Evaluation of a Binary Carrier System for the Dissolution Enhancement of a High Dose Poorly Soluble Drug

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ABSTRACT

The role of two surface active carriers, Gelucire® 44/14 and Lutrol® F127, for improvement of solubility and dissolution of the high-dose, poorly water-soluble drug, albendazole, using solid dispersion approach was evaluated. The solubility of albendazole in solutions of the studied carriers and binary mixtures showed improvement, with solutions containing higher percentages of Lutrol® F127 as best solvents. Albendazole was then incorporated in matrices made of either carrier alone or mixtures of the two carriers at different ratios using a melting procedure. The resulting particles were compressed into tablets. In vitro dissolution of particles and tablets showed fast dissolution. Increased wettability of albendazole by the carriers and formation of partial solid solutions of it in the carrier system were shown to be the mechanisms of the improvement in its dissolution.

Keywords: Albendazole, Gelucire®, Lutrol®, solid dispersions, dissolution enhancement, pharmaceutical tablets.

1. INTRODUCTION

Drug discovery strategies preoccupied with pharmacologic activity have resulted in the discovery of many potent drugs with poor pharmaceutical and biopharmaceutical properties. Solubility and dissolution of new chemical entities have been particularly affected by such strategies with up to 40% or more of new chemical entities discovered by pharmaceutical industry today considered hydrophobic compounds [1].

The solubility issues complicate the delivery of these new drugs as well as the delivery of many existing drugs. Low drug solubility and poor dissolution often manifest itself in a host of in vivo consequences including decreased bioavailability, incomplete release from dosage forms, and higher inter-patient variability, thus, an improvement in drug's solubility and dissolution behavior is expected to enhance their bioavailability [2-6].

Poorly soluble compounds create special formulation problems including severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to in vivo absorption [1].

Drug delivery technologies have been developed to improve drug solubility and dissolution through either chemical modification of the environment surrounding the drug molecule or by physically altering the characteristics of aggregates or drug particles.

These technologies include particle size reduction via comminution and spray drying, micellar solubilization, and cyclodextrin complexation, as well as solid dispersion strategies [7-9].

Solid dispersions are one of the most successful and promising strategies that can be used for improving solubility of poorly soluble drugs. Solid dispersions can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic polymeric matrix carriers [9].

Solid dispersions improve dissolution rate by reducing drug particle size to the molecular level, improving drug wettability and solubility, and amorphousization of drug particles.

Surfactant carriers or carriers of self emulsifying properties have been used in preparing solid dispersions with improved solubility/dissolution properties. These carriers have the ability to stabilize the drug in molecular

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dispersion form [9, 10].

Gelucire® grades are amongst the most commonly used solid dispersion carriers. Gelucires are glyceride-based excepients, composed of mixtures of mono-, di-, and tri-glycerides with polyethylene glycol esters of fatty acid which vary in fatty acid distribution in terms of hydrocarbon chain length and ratio of each chain resulting in different functional properties, for example, low HLB Gelucire® have been used to control the dissolution rate of drugs, while, those with high HLB have been used as dissolution enhancers [11, 12].

Gelucire® 44/14, lauroyl macrogolglyceride, is an inert semisolid waxy amphiphilic surfactant, which due to its unique constituents of surfactants (mono- and diesters of polyethylene glycol), cosurfactants (monoglycerides), and oily phase (di- and triglycerides), has self-emulsifying properties that produces fine oil-in-water emulsion when introduced into aqueous phase under gentle agitation that may be used to improve solubility and bioavailability of poorly water-soluble drugs [12 - 14].

Another dissolution-enhancing carrier class is the polymeric surfactants which are exemplified by Poloxamers or Pluronics. Poloxamers are tri-block copolymeric non-ionic surfactants. Poloxamers exist in solution as unimers but self-assemble into spherical micelles above its CMC [15, 16].

