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Formulation and Optimization of Solid Dispersion Tablets of Albendazole using Response Surface Methodology

Setia Anupama[1]*, Goyal Surinder[2], Shrivastva Birendra[3], Goyal N[1]

[1]Rajendra Institute of Technology and Sciences, Sirsa, Haryana, India
[2]Vidyasagar Institute of Pharmacy, Alhupur, Punjab, India
[3]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan

ABSTRACT

Albendazole is a benzimidazole drug having anthelminthic and antifungal activity. The major problem with this drug is its very low solubility in biological fluids, which results in poor bioavailability after oral administration. Therefore, solid dispersions of Albendazole with hydrophilic polymers Gelucire 44/14and PEG 8000 were prepared by melting method and evaluated with a view to increase its water solubility and hence to improve the dissolution profile. Solid dispersions were prepared using 4^2 experimental design and evaluated for dissolution studies. Solid dispersions showing maximum dissolution were selected on the basis of data analysis and were formulated into tablet. The tablets were exposed to routine quality control tests like hardness, friability, weight variation and disintegration. The dissolution profiles of these formulations were studied in 0.1 N HCl and compared with marketed tablet .At the end of 60 min, formulation SDT17 gave the highest drug release that is 97.2. %, followed by SDT 12 (96.2%) whereas marketed tablet39.33% .The present study conclusively demonstrated that, dissolution profile of albendazole was significantly improved by preparing solid dispersion with hydrophilic polymers.

Key words: Albendazole, solid dispersions, Gelucire 44/14, PEG 8000

Corresponding author
Email: setia.ani123@gmail.com

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INTRODUCTION

ABZ is a benzimidazole carbamate with a broad anti-parasitic spectrum [1]. ABZ was first approved for treatment of helminth infections in sheep in 1977, and subsequently approved for human use in 1983 [2]. In general, most ascariasis, trichuriasis, enterobiasis and hookworm infections can be successfully treated with single dose ABZ and strongyloidiasis with multiple doses of ABZ. ABZ has also used in the treatment of capillariasis, gnathostomiasis, and trichostrongyliasis, the cestode infections hydatidosis, taeniasis and neurocysticercosis, and the tissue nematodes cutaneous larval migrans, toxicariasis, trichinosis and filariasis (in combination with other anthelmintics). ABZ has also been used successfully against mixed infections [2-4]. The biggest problem of albendazole is its low and erratic availability as a result of its low aqueous solubility.

Enhancement of bioavailability of hydrophobic drugs is one of the major challenges in drug development. Of the plethora of pharmaceutical technologies available to address this issue viz. micronisation, the use of surfactants and the formation of solid dispersions [5], solid dispersion is one of the useful methods for the dispersion of the drug into an inert, hydrophilic polymer matrix [6,7]. Solid dispersions display an enhanced solubility of drug because of the conversion of the drug's crystal lattice into an amorphous form, particle size reduction and increased wettability by the hydrophilic polymer. Therefore, the same pharmacological results can be obtained from a reduced amount of drug given to the patient.

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability of a range of hydrophobic drugs. Although a large number of studies have been published but the mechanisms underpinning the observed enhancement of the rate of drug release are not yet understood.

The use of solid dispersions as an effective source of improving the dissolution rate of poorly soluble drugs has been well studied and demonstrated [6,8,9].

PEG and gelucire are among the several carriers which have been employed in preparing solid dispersions [10-14]. PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydrophilicity. Gelucire is a family of vehicles derived from the mixtures of mono- di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These are available with a range of properties depending on their hydrophilic-lipophilic balance (HLB) and melting point range (33–65 °C). They have a wide variety of applications in pharmaceutical formulations as the preparation of fast release and sustained release formulations [10-17].

The aim of the present study was to formulate solid dispersion tablets with PEG 8000 and Gelucire 44/14 at different ratios and to optimize the batch based on RSM.

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MATERIALS AND METHODS

Preparation of Physical Mixture

Physical mixtures (PMs) of ABZ with PEG 8000 or Gelucire 44/14 or combination, at different ratios as per table 2, were prepared by blending them by trituration for 10 min followed by sieving (500 µm).

Preparation of solid dispersion

Solid dispersions (SDs) at various weight ratios were prepared by melting method. ABZ was added to the molten base comprising PEG 8000 or Gelucire 44/14. The blend was heated 10 ºC above the melting point of each carrier for 5 minutes with continuous stirring. The systems were placed in a freezer at -20 ºC for 24 h. The mass was crushed, ground gently with a mortar and pestle and passed through 500-µm sieve.

