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Original Article

APPLICATION OF LIQUISOLID TECHNOLOGY TO ENHANCE THE DISSOLUTION OF CEFIXIME FROM ITS ORAL CAPSULES

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ABSTRACT

Objective: Oral drug delivery is the most desired route for drug administration for its well-known features. Therefore, many attempts were implemented to improve the poor solubility of many active ingredients in order to enhance their dissolution and absorption via the oral route. From these, the liquisolid system is a very promising technology for enhancing solubility and bioavailability of poorly soluble drugs.

Methods: In this research, oral capsules of cefixime were prepared by liquisolid technique after mixing different concentrations of the drug with propylene glycol (non-volatile solvent), followed by their addition to different proportions of microcrystalline cellulose and aerosil i.e. different carrier: coating (R-value). The liquisolid capsules were evaluated for *In vitro* disintegration and dissolution in addition to content uniformity and weight variations. Furthermore, solubility studies, scanning electron microscope (SEM) were performed to the optimum formula. Finally, the release profile of the optimum formula was compared with the marketed cefixime capsules.

Results: Liquisolid formula (F3) with 70% cefixime and R-value equals 10 was selected as the optimum formula having higher % release in 45 min (99.5%±0.53) compared to other formulas with faster release rate in the first 20 min than marketed capsules. It had an acceptable disintegration time (25 min±0.76), content uniformity (197.6±0.92) and weight variation (698.04±0.16). Results of solubility study, SEM assured enhancement in solubility and dispersibility of the drug.

Conclusion: This research proved that liquisolid system is a promising technology in improving the solubility and dissolution of cefixime from its capsules and hence it may improve its absorption and oral bioavailability.

Keywords: Cefixime trihydrate, Liquisolid, Microcrystalline cellulose

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INTRODUCTION

Despite of plenty of different routes for administrating a drug, yet oral route solely remains the preferred one, simply because of its convenience, optimum patient compliance as well as low costs of production. However, for a scientist to formulate a drug into, any oral dosage form, a drug must possess sufficient water solubility, therefore, it is quite challenging to formulate any drug in oral dosage form since nearly half of the active substances being identified are either insoluble or poorly soluble in water. The poor dissolution rates of water-insoluble or poorly soluble drugs are significant problem confronting the pharmaceutical industry as it is considered the rate limiting step for absorption and hence for bioavailability.

Different methods are employed to improve the dissolution characteristics of poorly water-soluble drugs like pH adjustment, cosolvents solubilisation, microemulsion, polymeric modification, solid dispersion, drug complexation, micronization, self-emulsification, use of a surfactant as a solubilizing agent, lyophilisation, the pro-drug approach, microencapsulation and inclusion of drug solutions into soft gelatin capsules. Recently, better approaches are available to prepare the liquid oily medications, and drug solutions of water-insoluble solid drugs and the most promising one is the use of the liquisolid system or powder solution technology [1-6].

Liquisolid system is a novel technique developed by Spireas *et al.*, it is a powdered form of liquid drug formulated by dissolving or dispersing the slightly soluble drug in an appropriate non-volatile solvent like polyethylene glycol (PEG) 200 or 400, propylene glycol (PG) or tween 80, that is absorbed or adsorbed into and onto the carrier like microcrystalline cellulose (MCC) PH 101 or 102 followed by its adsorption onto the surface of suitable coating material like aerosil 200. Hence, the increased surface area of the drug in powder form, enhanced wettability and enhanced dissolution might improve the bioavailability of the drug in the body. This technique was effectively applied to low dose water-insoluble drugs. On the other hand formulation of the high dose was impractical because of the high levels of carrier and coating materials that should be added and in turn will increase the weight of each tablet above 1 g which is very difficult to swallow. Therefore, to overcome this limitation, some hydrophilic materials can be added to the liquid medication like polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose or PEG 35000 which produce dry powder formulations containing a liquid with a high concentration of drug using a lower amount of the carrier and coating materials [7-12].