Lutrol® F127 is a pharmaceutical grade Poloxamer that has been used as a polymeric surfactant carrier in solid dispersions of poorly water-soluble actives where it promoted faster and more completed dissolution [5, 10, 15, 17-21].

This work examined the potential synergistic effect resulting from the use of combinations of Lutrol® F127 and Gelucire® 44/14 in the preparation of a solid dispersion of a poorly water-soluble compound.

Albendazole (ALB), benzimidazole carbamate, is a potent broad-spectrum benzimidazole anthelmintic agent widely used in the management of intestinal helminth infections in mammals [22]. Albendazole was chosen as a model drug in this study because of its extremely low solubility and high-dose (200 - 400 mg per dose), making it a highly challenging molecule to formulate.

2. MATERIALS AND METHODS

2.1. Materials

The following materials were generously donated by their suppliers: Gelucire® 44/14 (Gattefossé, Lyon, France), Lutrol® F127 (Poloxamer 407) (BASF, Ludwigshafen, Germany), albendazole (ALB) (JOSWE Medical, Naor, Jordan), cross-linked polyvinyl pyrrolidone (CrosPovidone®) (ISP Chemicals,Wayne, New Jersey, USA), spray dried lactose (JOSWE medical, Naor, Jordan). Aerosil® was purchased from BDH Chemical Ltd (Poole, England). Other reagents and solvents were of analytical grade and used as received.

2.2. Methods

2.2.1. Solubility Measurement

The solubility of ALB was measured in triplicates in different carrier solutions (each alone and in binary mixtures) with total concentrations between 0 and 12 mg%. Excess amount of ALB (100 mg) were added to a 30 mL test tube containing 10 mLs of the carrier solution. The sample tubes were sealed with screw caps to prevent any loss and shaken for 24 hours at 37 ± 0.5 °C in shaking incubator (model LSI-3016A, Daihan Labtech Co., LTD., Korea). Afterwards, a sample of the solution was filtered using 0.45 μm nylon filters to remove undissolved drug particles, and the concentration of solubilized drug was determined through spectrophotometric measurements (SpectroScan 80D, Biotch Engineering Management Co., LTD., USA) at a wavelength of 230 nm, the concentration was calculated using an extinction coefficient of 1.018 $mg\%^{-1}cm^{-1}$, determined from calibration curve constructed using methanolic HCl (50 % H_2O, 49 % methanol, 1 % HCl) solutions.

2.2.2. Determination of Critical Micellar Concentration (CMC)

The CMC value of the studied amphiphilic carriers and their mixtures in water were determined from the surface tension (γ) versus concentration (C) plots [23]. Surface tension measurements were made with a Krüss K100 MK2 Processor Tensiometer (Germany) using the platinum ring detachment method. All measurements were made at room temperature in triplicates.

2.2.3. Measurement of Intrinsic Dissolution of Albendazole

The effect of carrier solutions on ALB intrinsic dissolution rate was evaluated using tablets containing 200 mg ALB without excepients. The tablets were prepared by compressing ALB in 9 mm diameter round dies using flat surface punches at a compression force of 10 kN for 10 seconds using a hydraulic press (Model 3851-0, Carver Inc., USA).

The prepared ALB tablets were placed in specially modified dies such that the top surface only (area = 0.6364 cm^2) is exposed for dissolution medium.

The ALB dissolution was determined in 900 mL-carrier (single component and binary mixtures 1:1 w/w) solutions, with concentrations ranging between 0 and 15 mg %, as dissolution media maintained at 37 ± 0.5 °C and stirred at rate of 100 rpm using a USP Apparatus 2 (paddle) (VK 7000, Varian, USA). Samples (5 mL) were collected and filtered using 0.45 µm nylon filters at predetermined time intervals up to 12 hours. An equal volume of fresh dissolution medium kept at the same temperature was transferred to the vessel after sample withdrawal.

Quantities of the dissolved drug were measured spectrophotometrically at 230 nm using a SpectroScan 80D UV-VIS spectrophotometer (Biotech Co., LTD., USA).