Experimental Design

A 4^2 full factorial design was employed to systematically study the joint influence of the effect of independent variables X1 and X2 on the dependent variables (Table 1) In this design, 2 factors are evaluated, each at 4levels, and experimental trials are performed at all 16 possible combinations.. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X21 and X22) are included to investigate nonlinearity. The composition of the factorial design batches are shown in Table 2. It also shows actual values of independent variables and levels of independent factors.

Table 1: Level and Factors for factorial design

FACTORS	LEVELS			
	0	1	2	3
X_1- Amount of Gelucire 44/14(mg)	0 mg	100mg	200 mg	300mg
X_2- Amount of 50/13 (mg)	0 mg	100mg	200 mg	300mg

Table 2: Four Level Factorial design

Batch No. Physical Mixtures)	Batch No. (solid dispersions)	Coded value		Actual value (in mg)		
		Gelucire 44/14	PEG 8000	Drug	Gelucire 44/14	PEG 8000
PM1	SD1	0	0	200	0	0
PM2	SD2	1	0	200	100	0
PM3	SD3	2	0	200	200	0
PM4	SD4	3	0	200	300	0
PM5	SD5	0	1	200	0	100

PM6	SD6	0	2	200	0	200
PM7	SD7	0	3	200	0	300
PM8	SD8	1	1	200	100	100
PM9	SD9	1	2	200	100	200
PM10	SD10	1	3	200	100	300
PM11	SD11	2	1	200	200	100
PM12	SD12	2	2	200	200	200
PM13	SD13	2	3	200	200	300
PM14	SD14	3	1	200	300	100
PM15	SD15	3	2	200	300	200
PM16	SD16	3	3	200	300	300
PM17	SD17	--	--	200	272.3	214.51

Evaluation of Solid Dispersion

Content Uniformity

Solid dispersion containing an equivalent amount of 4mg of albendazole was added to a volumetric flask containing acidified methanol. The flask was shaken for 10 min and final volume was made up using buffer pH 6.8 & filtered through 0.45 µm membrane filters. The sample was diluted and analyzed spectrophotometrically at 291 nm using (Lab India UV3000+) UV-Visible Spectrophotometric method.

In vitro Dissolution studies

Drug dissolution studies was carried out using USP dissolution apparatus 2 using a paddle at a speed of 100 rpm with 900 mL of 0.1 M HCl as dissolution medium at 37^0C. Solid dispersion powders containing 100 mg of albendazole were dispersed on the surface of the dissolution medium and the time was recorded. At intervals, 5 mL samples were withdrawn through a filter. The amount of released drug was determined by UV spectrophotometer at 291 nm

Data Analysis

The response surface methodology is a collection of mathematical and statistical techniques used for modeling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response. The run or formulation, which are designed based on factorial design are evaluated for the response. The response values are subjected to multiple regressions analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis are T10 min (cumulative drug release in 10 minutes) & T60 min (cumulative drug release in 60 minutes) The multiple regression analysis was done using DE-SIGN EXPERT 8.0.1 (STAT-EASE) demo version software, which specially meant for this optimization process. Analysis of data was carried out using ANOVA and the individual parameter was evaluated with

F-test. Using the regression coefficient of factor, the polynomial equation for the each response is generated [18].

Formulations Optimization

The computation for optimized formulation was carried using software, DESIGN EXPERT 8.0.1 (STAT-EASE). The response variable considered for optimization were T10 min (cumulative drug release in 10 minutes) & T60 min (cumulative drug release in 60 minutes)The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). Constraints for responses and factors are shown in Table 3. By utilizing DESIGN EXPERT 8.0.1 (STAT-EASE) demo version software, we got one solution for optimized formulation**.** The optimized formulation is prepared and evaluated for T10min & T60 min.

Table 3: Constraints for responses and factors

Name	Goal	Lower Limit	Upper Limit
Amt. of Gelucire 44/14	In range	0 mg	300 mg
Amt. of PEG 8000	In range	0 mg	300 mg
T10 min	Maximize	0	75
T60 min	Maximize	0	100

Characterization of Optimized solid dispersions

Differential Scanning Calorimetric

Thermal properties of the untreated drug and the prepared solid dispersion were analyzed by DSC (TA Instruments, USA, and Model: Q10). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 ^{o}C at a heating rate of 10 ^{o}C/ min, using nitrogen as blanket gas.

X-ray diffraction studies

Powder X-ray diffraction pattern were traced employing X-ray diffractometer (XPERT PRO, PAN analytical, India) for the samples, using Ni filtered CuK (α) radiation, a voltage of 45 kV, a current of 20 mA. The sample was analyzed over 2θ range of 0-50^{o} with scan step size of 0.0170^{o} (2θ) and scan step time 20 s.

