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European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 342–347
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique

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Received 23 June 2007; accepted in revised form 10 September 2007
Available online 18 September 2007

Abstract

The aim of the work was to improve the dissolution properties of the practically insoluble antiepileptic drug, Carbamazepine (CBZ) by adopting the liquisolid compaction technique. Reported liquid load factors, and excipient ratios were used to calculate the required amounts of excipients necessary to prepare the compacts or tablets according to a mathematical model. Avicel PH 102, and Aerosil 200 were used as the carrier and the coating materials, respectively, and explotab was used as disintegrant to prepare four tablet formulae, out of which formula 1 was successfully compressed into tablets. The dissolution patterns of liquisolid CBZ tablets, carried out according to the USP, were comparable to those of Tegretol®. The protection of male albino mice against the convulsion, induced by electroshock, was lower in case of liquisolid tablets compared to Tegretol® suspension and tablets probably due to the precipitation of CBZ in the silica pores resulting from its high dose.

Keywords: Carbamazepine (CBZ); Liquisolid; Liquid load factor; Excipient ratio; Carrier; Coating material; Tablets; Compacts

1. Introduction

Carbamazepine is considered a first line drug in the treatment of Epilepsy [1]. It is practically insoluble in water. The oral absorption of CBZ is slow, erratic and unpredictable in humans owing to slow dissolution [2]. Many studies were done in trial to improve the bioavailability of CBZ. The liquisolid technique was adopted in an attempt to improve the dissolution properties, and hence, the bioavailability of CBZ.

From the historical point of view, liquisolid compacts were evolved from 'Powdered Solutions' which depended on preparing a true solution of the drug in a high boiling point, water-miscible solvent, which was carried out on the extensive surface of an inert carrier such as silica [3]. In such systems, the drug existed in a molecular state of subdivision [4]. Also, these systems were free flowing, non-adherent, dry looking powders [5]. In further studies, compression enhancers were added to these powdered solutions, as microcrystalline cellulose [6]. However, the compression of these latter systems resulted in a significant 'Liquid Squeezing Out' phenomenon [7].

Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, whereas silicas of very fine particle size can be used as coating materials.

The liquid medication is to be mixed with the excipients and then compressed to tablets. It was proved that the smaller the drug concentration in the liquid medication, the more rapid the release rates, since drugs in a high concentration tend to precipitate within the silica pores [8].

Silicas possessing large surface areas, and microcrystalline cellulose of fine particle size and granular grades produced good flow and compression properties, resulting in acceptable tablets [9].

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doi:10.1016/j.ejpb.2007.09.003

A formulation mathematical model by Spireas [7] of liquisolid systems enabled calculation of the appropriate amounts of both the carrier and the coating material to be added to produce acceptable flow and compressibility. This model of liquisolid systems is based on the Flowable (Φ-value) and the Compressible (Ψ-number) Liquid Retention Potentials of the constituent powders.

The Flowable Liquid Retention Potential of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability. This Φ-value is determined by recording powder flow [7,10].

The Compressible Liquid Retention Potential of a powder is the maximum amount of liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable hardness, and friability, with no liquid squeezing out phenomenon during the compression process. The Ψ-number of powders can be determined by using pacticity theories [7,11].

The excipient ratio R of the powder substrate is defined in the following equation as:

$$R = Q/q \tag{1}$$

where R is the fraction of the weights of carrier Q and coating q materials present in the formulation. The amounts of excipients used to prepare the tablets are related to the amount of liquid medication W through the 'Liquid Load Factor' (L_f) as shown in the following equation:

$$L_f = W/Q \tag{2}$$

For a given excipient ratio R, there exists a specific Flowable L_f factor denoted as ${}^{\Phi}L_f$, as well as a specific compressible L_f factor denoted as ${}^{\psi}L_f$.

The optimum liquid load factor L_o that produces acceptable flow and compression characters is equal to either ${}^{\Phi}L_f$, or ${}^{\psi}L_f$, whichever possesses the lower value.