2.2.4. Preparation and Testing of Solid Dispersion Lipid-based Formulas

2.2.4.1. Preparation of Solid Dispersions Lipid-based Formulas

Solid dispersion lipid-based formulas containing 40, 50, 60 and 80% w/w ALB were prepared using Gelucire® 44/14 and Lutrol® F127 as drug carriers in different ratios (Table 1) by the melting method. Accurately weighed amounts of Gelucire® 44/14 and Lutrol® F127 were heated with continuous stirring in a water bath maintained at 60°C, and then accurately weighed amount of ALB was added to the fused mixture. After that, the mixture was stirred for 5 minutes to disperse ALB homogenously within the melt. The fused mixture was allowed to cool slowly to room temperature while stirring and the congealed mass was then sieved through a 25 mesh sieve (710 µm) with the resultant granules stored at room temperature in closed containers until further use.

Table 1. Drug:Lipid ratios and Lipid System compositions in the prepared solid dispersion systems.

Formula Code	ALB, % w/w	Lipid System Ratio		
		Gelucire® 44/14	:	Lutrol® F127
A40(1G:1L)	40	1	:	1
A40(2G:1L)	40	2	:	1
A40(1G:2L)	40	1	:	2
A50(1G:1L)	50	1	:	1
A50(2G:1L)	50	2	:	1
A50(1G:2L)	50	1	:	2
A60(1G:1L)	60	1	:	1
A60(2G:1L)	60	2	:	1
A60(1G:2L)	60	1	:	2
A80(1G:1L)	80	1	:	1
A80(2G:1L)	80	2	:	1
A80(1G:2L)	80	1	:	2
A80(1G:0L)	80	1	:	0
A80(0G:1L)	80	0	:	1
A60(0G:1L)	60	0	:	1
A50(0G:1L)	50	0	:	1
A40(0G:1L)	40	0	:	1

2.2.4.2. Preparation of ALB Tablets

Tablets were prepared from the generated granules above using specific granules amount such that ALB quantity is 200 mg per tablet in addition to 300 mg spray dried lactose per tablet. CrosPovidone® was used as a disintegrant at 5% w/w level and Aerosil® was added to the formulation at a 1% w/w level as a glidant. The materials were mixed manually in a plastic bag and the mixtures were compressed in a 12 mm round die and flat punches using a hydraulic press (Model 3851-0, Carver Inc., USA) at a compression force 10 kN for 10 seconds.

2.2.4.3. In vitro Dissolution of Solid Dispersion ALB Granules

The release of ALB from the granules was measured in triplicates using a USP apparatus 2 (Vankel VK 7000, Varian Inc., USA). Granules containing an equivalent to

200 mg ALB were first suspended in 10 mL of the dissolution medium then added to dissolution vessels containing 890 mL of 0.1 M HCl maintained at 37 ± 0.5 °C and stirred at a rate of 50 rpm. At predetermined time intervals, samples of 5 mL each were withdrawn from dissolution medium, filtered through 0.45 µm nylon filters and assayed spectrophotometrically for ALB at 230 nm using UV-VIS spectrophotometer (SpectroScan 80D, Biotech Co., USA). An equal volume of fresh dissolution medium kept at the same temperature was transferred to the vessel after sample withdrawal. Dissolution experiments were carried out in triplicates.

The dissolution efficiencies were calculated up to 30 minutes and 1 hour points using the following equation:

$$\text{Dissolution Efficiency (D.E.)} = \frac{\int_{t_1}^{t_2} y.dt}{y_{100}.(t_2 - t_1)} \qquad (1)$$

Where y is the percentage of dissolved product and accordingly, D.E. is the area under the dissolution curve (AUC) between time points t_1 and t_2 expressed as percentage of the curve at maximum dissolution. The integral of the numerator, i.e. the area under the dissolution curve was calculated using the trapezoidal rule. The area under the curve is the sum of all the trapeziums defined by:

$$\text{AUC} = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{2} \qquad (2)$$

Where t_i is the i th time point and y_i is the percentage of dissolved product at t_i [24].