Scanning Electron Microscopy

Sample of pure drug, carrier and the solid dispersion formulation were mounted onto the stubs using double-sided adhesive tape and then coated with gold palladium alloy (150-200 A^{o}) using fine coat ion sputter (Joel, fine coat ion sputter, JSM6100). The samples were subsequently analyzed under the scanning electron microscopy (SEM) for external morphology.

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Preparation and In-Vitro Evaluation of Tablet

The optimized Solid dispersion prepared as described previously were used for preparation of tablets which are equivalent to 200 mg of the ABZ. The solid mixtures were mixed well with talc (1.5% w/w) and magnesium stearate (1.5% w/w). The mixture of solid mixtures powder and excipients weighing the equivalent of 825 mg was compressed into tablet using a 13mm flat faced punch on a Cadmach single punch tablet machine (Table 4). Each time, tablets of 50 were prepared for all the batches. Tablets were characterized for ABZ content, dissolution rate (Veego), friability (Roche Friabilator), hardness, weight variation, thickness and diameter. The dissolution rate of the optimized formulation was compared with the dissolution rate of marketed tablet.

Table 4: Formula for compression of tablets of solid dispersions of selected batches

Batch No. (solid dispersions)	Drug (mg)	Gelucire 44/14 (mg)	PEG 8000 (mg)	M C C (mg)	Talc (mg)	Mg Stearate (mg)	Total weight of tablet (mg)
SDT12	200	200	200	200	12.5	12.5	825
SDT17	200	300	300	0	12.5	12.5	825

RESULTS AND DISCUSSION

In Vitro Drug Release Studies of solid dispersions

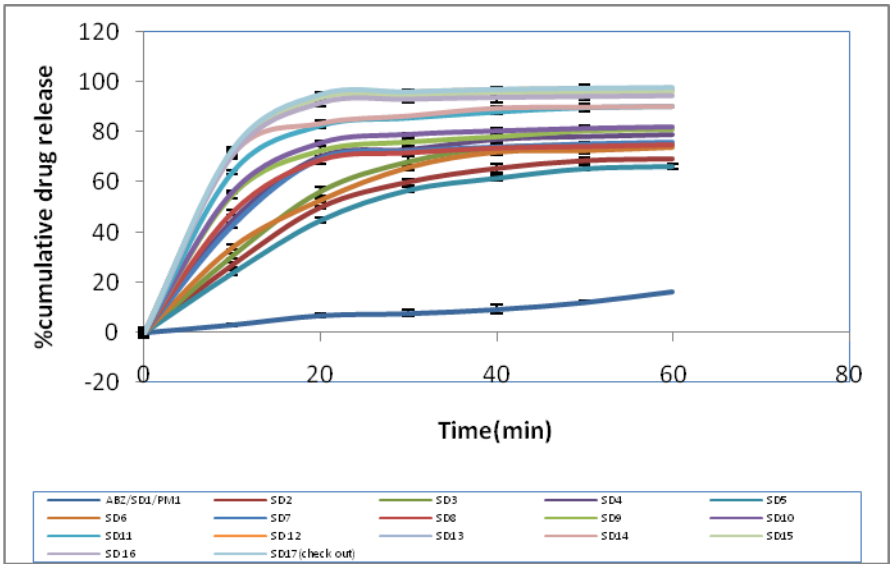

Figure 1: Dissolution profiles for pure ABZ and Solid Dispersions.

Results of in vitro drug release from different formulations of solid dispersions shown in figure 1. In vitro dissolution studies showed that value of % age cumulative drug release for

pure drug (16.3%) was increased to 36.9% in PMs and up to 97.2% in SDs. The release values revealed more dissolution improvement of ABZ in SD with Gelucire 44/14 than SD with PEG 8000 at same carrier concentration among the batches containing individual polymer. However when both the polymers were used in combination, there were higher dissolution (up to 97.2%) as compared to batch containing single polymers (up to 79%).

During dissolution experiments it was noticed that the solid dispersion powders sank immediately to the bottom of the dissolution vessel, whereas the pure drug floated for a long period on the surface of the dissolution medium. As a consequence, the solid dispersion remains in contact with water for a longer time of period leading to an improvement in the drug dissolution rate. We postulated that the 'wetted' surface of the polymer increases in the solid dispersion and drug release is thus improved. As shown in figure 1, an increase in the concentration of the polymer increased the drug dissolution rate, which can be explained on the basis of the wetting and solubilizing effect of the carrier.

