n=6) of the solid dispersion 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, Danazol by almost 3.5-fold(**Table 1**).

FTIR spectrum of Danazol showed a peak at 3510.64 cm^{-1}, which corresponds to O-H stretching of the hydroxyl group at the 17 position. This peak remained unaffected in the solid dispersion indicating absence of any chemical interaction due to melting-solvent evaporation technique[17](**Figure 1**). **Figure 2** shows the cumulative percent drug dissolved from solid dispersions as also pure drug. The dissolution rate of SD expressed by $t_{50\%}$ ($t_{50\%}$ = 158 minutes) and MDT of 98.58 mins was faster than that of pure drug alone having $t_{50\%}$ > 300 minutes and MDT of 108.39mins. The dissolution of drug exhibited first-order kinetics whereas SD showed Hixon-Crowell kinetics.

The DSC thermograms for pure Danazol, PEG, and SD are shown in **Figure 3.** DZ showed a melting peak at 222.19 °C with an enthalpy of fusion (ΔH_f) of 221.62 J/g. SD showed complete absence of drug peak at 222.19°C but slight shifting of PEG peak to 67.81 °C. This complete absence of the drug peak and lower magnitude of ΔH_f indicates that drug is amorphous or is in a solid solution inside the PEG matrix. Extent of crystallinity of drug is an essential criterion determining solubility and dissolution rate of poorly water-soluble APIs. The solid dispersion showed the characteristic diffraction peaks of danazol at 15.8, 17.18, and 19.0° (2θ) which were suppressed whereas characteristic peaks of PEG peaks were reduced in intensity(**Figure 3**). This indicates that danazol contained in SD existed in an amorphous state or partly crystalline state[18]. Thus, it can be concluded that the drug might have lost its crystalline structure partially and has been converted into amorphous or microcrystalline state in SD.
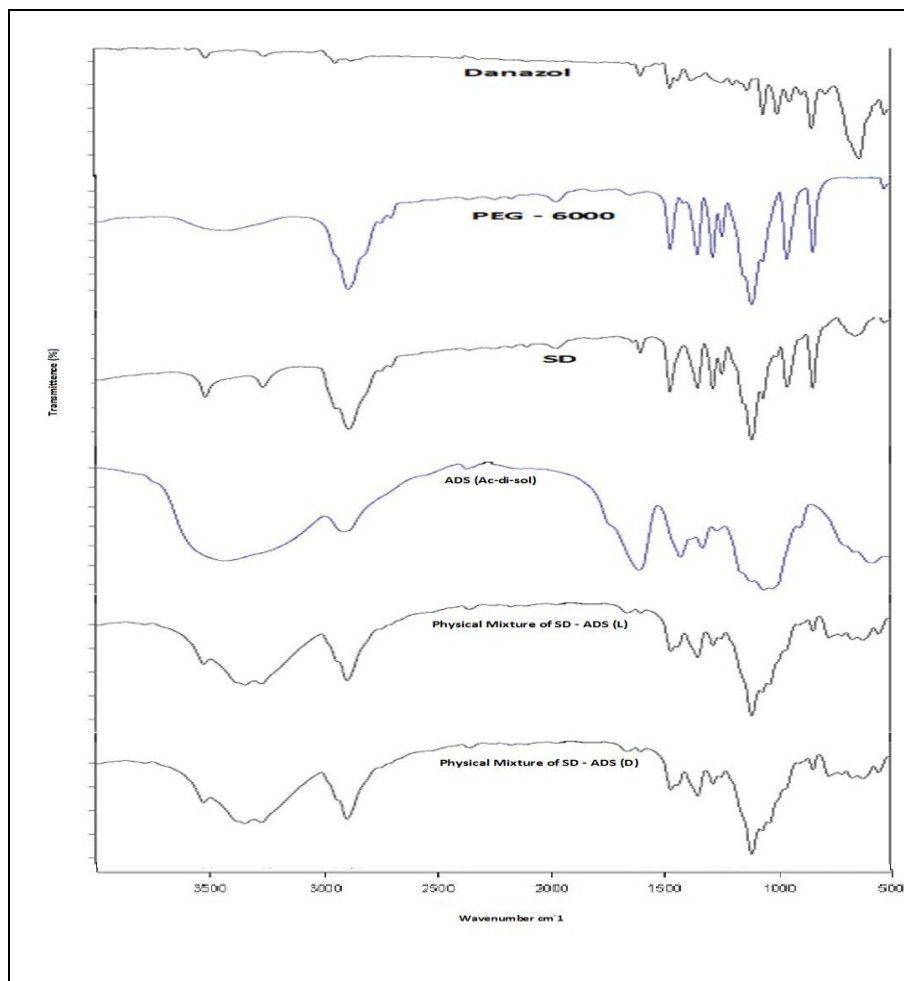
Figure 1: FTIR spectra of Danazol, PEG 6000, DZ-SD, Ac-di-sol, Physical mixture of SD-ADS-L and Physical mixture of SD-ADS-D.
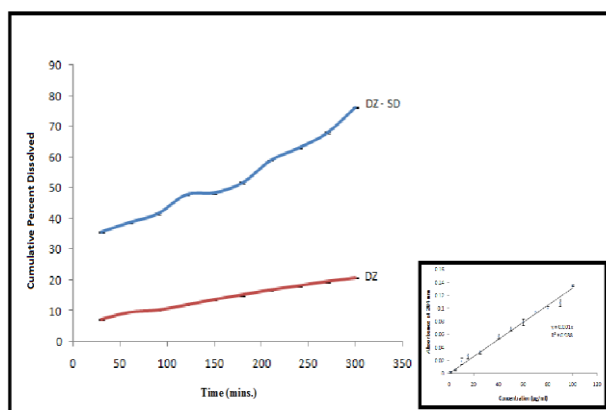