This technique of liquisolid compacts has been successfully employed to improve the in-vitro release of poorly water soluble drugs as hydrocortisone [12], methylclothiazide [13], hydrochlorothiazide [8], prednisolone [14], and the liquid drug clofibrate [15]. Also several water insoluble drugs, namely, nifidipine, gemfibrosil, and ibuprofen, have exhibited higher bioavailability in rats as compared to their commercial counterparts [12].

The in-vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs showed that the absolute bioavailability of the drug from liquisolid tablets was 15% higher than from commercial tablets [16].

2. Experimental

2.1. Materials

Carbamazepine (CBZ) and explotab were kindly provided by CID Co., Giza, Egypt; Avicel PH 102 (MCC.N.F, FMC. International-Little Island, Cork, Ireland); Aerosil 200, propylene glycol (PG), methyl alcohol, and sodium lauryl sulfate (ADWIC- El-Nasr Co., Egypt).

2.2. Methodology

2.2.1. Determination of the angle of slide for Aerosil 200

The Angle of slide for Aerosil 200 was measured as follows:

Ten grams of Aerosil 200 were weighed accurately and placed at one end of a metal plate with a polished surface. This end was raised gradually until the plate made an angle with the horizontal at which the powder was about to slide. This angle θ represented the angle of slide. It was taken as a measure for the flow characters of powders. An angle of slide corresponding to 33° corresponded to optimal flow properties [9].

2.2.2. Determination of Flowable Liquid Retension Potential for Aerosil 200 (Φ-value)

To the 10 g of Aerosil 200 powder, increasing amounts of liquid paraffin were added and mixed well. The Aerosil adsorbed liquid paraffin resulting in a change in its flow properties. At each concentration of liquid paraffin added, the angle of slide for Aerosil was re-determined as stated above. The corresponding Φ-value was calculated from the following equation [9]:

$$\Phi\text{-value} = \text{weight of liquid/weight of solid}$$

The Φ-values were plotted graphically against the corresponding angles of slide θ. The Phi-value corresponding to an angle of slide of 33° represented the Flowable Liquid Retention Potential of Aerosil 200.

The Φ-value for Avicel PH 102 was reported to be 0.15 [9] and hence there was no need to determine it practically.

2.2.3. Preparation and mixing of the powders

The amounts of excipients depended on their Φ-values, as well as liquid load factors.

Aerosil 200 was used as coating material, while Avicel PH 102 was used as carrier.

Two liquid load factors reported [12,14] were used

$$L_f = 0.25 \text{ and } 0.47$$

With either of the two L_f's the dose of CBZ was 100 mg in each tablet. CBZ was suspended in propylene glycol (PG), and the suspension was made into slurry by mixing it with Avicel PH 102 first (carrier). The excess fluids were adsorbed by Aerosil 200 (coating material), that was added later. This order of mixing had proved to produce the most optimal release rate [3]. Explotab was finally added to the powders to make 5% of the tablet weight.

CBZ was suspended in PG at concentrations (C_d) of 30%, 40%, and 50% w/w.

Table 1 shows the amounts of carrier, coating material, drug concentration C_d % (w/w) and L_f used to prepare four liquisolid tablets (LST-1, -2, -3, -4).

Table 1
Formulation characteristics of prepared CBZ liquisolid tablets

Liquisolid tablet (LST)	L_f	C_d (% w/w)	Q (g)	q (g)	R	Tablet weight (g)
1	0.25	50	0.8	0.04	20	1.09
2	0.47	40	0.532	0.106	5	0.938
3	0.47	40	0.532	0.0665	8	0.893
4	0.47	30	0.638	0.058	11	1.05

C_d, drug concentration in PG; q, weight of coating material (Aerosil 200); L_f, liquid load factor; R, excipient ratio (Q/q); Q, weight of carrier (Avicel PH 102).