2.2.4.4. In vitro Dissolution of Solid Dispersion ALB Tablets

ALB release from compressed tablets was performed using the same method described in the previous section.

2.2.5. Contact Angle Measurement

The contact angles of the prepared formulas with distilled water were measured in triplicates on a Krüss K100 MK2 Processor Tensiometer (Germany) using the standard rod method [25] (Cylindrical accessory 13 mm in diameter and 35 mm in height).

2.2.6. Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of ALB, carriers, and solid dispersion formulation using Mettler Toledo DSC823^e DSC (Mettler Toledo, Switzerland) equipped with an intracooler. Samples (5.100 - 5.800 mg) were heated on an aluminum pan a rate of 10 °C/min over temperature range of 25 and 250 °C. Purge gas used was nitrogen flowing at the rate of 80 mL/min.

3. RESULTS AND DISCUSSION

3.1. ALB Solubility Results

Solubility of ALB in water was found to be 0.0252 ± 0.0020 mg%, which tallied well with the literature value [26]. As can be seen in Figure 1, the solubility of ALB increased as the carriers in the aqueous solutions increased, this can be explained by the amphiphilic nature of Lutrol® F127 (L) and Gelucire® 44/14 (G).

An additive solubilizing effect was observed in mixtures of Gelucire® 44/14 and Lutrol® F127. The improvement in the solubility in mixed systems was most evident in the 2G:1L combinations where the ALB solubility was highest in comparison the other combinations.

However, at higher carrier concentrations (beyond 4 mg%) the effect of the carrier mixtures is not superior to that of Lutrol® F127.

The solubility increased markedly above the CMC of the single- and mixed-surfactant solutions, indicating micellar solubilization mechanism.

3.2. Determination of Critical Micellar Concentration (*CMC*)

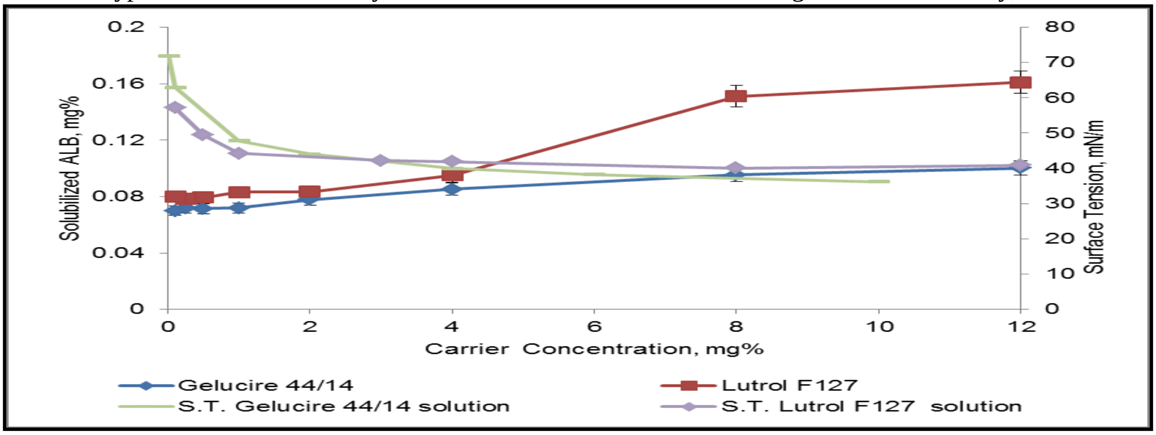
CMC values were determined using the surface tension method. Figure 1 shows seven different plots of surface tension (γ) against total concentration in mg% for the two single-component systems together with three selected mixed systems of Gelucire® 44/14 with Lutrol® F127.