Figure 2: Comparative dissolution profiles of the pure drug, danazol (DZ) and its solid dispersion (DZ-SD) in distilled water containing 0.02% wt/vol Tween 80. Inset shows the standard curve of danazol in the medium at 284nm.(Values in the parentheses indicate mean ± standard deviation; n=3).
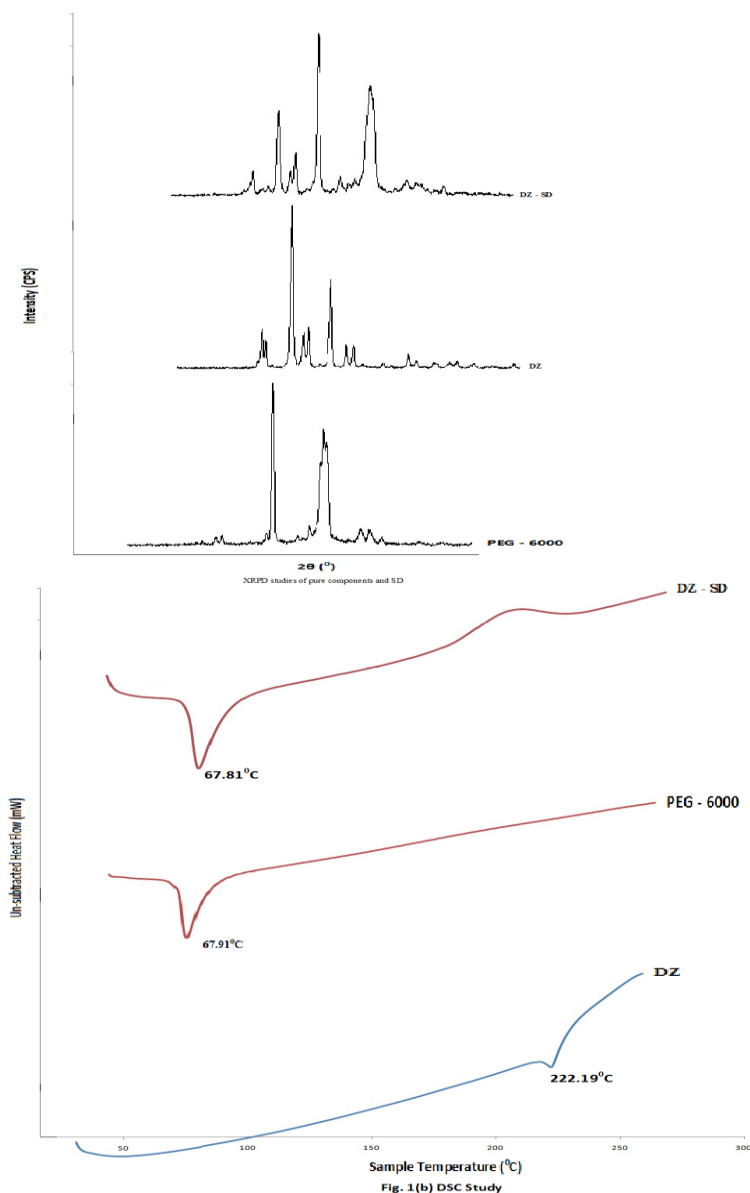
Figure 3: Upper: Overlaid diffractograms of Danazol, PEG 6000 and DZ-SD; Lower: Overlaid DSC thermograms of Danazol, PEG 6000 and DZ-SD.

Pre-compression powder behaviour

In the FTIR spectra of powder mixtures prior to compression, the characteristic peaks of both PEG 6000 and danazol could be observed (**Figure 3**). Pre-compression powder possessed fair to passable flow property since the angle of repose was found to lie between 22.68-26.61°, Compressibility index varied between 15.73 and 18.92% and Hausner ratio in the range of 1.14 to 1.19.