2.2.4. Determination of the flow properties of prepared powders

The flow properties were assessed through measuring the compressibility index C_i % [17]. An amount of each powder of 20 g was accurately weighed, passed through a 1 mm screen to break up agglomerates and placed in a 50 ml volumetric cylinder without compaction. The apparent volume V_o was recorded. Then the cylinder was tapped by raising it to a height of 12–14 mm and then allowing it to fall under its own weight. This was repeated until no change in volume occurred. This final volume V_f was recorded [17]. The C_i % was determined from the following relation:

$$C_i\ \% = (V_o - V_f)/V_o \times 100$$

The smaller the value of the C_i %, the better will be the flow properties of the powder [18].

2.2.5. Compression into tablets

A single punch machine was used to compress the successful formulae into tablets, where batches of 100 tablets, containing 100 mg of CBZ per tablet, were prepared and exposed to further investigation.

2.2.6. Evaluation of liquisolid tablets

Tablets were evaluated by carrying out tests for weight variation, uniformity of tablet thickness and diameter, humidity content using karl fisher method, friability, hardness, disintegration, dissolution, and content uniformity. All the tests were carried out in triplicate and according to the compendial specifications [19,20].

For content uniformity test tablets should contain not less than 95% and not more than 105% of the labeled potency [20].

The disintegration test was carried out on six tablets in distilled water at 37 ± 2 °C using the USP disintegration apparatus [19].

The dissolution test was used to compare between liquisolid tablets and Tegretol® 200 tablets. The USP Apparatus 2 was used with 900 ml of 1% sodium lauryl sulfate solution (1% SLS) at 37 ± 0.5 °C, and the apparatus was run at 75 rpm. One milliliter samples were withdrawn after 5, 10, 15, 20, 25, 30, 45, and 60 min, and were compensated by equal amounts of the dissolution medium. The samples were properly diluted and the concentrations of CBZ were determined spectrophotometrically at 287 nm [19].

The dissolution results of liquisolid tablets and Tegretol® after 30 and 60 min were compared using a 2-tailed unpaired Student's t-test at $P < 0.05$.

2.2.7. Determination of the anticonvulsant activity

The anticonvulsant activity of CBZ in liquisolid tablets as well as Tegretol® 200 tablets and Tegretol® Suspension was determined using the maximal electroshock method.

Male albino mice, weighing 20–25 mg, were fasted overnight and divided into four groups, each consisting of six animals. CBZ, supplied from the different above products to mice in a dose of 35 mg/kg body weight [21], was given orally to the animals using an oral tube as follows:

Group 1: received 0.2 ml distilled water as control.
Group 2: received 0.2 ml of diluted Tegretol® suspension.
Group 3: received powdered Tegretol® tablets suspended in 0.2 ml distilled water, such that these volumes contained the required dose.
Group 4: received an amount of the powdered successful formula containing the animal dose suspended in 0.2 ml distilled water.

Maximal electroshock seizure (MES) was induced using an electrical simulator with ear electrodes to deliver stimuli [22]. An electrical stimulus (50 mA, 60 Hz) was delivered for 0.2 s to the animal after 60 min of drug administration. The animals were restrained by hand and released at the moment of stimulation in order to permit the observation of the entire seizure. Absence of hind limb tonic extensor component indicated that the drug received could prevent MES spread.

The results were expressed as percentage of the animals protected.

3. Results and discussion

3.1. Determination of the angle of slide for Aerosil 200 and its Φ-value

Table 2 shows the angles of slide and the corresponding Phi-values. Fig. 1 illustrates the relation between these two variables and shows that the Flowable Liquid Retension

Table 2
Determination of the angle of slide and Φ-value of Aerosil 200

Angle of slide (°)	Φ-value (w/w)
27.04	0
27.8	0.5
29	1
33.8	1.5
35	2.01

Φ = wt. of liquid/wt. of solid.