The plots give a distinct break in the trend of $\frac{\Delta\gamma}{\Delta C}$ at CMC [27].

The CMC values of the studied single as well as mixed surfactant systems are presented in Table 2.

The low γ_{CMC} (γ_{CMC} = 35.230 ± 0.275 mNm^{-1}) for Gelucire® 44/14 is indicative of its ability to better wet the surfaces of ALB particles in comparison to Lutrol® F127 this is a reflection of its lower HLB value in comparison to Lutrol® F127.

This hypothesis was tested by measurement of the contact angle of water with ALB and solid dispersions where the results have shown that increasing the Gelucire® 44/14 content resulted in a lower contact angle indicating a better wettability, Table 3.



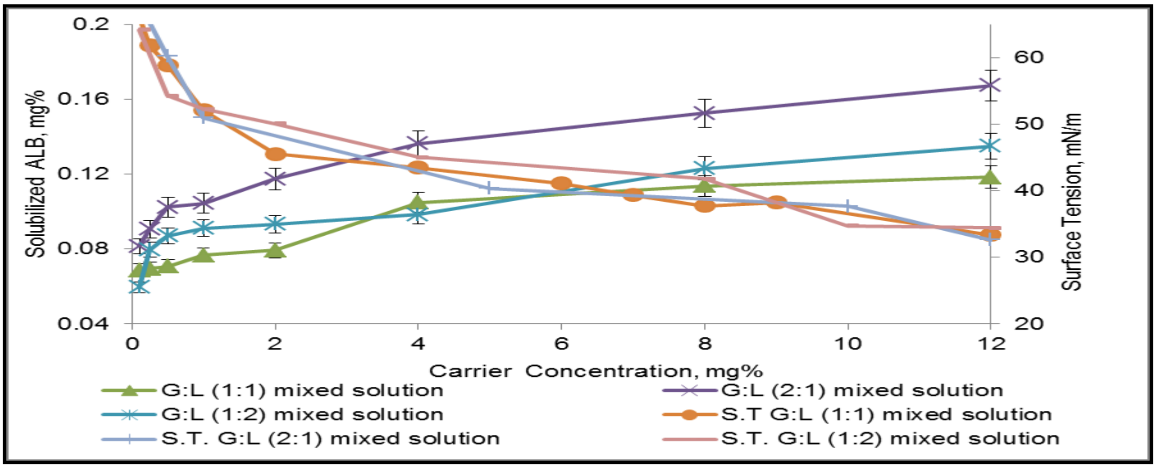


Figure 1. Effect of carrier system combinations and concentration on the ALB solubility and measured surface tension of the carrier system solution. (S.T.; Surface Tension, G; Gelucire® 44/14, L; Lutrol® F127).

Table 2. CMC and Surface Tension values of carrier solutions

Solution		CMC, mg%	γ_{CMC} (mNm^{-1}) (Mean ±SD, n=3)
Components	Ratio		
G	-	2	35.230 ± 0.275
L	-	1	44.280 ± 0.308
G-L	1:1	2	45.533 ± 0.537
G-L	2:1	3	45.389 ± 0.300
G-L	1:2	2	50.070 ± 0.436
G-L	3:1	3	39.970 ± 0.238
G-L	1:3	2	42.808 ± 2.090

Table 3.Contact Angle Results

Solid Dispersion Composition by Weight ALB:G:L	Contact Angle (º) (Mean ±SD, n=3)
100:00:00	61.62±3.17
80:10:10	57.14±7.27
80:13.4:4.6	53.38±4.07

3.3. Intrinsic Dissolution of Albendazole

Measurement

The intrinsic dissolution rate showed a minimal increase upon increasing the concentration of the carriers in the dissolution medium. The increase in the dissolution rate was expected as the carriers in solution can act as wetting agents and solubilizers (above CMC). However, the change in the IDR was at best marginal with the highest percentage change of 4.1% achieved using a 15 mg% 1:1 Gelucire® 44/14-Lutrol® F127 mixture as can be seen in Figure 2.