Data Analysis

The responses were recorded and analysis of data was carried out using ANOVA in (STAT- EASE). The individual parameter was evaluated using F-test and a polynomial equation for each response was generated using MLRA. The design and response summary data are represented in table 5.

Table 5: Design Layout of Factorial Design and Summary of Experimental Results

Batch No. (solid dispersions)	Factors		Responses	
	Gelucire 44/14 (mg)	PEG 8000 (mg)	T10 min %age	T60 min %age
SD1	0.00	0.00	3.1	16.3
SD2	100.00	0.00	26.9	69.1
SD3	200.00	0.00	30.6	75
SD4	300.00	0.00	44.8	79.1
SD5	0.00	100.00	23.7	66.4
SD6	0.00	200.00	33.9	73.8
SD7	0.00	300.00	42.7	76
SD8	100.00	100.00	47.9	74.9
SD9	100.00	200.00	54.7	80.8
SD10	100.00	300.00	55.9	81.9
SD11	200.00	100.00	63.9	90.2
SD12	200.00	200.00	72.3	97.2
SD13	200.00	300.00	72.1	96.9
SD14	300.00	100.00	70.8	90
SD15	300.00	200.00	72.2	96.2
SD16	300.00	300.00	70.6	94.3
SD17	272.93	214.51	75.0	97.7

Response: T10 min (Y1)

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In ANOVA table 6, values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X1, X2, X1X2 are significant model terms.

Table 6: Analysis of Variance (ANOVA) of Dependent Variable (T10 min %age)

Source	Sum of Squares	df	Mean Square	F Value	p- value Prob > F
Model	6532.71	5	1306.54	70.21	< 0.0001
X1-gelucire	3360.53	1	3360.53	180.59	< 0.0001
X2-peg 8000	2359.88	1	2359.88	126.82	< 0.0001
X1X2	31.08	1	31.08	1.67	0.2253
$X1^2$	244.14	1	244.14	13.12	0.0047
$X2^2$	537.08	1	537.08	28.86	0.0003
Residual	186.09	10	18.61		
Cor Total	6718.79	15			

Final Equation in Terms of Coded Factors:

$$T10 = +61.26 +19.44 * X1 +16.29 * X2 -2.51 * X1 * X2 -8.79 * X1^2 -13.04 * X2^2$$

Response: T60 min (Y2)

In ANOVA table 7, Values of "Prob > F" less than 0.0500 indicate model terms are significant.

Table 7: Analysis of Variance (ANOVA) of Dependent Variable (T60 min %age)

Source	Sum of Squares	df	Mean Square	F Value	p- value Prob > F
Model	5034.59	5	1006.92	15.26	0.0002
X1-gelucire	2353.37	1	2353.37	35.67	0.0001
X2-peg 8000	1577.98	1	1577.98	23.92	0.0006
X1X2	352.88	1	352.88	5.35	0.0433
$X1^2$	341.33	1	341.33	5.17	0.0462
$X2^2$	409.05	1	409.05	6.20	0.0320
Residual	659.82	10	65.98		
Cor Total	5694.41	15			

In this case X1, X2 are significant model terms.

Final Equation in Terms of Coded Factors:

$$T 60 = +90.72 +16.27 * X1 +13.32 * X2 -8.45 * X1 * X2 -10.39 * X1^2 -11.38 * X2^2$$

As the amount of gelucire 44/14 and PEG 8000 increased, T10 and T60, increased due to hydrophilic and solubilizing nature of polymers so when amount of polymers increases

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formulation dissolve quickly but as the amount of polymer increases beyond a certain limit the increase in drug release was almost negligible or started decreasing. The release values revealed more dissolution improvement in formulation with Gelucire 44/14 than that of with PEG 8000 at same carrier concentration among the batches containing individual polymer. However when both the polymers were used in combination, there were higher dissolution as compared to batch containing single polymers.

The relationship between the dependent and in-dependent variables was further elucidated using contour plots (Figure 2 and 3). Here, logically predecided to obtain the values of the T10 min and T60 min to 75% and 100% respectively from the formulated products. In contour plot only formulation SD12 showed T10 min and T60 min near to desired T10 min and T60 min (Figure 4). It was decided to obtain the values of the drug release up to 100% from the formulated products.

Exact amount of gelucire 44/14 and PEG 8000 for achieving desired response was found out from optimization.