Cefixime is slightly soluble powder with a low bioavailability when given orally (22-54%), belongs to the third-generation cephalosporin antibacterial and is given at 200 and 400 mg orally in the treatment of susceptible infections, including gonorrhea, otitis media, pharyngitis, lower-respiratory-tract infections such as bronchitis, and urinary tract infections [13, 14].

In this study; liquisolid technique was applied to enhance the solubility of cefixime trihydrate using different concentrations of the drug in the non-volatile solvent and different ratios of the carrier and coating materials in an attempt to improve the drug dissolution in comparison to the commercial capsule and hence its oral bioavailability as well as reducing its effective dose.

MATERIALS AND METHODS

Materials

Cefixime trihydrate (Lupi Medico, India), MCC PH 102, aerosil 200 (Samara, Iraq), PG (Samara, Iraq), PVP (Samara, Iraq), marketed cefixime 200 mg capsule (Ritemed, Japan). All other chemicals, reagents and solutions used were of analytical grade.

Mathematical modeling for the preparation of the liquisolid system

A mathematical model was employed to accomplish the formulation design of the liquisolid system; such model was described by Spireas

et al. In this study, PG was used as a liquid vehicle; MCC PH 102 and aerosil 200 were used as the carrier and coating materials, respectively. The concentration of the drug in PG was taken as 70, 75, and 80 g% and the carrier: coat ratios (R) used were 6, 8 and 10. According to new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability and compressibility.

The weight of carrier powder (Q) in the system was obtained after calculating the weight of liquid medication (W) for each concentration and after obtaining liquid load factors Lf of the formulations for each R ratio used by the application of the following equations:

$$Lf = \Phi + \Phi (1/R) \quad \ldots\ldots (1)$$

$$Lf = W/Q \quad \ldots\ldots (2)$$

Where, Φ and Φ are the flowable liquid retention potential (Φ value) of powder excipients which is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce and acceptably flowing liquid/powder admixture.

After that the amount of the coating material (q) in each formula was calculated as follows:

$$R = Q/q \quad \ldots\ldots (3)$$

By using the above mathematical model, liquisolid mixtures were formulated (table 1) first by preparation the liquid medication after dissolving the 200 mg cefixime in PG at 80 °C in shaking water bath for 15 min, followed by the addition of 10% PVP prior to its mixing with the carrier and the coating material using the standard mixing process mentioned by spireas [15-17] by one rotation per second in three mixing steps. The first step involved uniform mixing for about one min to ensure uniform distribution of the liquid medication into the powder, followed by evenly distributing it as a uniform layer on the surface of the mortar and leaving it for about 5 min to allow the drug solution to be incorporated into and onto the powder. The third step involved the addition of 4% CCS as a super disintegrant that was mixed for another 30 s using the same standard mixing process.

The liquisolid mixtures were incorporated after that into capsules by dipping technique to be evaluated.

Table 1: Content of the prepared formulas containing liquisolid cefixime

Formula	% of drug (w/w)	R	Lf	W (mg)	Q (mg)	Q (mg)	Total weight (mg)
F1	70%	6	0.71	285.7	200.7	33.4	601.7
F2	70%	8	0.57	285.7	249.3	31.1	655.2
F3	70%	10	0.49	285.7	290.9	29	701
F4	75%	6	0.71	266.6	187.3	31.2	561.6
F5	75%	8	0.57	266.6	232.6	29	611.6
F6	75%	10	0.49	266.6	271.5	27.1	654.33
F7	80%	6	0.71	250	175.6	29.2	526.5
F8	80%	8	0.57	250	218.1	27.2	573.3
F9	80%	10	0.49	250	254.5	25.4	613.4

*__Abbreviations:__ Carrier: coating ratio (R), loading factor (L_f), weight of liquid medication (W), weight of carrier (Q), weight of coating material (q).

Evaluation of the liquisolid powder mixture

Flowability assessment of the liquisolid powder

The flow properties of liquisolid formulations were studied by an angle of repose, Carr's index and Hausner's ratios. All studies were done in triplicate, where, the angle of repose was calculated by a fixed height cone method, while Carr's index and Hausner's ratios were measured using bulk and tapped densities [18, 19].