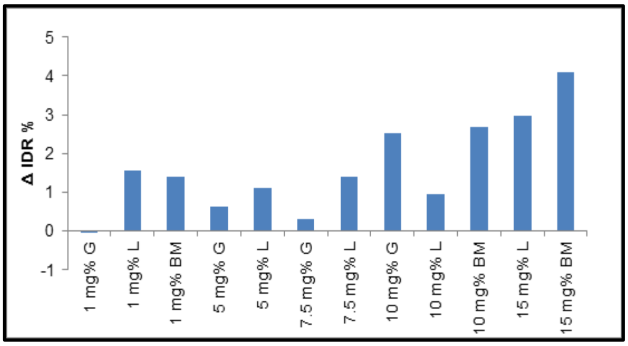


Figure 2. Changes in intrinsic dissolution rate relative to that in water (ΔIDR%) as function of dissolution media composition. (G; Gelucire® 44/14, L; Lutrol® F127, BM; Binary Mixture 1:1 w/w).

3.4. In vitro Dissolution of Solid Dispersion ALB Granules and Tablets

Dissolution results presented in Figure 3 show a faster drug release from granules and tablets prepared using mixtures of the two lipid carriers in comparison to those prepared using a single carrier. The same conclusion can be made from the results of dissolution efficiencies for the prepared granules and tablets presented in Tables 4 and 5.

Drug release from granules of mixed lipid carrier systems was observed to become faster as the lipid carrier ratio to the drug increased reaching a maximum in systems containing 40 % ALB and 60% of a 1:2 Gelucire® 44/14 to Lutrol® F127 weigh ratio (A40(1G:2L)). Dissolution efficiency of this formula was 0.870 and 0.970 after 30 minutes and one hour of dissolution, respectively.

When compared to their constituent granules, the prepared tablets showed a different trend. The dissolution rates from tablets became higher, as the drug content of the dispersion increased (decreased carrier content), this unexpected result is probably due to the binding effect of