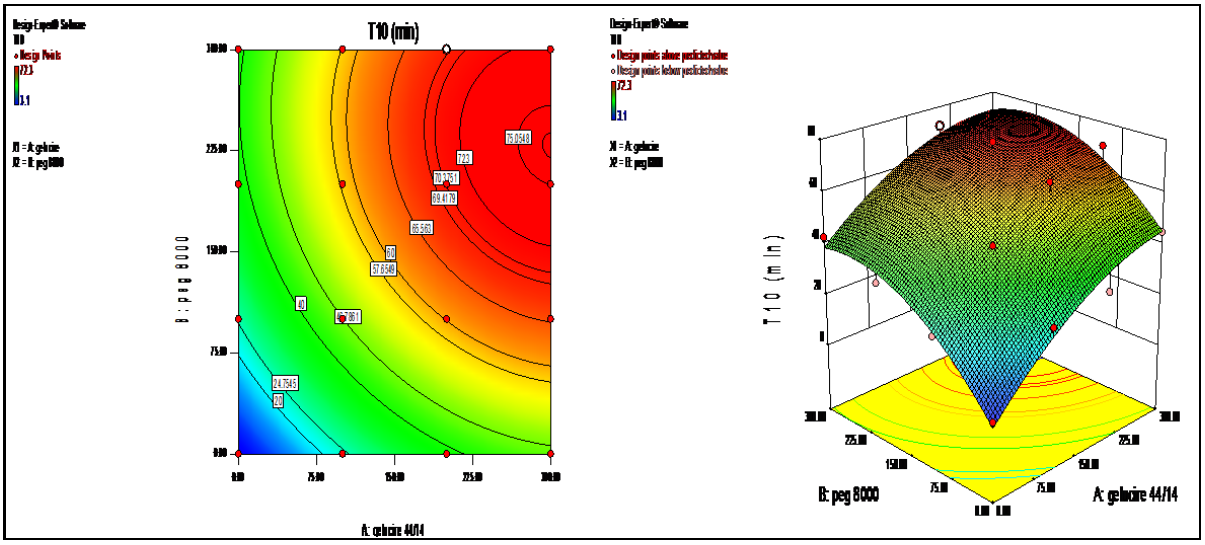

Figure 2: Surface and contour plots showing cumulative % release in first 10 min. of solid dispersions as a function of gelucire-44/14 and PEG 8000

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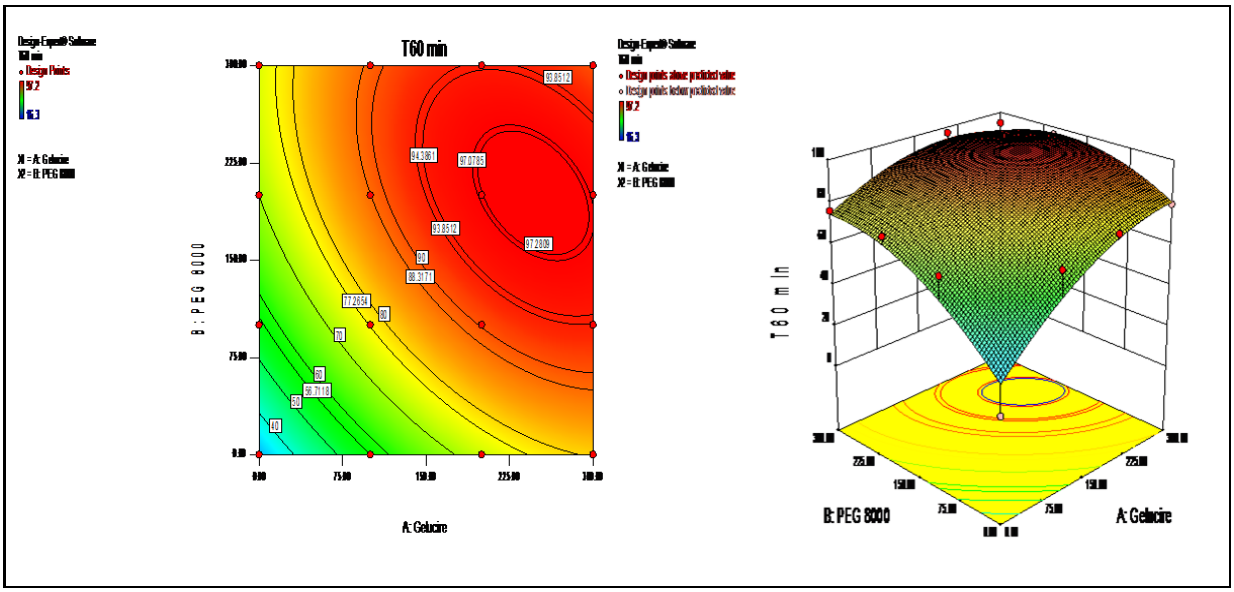