Solubility study

The saturated solubility of pure cefixime and optimum liquisolid formula (F3) were studied in distilled water and 7.4 phosphate buffer. An excess amount of each powder was added to each solution and sonicated at room temperature for 1 h, followed by mixing for 24 h at 25±0.1 °C. The samples were filtered and evaluated by a UV-spectrophotometer at 288 nm [20].

Scanning electron microscope (SEM)

The morphological behaviour of the drug alone and the liquisolid system of the optimum formula (F3) was detected by SEM (S-50 model, FEI company-Netherland), where the complete dis-appearance of the crystals in the liquisolid mixture assures complete solubility of the drug [21, 22].

Fourier transform infrared spectroscopy (FT-IR)

The possible interaction of all excipient along with the drug was assessed for the optimum formula (F3) using FTIR from 4000-400 cm^{-1} by using the pressed-disk technique [23].

Evaluation of the liquisolid capsules

Weight variation

It's done by individually weighing 20 capsules and the average weight is determined. If 2 capsules fall outside the range of 10%, then should take another 20 capsules. So the test requirement is met if 6 capsules fall outside the 10% range and none of the 6 capsules outside 25% range.

Content uniformity

It's performed by and dissolving 10 capsules individually in 7.2 phosphate buffer followed by measuring the amount of cefixime in each capsule by UV-spectrophotometer at 288 nm, the capsules met the requirements if only one falls outside±15% but not outside±25%. If more than two were in that range, then take 20 capsules that is assayed individually, they passed the test, if only 3 of the 30 capsules was outside the range±15% but not outside±25%.

Disintegration test

Disintegration time (DT) was measured to the prepared liquisolid capsules in pH 7.2 phosphate buffer at 37±0.5 °C by placing 6 capsules individually in each tube of the apparatus [24].

Dissolution test

The test was performed using USP type I apparatus (100 rpm) at 37±0.5 °C, by placing 3 capsules individually in 1000 ml pH 7.2 phosphate buffer for 45 min. Samples were periodically withdrawn and analyzed spectrophotometrically at 288 nm and the % drug release after 45 min (% $D_{45\ min}$) was calculated [25].

Statistical analysis

All the results were statistically analyzed using (ANOVA) single factor to compare and assess the significance of the results, where ($P<0.05$) considered to be significant.

RESULTS AND DISCUSSION

Flowability parameters of the liquisolid powder

Results of the angle of repose, Carr's index and Hausner's ratio with the corresponding type of flow are illustrated in table 2. According to the USP the results clearly demonstrate that all cefixime liquisolid powder had an acceptable flowability.

Table 2: Flowability parameters of cefixime liquisolid powder with their corresponding type of flow

Formula	Angle of repose	Carr's index	Hausner's ratio	Type of flow
F1	31.3±0.32	15.81±0.96	1.16±0.25	Good
F2	32.1±0.65	14.32±0.66	1.17±0.21	Good
F3	30.2±0.95	9.13±0.93	1.1±0.94	Excellent
F4	29.9±0.76	9.41±0.9	1.11±0.83	Excellent
F5	32.5±1.04	14.42±0.71	1.18±0.53	Good
F6	31±0.34	13.91±0.59	1.15±0.68	Good
F7	29.8±0.76	9.45±0.55	1.11±0.29	Excellent
F8	32±0.09	14.41±0.35	1.18±0.19	Good
F9	31.5±0.54	15.71±0.34	1.15±0.37	Good

*Results are expressed as mean±SD, n=3.

Solubility study

The results of the solubility study are illustrated in table 3. The data clearly show a significant improvement in the solubility of cefixime after its formulation as a liquisolid powder from sparingly soluble to freely soluble drug, which might be attributed to the increment in surface area and wettability of drug in liquisolid formula F3 in comparison to cefixime powder [26].