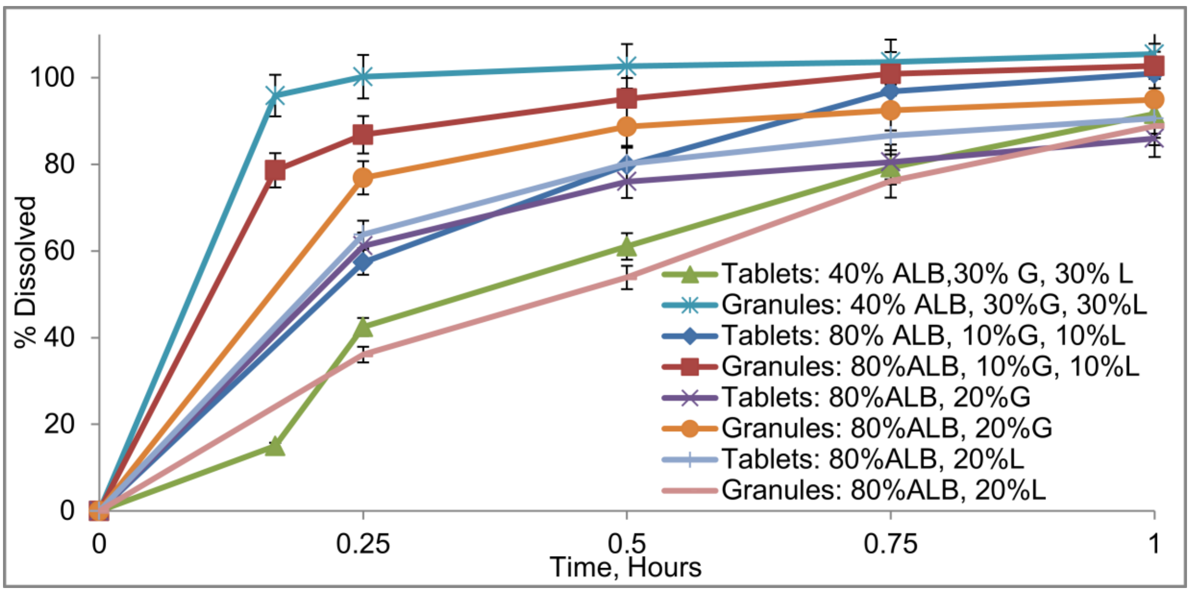


Figure 3. Selected dissolution profiles of prepared granules and tablets. G; Gelucire® 44/14, L; Lutrol® F127.

Table 4: Dissolution efficiencies of ALB from granules prepared by the melting procedure.

ALB %	Dissolution Efficiency within 1 hour *					Dissolution Effeciency within 30 minutes *				
	Gelucire® 44/14 : Lutrol® F127			Gelucire® 44/14	Lutrol® F127	Gelucire® 44/14 : Lutrol® F127			Gelucire® 44/14	Lutrol® F127
	01:01	02:01	01:02			01:01	02:01	01:02		
40	0.934±0.007	0.933±0.038	0.970±0.018	--**	0.770±0.006	0.830±0.013	0.832±0.045	0.869±0.028	--**	0.635±0.003
50	0.918±0.011	0.864±0.046	0.927±0.003	--**	0.846±0.010	0.804±0.013	0.735±0.051	0.770±0.002	--**	0.713±0.005
60	0.862±0.058	0.876±0.017	0.894±0.018	--**	0.800±0.022	0.724±0.084	0.742±0.013	0.767±0.009	--**	0.664±0.027
80	0.841±0.052	0.842±0.036	0.787±0.018	0.764±0.038	0.526±0.183	0.716±0.043	0.722±0.040	0.677±0.009	0.606±0.048	0.315±0.190

* Mean ± SD, n=3,

** Formulas were too soft and could not be sieved to prepare granules

Table 5: Dissolution efficiencies of ALB from tablets prepared from granules obtained by the melting procedure.

ALB %	Dissolution Effeciency within 1 hour *					Dissolution Effeciency within 30 minutes *				
	Gelucire® 44/14 : Lutrol® F127			Gelucire® 44/14	Lutrol® F127	Gelucire® 44/14 : Lutrol® F127			Gelucire® 44/14	Lutrol® F127
	01:01	02:01	01:02			01:01	02:01	01:02		
40	0.549±0.035	0.613±0.074	0.552±0.078	--**	0.477±0.042	0.313±0.035	0.370±0.083	0.294±0.048	--**	0.278±0.025
50	0.602±0.018	0.664±0.064	0.692±0.059	--**	0.598±0.084	0.333±0.050	0.426±0.068	0.441±0.081	--**	0.365±0.091
60	0.711±0.036	0.678±0.061	0.703±0.021	--**	0.611±0.049	0.487±0.049	0.464±0.068	0.489±0.019	--**	0.383±0.037
80	0.743±0.040	0.734±0.028	0.872±0.011	0.652±0.008	0.690±0.006	0.519±0.049	0.494±0.037	0.690±0.009	0.496±0.014	0.519±0.013

* Mean ± SD, n=3,

** Formulas were too soft and could not be sieved to prepare granules the lipid carriers especially when used at high levels which was observed to hinder the disintegration of the tablets and consequently reduce the surface area available for dissolution. The maximum dissolution efficiency was obtained with tablets made of formula A80(1G:2L) and were 0.690 and 0.872 after 30 minutes and one hour respectively.

3.5. Differential Scanning Calorimetry (*DSC*) of Solid Dispersions

Figure 4 shows the DSC thermograms of ALB, Gelucire® 44/14, Lutrol® F127, and their solid dispersion. The thermogram of ALB, Gelucire® 44/14, and Lutrol® F127 exhibit single endothermic peaks at ~ 217 °C, 47 °C, and 58 °C, respectively. The thermograms of the solid dispersion of different systems showed endothermic peaks for all system components. However, the calculated heat of fusion (in mJ/mg) for ALB peaks in all solid dispersion samples were less than the value for pure ALB (226.82 mJ/mg) which is a clear indication that ALB is present partially in a molecular dispersion in the system.