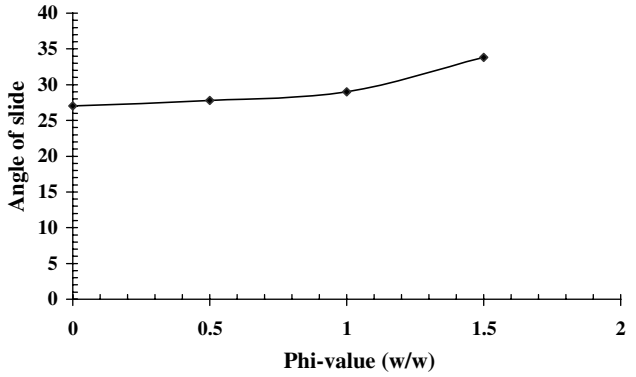

Fig. 1. Relationship between the angle of slide θ and Φ-value for Aerosil 200.

Potential (Φ-value) for Aerosil 200 corresponding to an angle of slide of 33° was equal to approximately 1.5. The obtained Φ-value from the curve is quite close to that reported for Syloid which was used in formulating liquisolid compacts.

Silica (Syloid 244 FP) 1.6 [9]

The Phi-value of Avicel PH 102 is known to be 0.15.

Thus it was possible to calculate the liquid load factor as follows:

$$L_f = \Phi + \Phi(1/R)$$

where Φ, Φ are the Φ-values of the carrier and the coating powders, respectively.

And, R, the excipient ratio $(Q/q) = 20$, 5 as recommended in references.

Therefore,

$$L_f = 0.15 + 1.5(1/20) = 0.225,$$
$$L_f = 0.15 + 1.5(1/5) = 0.45$$

It is clear that the above calculated L_f's – through our knowledge of the Φ-values of both Avicel 102 and Aerosil 200 – are close to those recommended in the literature. Consequently, the recommended L_f of 0.25, and 0.47 could be used to prepare CBZ liquisolid compacts. The former L_f (0.25) was a commonly used liquid load factor [14], whereas the latter L_f (0.47) was used to formulate the liquid drug clofibrate which resembled CBZ in having a high dose [9]. Thus the L_f's = 0.25, 0.47 and R values = 5, 20 were used to prepare the liquisolid tablet formulae listed in Table 1. Other excipient ratios of 8 and 11 were used in trial to improve flow and compression properties of liquisolid formulae.

3.2. Percentage compressibility C_i% of the powders prepared for liquisolid compacts

Table 3 shows the C_i % of the powders for liquisolid tablet preparation.

LST-1 possessed the best flowability due to having the least C_i %, and upon compression, resulted in tablets of uniform weight, and acceptable hardness.

Powder for LST-2, which contained the largest amount of Aerosil 200, was fluffy due to the low density of Aerosil (0.05) [23]. Presence of large amounts of Aerosil 200 in this formula resulted in the worst flow properties as indicated by its angle of slide given in Table 2. Powder segregation during mixing was observed, and resulting tablets were of non-uniform weight.

LST-3 and LST-4 showed improved flowability as clear from Table 3, due to reduction in the amounts of Aerosil. This reduction was achieved by raising the excipient ratio through addition of only enough amounts of Aerosil just to adsorb the excess liquid from the slurry, yet a liquid oozing out took place upon compression. Thus the rest of investigation was concentrated on LST-1, and the other formulae were neglected.

3.3. Evaluation of LST-1

Table 4 shows the results of the tests performed to evaluate LST-1. It was clear that the compacts conformed to the requirements that should be present in tablets as uniformity of weight, drug content, diameter and thickness. Tablets also possessed acceptable hardness, friability and humidity content.

Dissolution testing: Liquisolid tablets showed a non-significantly higher dissolution rate comparable to Tegretol® 200 tablets at $P < 0.05$. The results of this dissolution test are given in Table 5, and illustrated by Fig. 2. The liquisolid tablets released more than 75% of the labeled potency within one hour [19].