Figure 3: Surface and contour plots showing cumulative % release in first 60 min. of solid dispersions as a function of gelucire-44/14 and PEG 8000

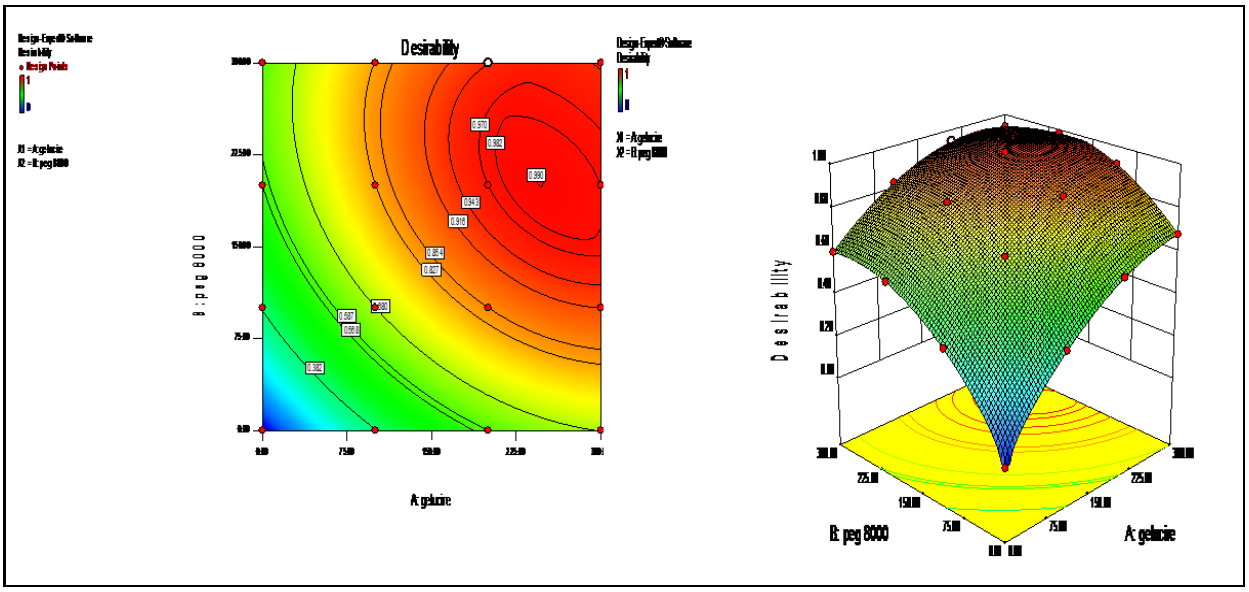

Figure 4: Surface and contour plots showing desirability of solid dispersions as a function of gelucire-44/14 and PEG 8000

Formulation Optimization and Validation

For the optimization of Solid dispersion formulations constraints was fixed for all factors and response (Table 3). Constraints were set in the range according to formulations, which would give desired response values. In the present study our aim was T10 min should be 75% and T60 min should be 100%. In optimization (Figure. 4) desirability .989 (maximum) indicated

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optimum formulation was achieved at 200 mg of gelucire 44/14 and 200 mg of PEG 8000. Validation of optimization technique done by preparing checkpoint batch and response were evaluated. The responses value observed in checkpoint batch was very near to optimized batch.

Differential Scanning Calorimetry

In a binary solid system, if the drug and polymer are soluble in common solvent, it leads to changes in the state of the drug as well as the polymer. Melting point of a crystalline molecule is higher than amorphous form, which can be concluded with the help of DSC of the formulations.

The DSC curve of Albendazole showing a sharp endothermic peak at 210.30^{o}C corresponding to its melting point, indicating its crystalline nature (Figure 5).

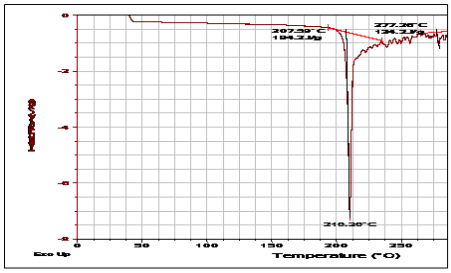

Figure 5: DSC Thermogram of drug (albendazole)