Evaluation of Danazol Solid Dispersion Tablets (DZ-SDT)

Water absorption percentage and Disintegration time

High hydrophilicity of Ac-Di-Sol resulted in higher water absorption of 60% and 52% into the tablet batches DZ-SDT(L)-2 and DZ-SDT(D)-2 respectively. Fibrous nature of the superdisintegrant allowed intra-particulate and extra-particulate wicking of water[19-20]. Previous studies indicate that superdisintegrants exert a significant effect on disintegration time in an insoluble system comprising of di-calcium phosphate dihydrate, than in a soluble or partially soluble system. It has been observed here that disintegration time of dicalcium phosphate-based batches is significantly lower than lactose-based formulations **(Table 3)**. **Figure 4** shows the main effects of tablet excipients on water absorption percentage and disintegration time.
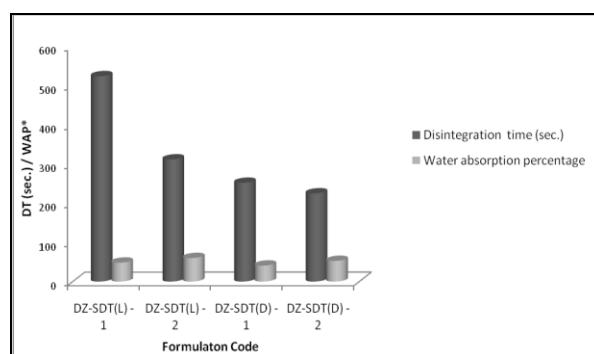

Figure 4: Effect of filler and superdisintegrant on water absorption percentage (WAP) and disintegration time (DT) of Danazol Solid Dispersion Tablets.

In vitro dissolution studies

Figure 5 depicts the comparative mean dissolution profiles of the four batches of Danazol Solid Dispersion Tablets to determine the effect of filler on superdisintegrant performance with respect to drug release and release kinetics. It was evident from the dissolution data (**Table 3**) that $t_{60\%}$ was reduced by more than 3-fold in DZ – SDT(D) - 2. Comparison of the values of % DE and MDT revealed that DZ-SDT (D) - 2 is better than DZ - SDT(D) - 1, whereas, the performances of the lactose-based formulations, DZ-SDT (L)-1 and DZ – SDT (L) - 2 are poor and almost similar as determined by statistically insignificant differences with Student's t-test. DZ – SDT (D) - 2 showed statistically significant different behavior. Disparity in the water absorption percentage and release parameters between lactose- and DCP-based batches indicate that incorporation of soluble lactose competes for the locally available water thus inhibiting the action of disintegrant and increases the viscosity of penetrating fluid leading to rapid widening of pores of tablet, through which drug transport occurs slowly. This reduces the effectiveness of Ac-di-sol in lactose-based formulations during disintegration as well as dissolution[21-22]. Moreover, incorporation of lactose causes mono-exponential drug release following first-order kinetics which is changed to Higuchi kinetics in case of DZ - SDT(D) -2. Thus, combination of di-calcium phosphate dihydrate and Ac-di-sol

imparts a matrix characteristic to tablet of Danazol solid dispersion which absorbs water sufficiently, promotes quite rapid disintegration and releases 60% of drug within 8 mins and results in 6-fold lowering in Mean Dissolution Time value.
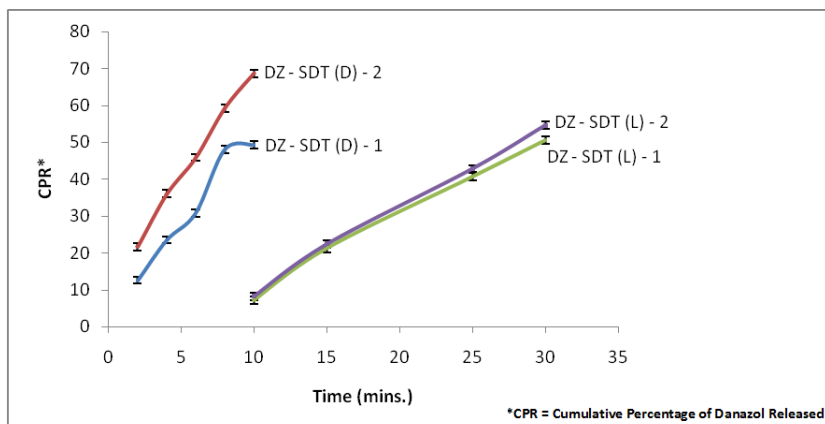

Figure 5: Comparative dissolution profiles of various batches of DZ-SDTs in distilled water containing 0.02% wt/vol Tween 80. (Values in the parentheses indicate mean ± standard deviation; n=3).

CONCLUSION

The present study clearly demonstrated that the aqueous solubility of a model BCS Class II drug, Danazol as well as its dissolution profile can be substantially improved with solid dispersion. In tablets prepared from solid dispersions by direct compression method, soluble filler actually hinders the development of disintegration force thereby reducing the effectiveness of Ac-di-sol and it tends to dissolve. However, once the tablet disintegrates, due to the addition of low concentration of superdisintegrant, insoluble filler improves drug release characteristics from the tablet matrix thus formed. Therefore, proper selection of filler in combination with superdisintegrant is absolutely necessary to achieve desired disintegration characteristics and release profile of drug from solid dispersion tablets manufactured by direct compression.

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