Anticonvulsant activity: The results of the maximal electroshock method for anticonvulsant activity are given in Table 6. The liquisolid tablets showed to be of poorer potency compared to Tegretol® suspension and tablets. This probably resulted from the high concentration of CBZ that caused its precipitation in the silica pores [8],

Table 3
% compressibility of powders used to prepare liquisolid tablet systems

Liquisolid tablet (LST)	% compressibility
1	26.67
2	37.5
3	28.6
4	29.4

Table 4
Results of the evaluation tests of liquisolid tablet-1

Average weight of tablet (g)	Content uniformity (%)	Thickness (cm)	Diameter (cm)	Humidity content (%)	% friability[a]	Hardness (Kp)	Disintegration time (s)
1.08185 (±0.0312)	96.87 (±2.5)	0.5 (±0.14)	1.5 (±0.14)	5 (±0.2)	0.83	5.8 (±0.28)	39.25 (±1.06)

[a] Test done on 20 tablets.

Table 5
% of CBZ released from its liquisolid and Tegretol® 200 tablets in 1% sodium lauryl sulfate (SLS)

Formula	% amount of CBZ released after the following time intervals[a] (min)							
	5	10	15	20	25	30	45	60
LST-1	32.98 (±2.33)	52.58 (±3.59)	61.006 (±7.19)	67.74 (±9.63)	71.878 (±7.22)	77.168 (±15.9)	82.82 (±14.6)	93.8 (±2.3)
Tegretol®	30.98 (±1.677)	54.825 (±2.63)	64.15 (±2.26)	67.24 (±5.529)	70.67 (±2.887)	75.97 (±4.239)	75.97 (±1.781)	85.05 (±4.791)

[a] Measurements are the average of three experiments.

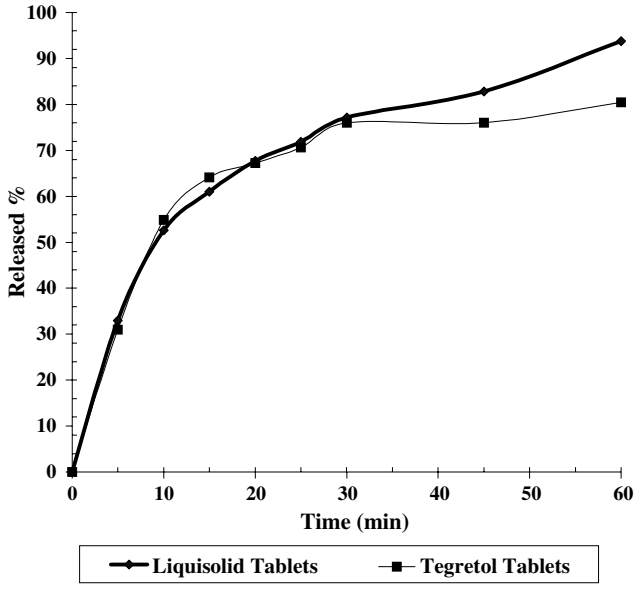

Fig. 2. Percentage of CBZ released from LST-1 and Tegretol® tablets in 1% sodium lauryl sulfate (USP).

Table 6
Protection against electroshock

Formula	No. of animals showing convulsion	% protection
Control (distilled water)	6/6	Zero
Tegretol® suspension (100 mg/5 ml)	3/6	50
Tegretol® tablet	3/6	50
Liquisolid tablet	4/6	33.3

and hence, hindered the rapidity of dissolution upon oral administration to the animals.

4. Conclusion

From the above results it was possible to conclude that the wettability of Carbamazepine was improved by making a suspension in propylene glycol, the water soluble, non-volatile liquid. CBZ liquisolid tablets could be prepared using Avicel PH 102 as a carrier, and Aerosil 200 as a coating material. A liquid load factor $L_f = 0.25$, and an excipient ratio $R = 20$, produced a powder of optimal flow properties and readily compressible into tablets without any liquid oozing out phenomenon. The prepared tablets showed good wettability, rapid disintegration, and acceptable dissolution rate comparable to the generic product. Better pharmacological activity could possibly be obtained had CBZ concentration been lower to avoid possible precipitation into the silica pores.

Acknowledgements

We are so much obliged to CID Company for helping us with this research, by allowing us to use their research laboratories in carrying out the tablet compression process and other quality control tests.

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