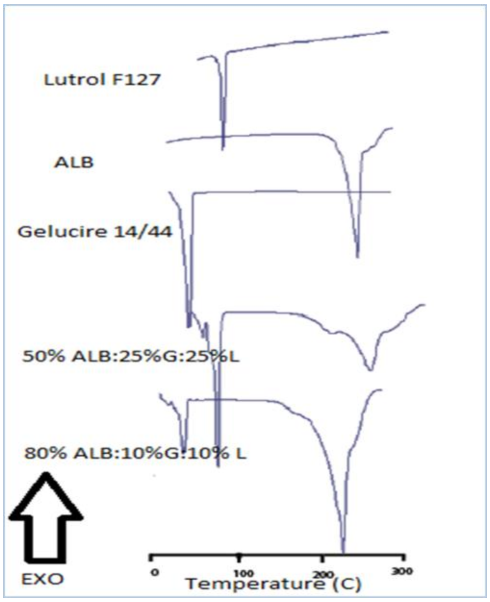


Figure 4. DSC thermograms of ALB, Lutrol® F127, Gelucire® 14/44, and two selected solid dispersions. G; Gelucire® 44/14, L; Lutrol® F127.

4. Conclusions

Two surface active carriers, Lutrol® F127 and Gelucire® 44/14, were investigated in the current study for potential application in dissolution enhancement of ALB. Single component and mixtures of the carriers enhanced the solubility and dissolution of ALB to varying degrees. There appears to be an additive effect of the carriers used. The enhancement was a function of carrier concentration and ratio of the two carriers in the system. The system was evaluated physically and shown to be, partially, a solid solution. The effect of the carriers is a result of their solubilizing and wetting ability and the physical form of ALB dispersed in them.

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تقييم نظام ثنائي حامل للدواء لتسريع ذوبان دواء قليل الذائبية في الماء ذو جرعة عالية

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تم تقييم اداء سواغين فعالين سطحياً، الجيلوسير 14/44 و اللترول ف127، في عملية تحسين الذائبية وسرعة الذوبان لدواء البيندازول قليل الذائبية في الماء و عالي الجرعة باستخدام اسلوب الموزعات الصلبة. أبانت فحوصات الذوبان المخبرية تحسن فاعلية الذوبان لدواء البيندازول بدرجات مختلفة في محاليل السواغات المستخدمة و مخاليطها كما و ظهر من دراسة ذائبية البيندازول أن ذائبية البيندازول في محاليل اللترول ف127 هي الأعلى بالمقارنة مع المحاليل الأخرى المدروسة. تم اشراك الدواء في منظومات مكونة من أحد السواغين أو مخلوط منهما باستخدام تقنية الصهر ومن ثُم تم تحضير مضغوطات من الحبيبات الناتجة و دراسة ذوبان البيندازول منها في المختبر حيث تمت ملاحظة تسارع الذوبان واعتماده على نوع السواغات و كميتها. بدراسة زاوية الأتصال تم استنتاج أن السواغات المستخدمة تعمل على تحسين تَرَطُّب البيندازول بالماء كما و تم من خلال دراسة الصفات الحرارية لمخاليط الدواء و السواغات الاستنتاج أن النظام الموجود في المحاليل المدروسة هو موزع صلب و محلول صلب من ناحية وجود البيندازول. تم الاستنتاج بأن فعالية السواغات في تحسين الذوبان تعود لقدرتها على التأثير في ذائبية الدواء و ترطبه بالماء و شكله الفيزيائي.

الكلمات الدالة: البندازول, جيلوسير, لوترول, فعالية الذوبان, الموزعات الصلبة, أقراص دوائية