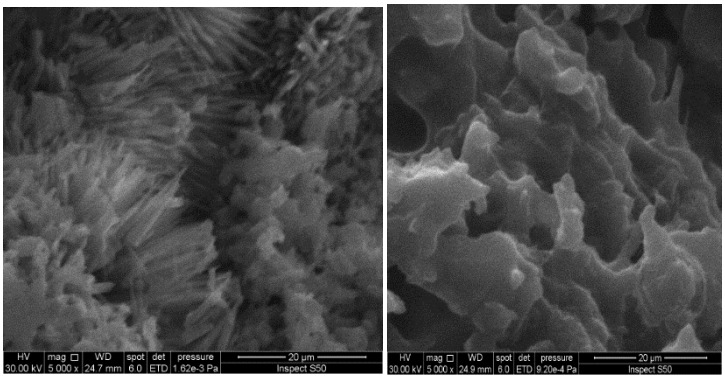
Table 3: Solubility data for the cefixime and optimum formula (F3) expressed in g/l

	Cefixime powder	F3
pH 7.2 phosphate buffer	0.029±0.93	0.375±0.29
Distilled water	0.027±0.77	0.361±0.33

*Results are expressed as mean±SD, n=3.

Scanning electron microscope (SEM) study

Fig. 1 clearly assures the conversion of cefixime trihydrate by liquisolid technique from a crystalline form (A) to the amorphous state (B), which proved the complete solubilization or dispersion of the drug in the liquisolid system that enhances the dissolution of the cefixime from the liquisolid formulas [27].



-A- **-B-**

Fig. 1: SEM image for (A) cefixime trihydrate powder (B) optimum liquisolid formula (F3) containing cefixime trihydrate

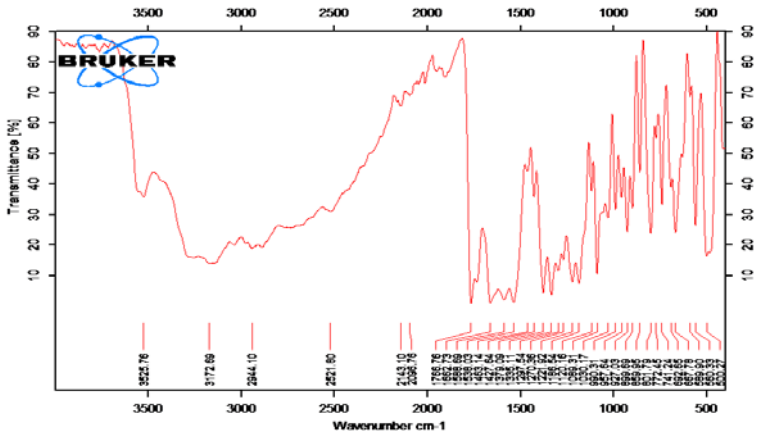


Fig. 2: FT-IR spectrum of cefixime trihydrate

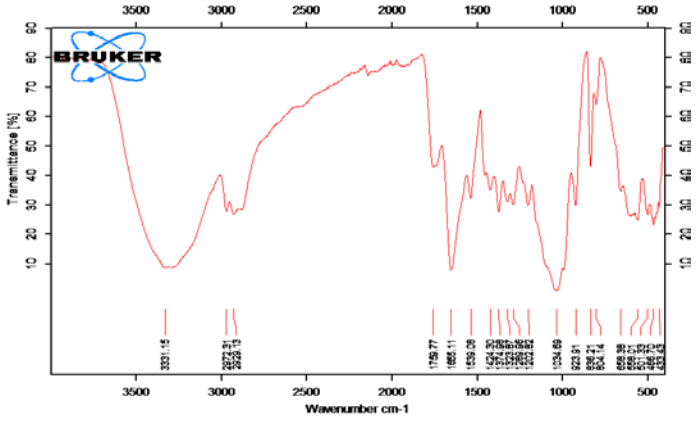


Fig. 3: FT-IR spectrum of optimum liquisolid formula (F3)

Fourier transform infra-red spectroscopy (FT-IR) study

FT-IR spectrum of cefixime trihydrate and optimum formula (F3) were shown in fig. 2 and 3 respectively. Fig. 1 clearly demonstrates the characteristic peaks of the drug at 3525 cm^{-1} which results from OH stretching vibration, peaks at 3172 and 2944 cm^{-1} resulting from NH stretching vibration of 1 ° and 2 ° amine, while the stretching vibration of C=O of ketone, carboxyl and lactam was clearly demonstrated at the bands from 1870-1540 cm^{-1}. On the other hand, a little shifting was observed in the peaks the optimum liquisolid formula (F3) to a lower frequency might be explained by the H-bond formation which might be responsible for solubility enhancement of cefixime in the liquisolid system [28, 29].