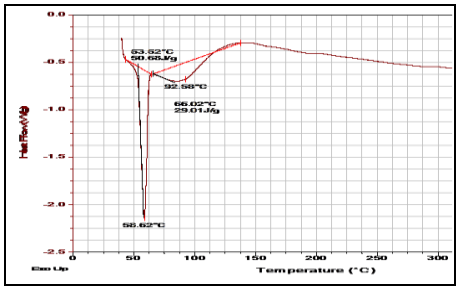

Figure 6: DSC Thermograms of batch SD17

The absence of ABZ melting peak and the presence of one exothermic peak in SD (Figure 6) suggest that ABZ was completely soluble in the liquid phase of the polymer or the absence of a crystalline form of ABZ. The exothermic peak might be due to crystallization above Tg (glass transition temperature). The molecular motion of amorphous solids depends on temperature. The kinetic energy of amorphous solids increases significantly as the temperature gets close to Tg. Due to the thermodynamic instability of amorphous solids, compared to the crystalline state; spontaneous crystallization is always possible as soon as molecular mobility is above the threshold of nucleation. . Absence of an endothermic peak of drug in SDs has also been reported by other researchers. It is speculated that ABZ dissolved in molten PEG 8000 and

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Gelucire 44/14 during the DSC measurement, and that only one endothermic peak at 63.4 °C or below that corresponding to melting of PEG 8000 & Gelucire 44/14 was observed.

X-ray diffraction studies

XRD Spectra of Albendazole and optimized formulation SD17 is shown in figure 7 & 8. The crystalline peaks located at 7.01º, 11.22º, 13.83º, 17.87º, 19.50º, 20.71º, 22.10º, 27.10º, and 28.16º (2 θ) corresponding to albendazole crystals were observed in figure 7 owing to the crystalline nature of drug.

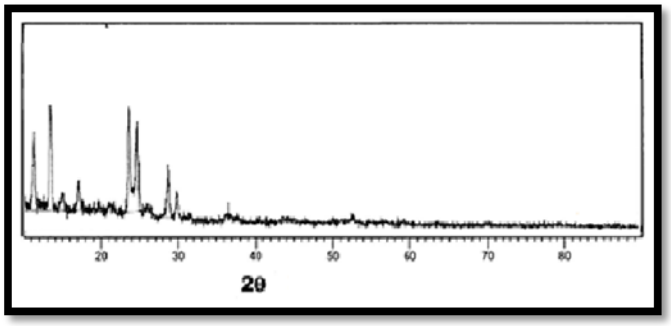

Figure 7: X-RD Diffractogram of the drug Albendazole

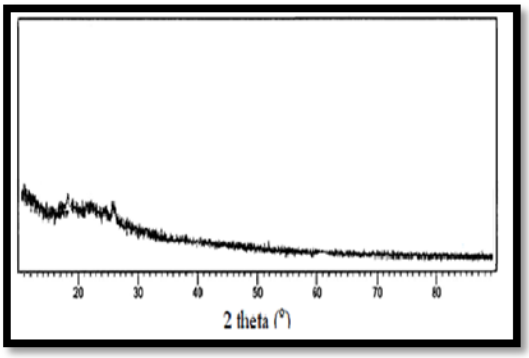

Figure 8: X-RD Diffractogram of SD17

The extent of crystallinity of the phases will influence the dissolution of the dosage forms. An amorphous or metastable form will dissolve at the fastest rate because of its higher internal energy and greater molecular motion which enhance thermodynamic properties relative to crystalline materials. XRD patterns of solid dispersion lacked the intense diffraction peaks associated with crystalline ABZ implying the solid dispersion contains amorphous drug. The relative reduction of diffraction intensity of albendazole in SD (Figure 8) suggests that the size of the crystals was reduced to that of microcrystals. The results of this study imply that albendazole is present in partially crystalline or microcrystalline form in the SDs which lead to its solubility enhancement.

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Scanning Electron Microscopy

SEM photographs for ABZ and optimized formulation are shown in figure 9 and 10 the drug crystals seemed to be smooth-surfaced, irregular in shape and size. The drug surface in Solid dispersion seems to be more porous in nature. Solid dispersion appeared as uniform and homogeneously mixed mass with wrinkled surface.Drug crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