Weight variations and content uniformity data

Table 4 demonstrated the weight variation and content uniformity of cefixime liquisolid preparation, the result clearly shows that all formulas complied with the USP specifications, which suggests a uniform distribution of the active ingredients and formulas within the capsule dosage form.

Table 4: Weight variations and content uniformity parameters for cefixime liquisolid capsules (mg)

Formulas	Weight variation	Content uniformity
F1	595.4±0.86	195.2±0.54
F2	645.8±0.56	196.5±0.94
F3	698.04±0.16	197.6±0.92
F4	556.32±0.65	196.53±0.65
F5	603.4±0.72	197.4±0.45
F6	651.63±0.43	195.8±0.83
F7	522.3±0.54	197.04±0.17
F8	568.34±0.23	198.34±0.84
F9	609.52±0.95	197.05±0.67

*Results are expressed as mean±SD, n=3.

***In vitro* disintegration and dissolution test**

Results of *In vitro* disintegration and dissolution, in addition to the dissolution profiles for cefixime liquisolid formulas are illustrated in table 5 and fig. (4-6). The results clearly show that disintegration time for all formulas was less than 30 min with no significant differences between formulas.

While, the dissolution results demonstrated a significant increment in $\%D_{45\,min}$ upon increasing carrier/coat ratio (R) from 6 to 10 in the formulas (F1-F3), (F4-F6) and (F7-F9), which might be attributed to enhanced wicking, deaggregation and disintegration properties that resulted from low liquid/powder ratio, high amount of cellulose and low amount of silica (aerosil) which accompanies higher R values. On the other hand, the data revealed a significant reduction in $\% D_{45\,min}$ upon increasing % drug from 70% to 80% in formulas (F1-F3), (F4-F6) and (F7-F9) due to the possible precipitation of the drug on aerosil pores at higher concentration, or might be due to the reduced amount of solubilized drug resulting from the lesser amount of solvent used in higher drug concentration.

Therefore, F3 with higher R value and lower % of the drug was selected as the optimum formula having $\% D_{45\ min}$ equals to 99.5%±0.53.

Furthermore, the comparative release profile of the optimum liquisolid formula (F3) and the marketed cefixime capsule (200 mg) is illustrated in fig. 7. The fig. shows no significant differences in $\% D_{45\,min}$, although, a significant differences were observed in the first 20 min with a greater release rate for F3, which can be explained according to the "Noyes–Whitney" equation and the "diffusion layer model" dissolution theories where the dissolution rate of a drug (DR) is equal to.

$$DR= (D/h)\ S\ (C_s\text{-}C)$$

Since both D (diffusion coefficient of the drug molecules transported through it) and h (thickness of the stagnant diffusion layer formed by the dissolving liquid around the drug particles) were constants, then DR directly proportional to the S (surface area of the drug available for dissolution) and C_s-C (concentration gradient where C is the drug concentration in the bulk of the dissolving medium, and finally Cs is the saturation solubility of the drug in the dissolution medium).

For this reason, dissolution rate increased in liquisolid systems as it contains a solution of the drug in a suitable solvent (PG), therefore, drug surface available for dissolution was tremendously increased compared to the marketed drug. Another explanation is to the possible increment in the Cs in the case of liquisolid system due to the presence of small quantities of PG that act as cosolvent with the aqueous dissolution medium of the stagnant diffusion layer, resulting in a larger drug concentration gradient (Cs _ C), thereby increasing the dissolution rate [30].