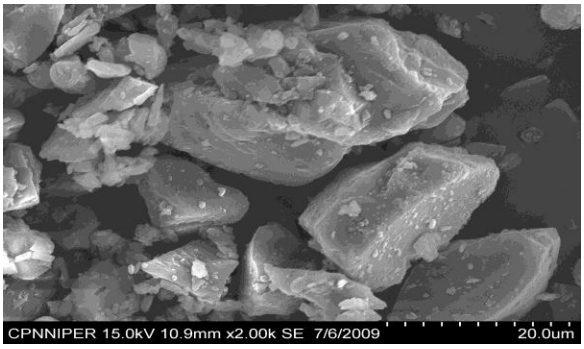

Figure 9: SEM Photograph of Albendazole

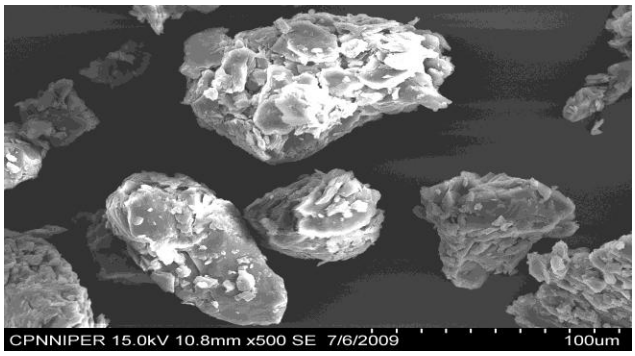

Figure 10: SEM Photograph of SD17

Solid state characterization studies revealed partial loss of drug crystallinity which can bring about significant changes in the drug dissolution rate. However, other factors like reduced particle size, surface area and closer contact between the hydrophilic carrier and the drug may also be influential in enhancing drug solubility and dissolution rate observed with solid dispersion particles.

In-Vitro Evaluation of Tablets

A significant improvement in the dissolution rate profile of the tablets of optimized formulation was obtained over the marketed tablets (Figure. 11). The ABZ content, hardness, friability,

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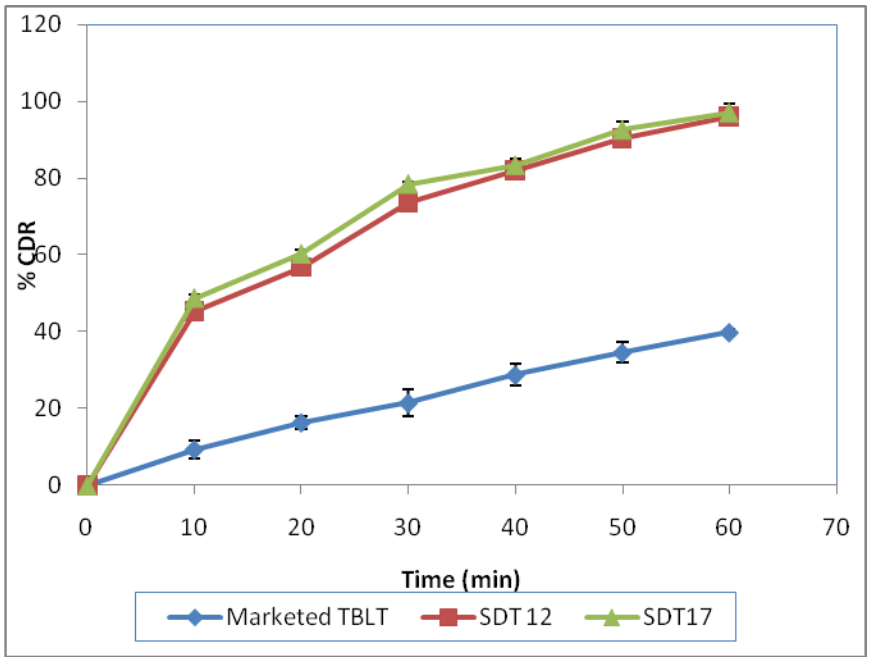

Figure 11: Dissolution profiles of optimized solid dispersion tablets and marketed tablets

Average weight, thickness, and diameter of the tablets were determined and the values are shown in table 8.

Table 8: Post-Compression Parameters for Solid dispersion Tablets

S.No.	Batch Code	Thickness (mm)	Diameter (mm)	Weight Variation (mg)±S.D	Hardness (kg/cm^2) ±S.D	Friability (%)	Disintegration Time(min.) ±S.D	Drug Content (%)
1.	SDT 12	3.13±0.32	12.7±0.43	824±4.2	4.2±0.7	0.48±0.05	8.1 ±0.34	98.6±0.7
2.	SDT17	3.16±0.17	13.0± 0.40	822±3.9	3.3±0.3	0.28±0.06	9.4±0.32	99.8±0.9

All values are expressed as mean ± S.D

CONCLUSION

The present study has shown that it is possible to increase the dissolution rate of poorly soluble drug albendazole by preparing solid dispersions with hydrophilic polymers like Gelucire 44/14&PEG 8000. The higher dissolution characteristics of solid dispersions may be due to solubilizing effect of carrier or crystallization of drug entrapped in molecular state by carrier. Based on the study it may be concluded that albendazole tablets prepared by solid dispersions with gelucire 44/14 & PEG 8000 could be considered as better choice for improving dissolution rate and bioavailability.

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