Table 5: *In vitro* disintegration and dissolution parameters for cefixime liquisolid capsules

Formulas	DT (min)	% $D_{45\ min}$ (%)
F1	27±0.35	92.07±0.23
F2	26±0.41	97.9±0.41
F3	25±0.76	99.5±0.53
F4	26±0.24	79.6±0.31
F5	27±0.34	91.2±0.18
F6	26±0.21	95.1±0.17
F7	25±0.09	78.5±0.31
F8	26±0.45	85.1±0.24
F9	27±0.32	85.44±0.45

*__Abbreviations:__ Disintegration time (DT), % drug release after 45 min (% $D_{45\ min}$). Results are expressed as mean±SD, n=3.

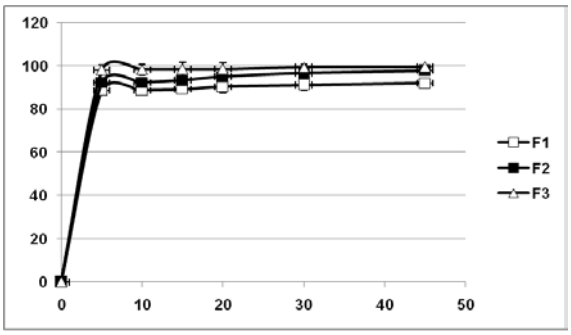


Fig. 4: *In vitro* release profile for liquisolid formulas (F1-F3) containing 70% cefixime and with R-values (6, 8 and 10) respectively in phosphate buffer pH 7.2 (Results are expressed as mean±SD, n=3)

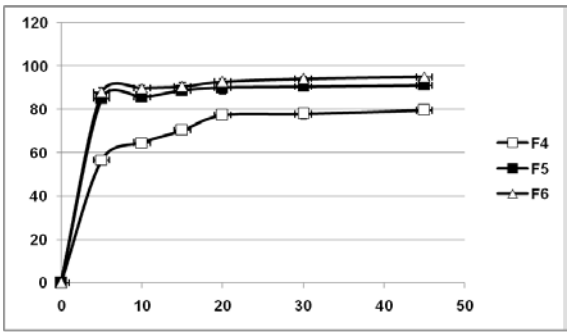


Fig. 5: *In vitro* release profile for liquisolid formulas (F4-F6) containing 75% cefixime and with R-values (6,8 and 10) respectively in phosphate buffer pH 7.2 (Results are expressed as mean±SD, n=3)

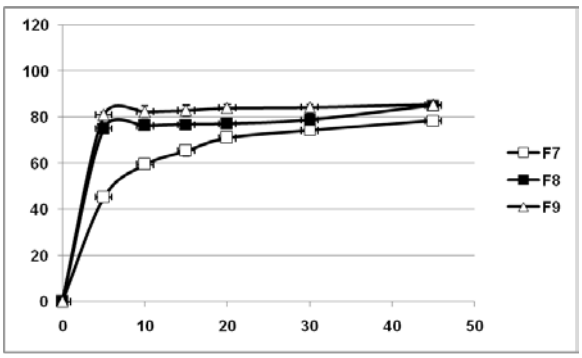


Fig. 6: *In vitro* release profile for liquisolid formulas (F7-F9) containing 80% cefixime and with R-values (6, 8 and 10) respectively in phosphate buffer pH 7.2 (Results are expressed as mean±SD, n=3)

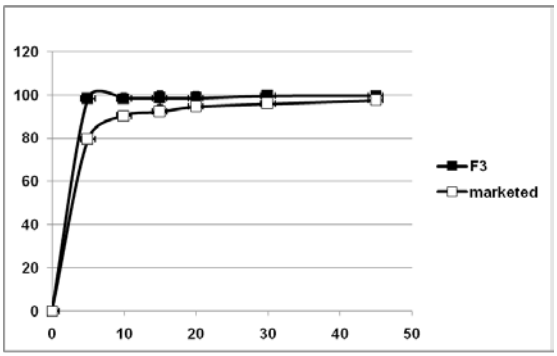


Fig. 7: *In vitro* release profile for optimum formula (F3) and cefixime marketed drug in phosphate buffer pH 7.2 (Results are expressed as mean±SD, n=3)

CONCLUSION

In this research, it is proved that liquisolid technology can be implemented to enhance the solubility and dissolution of cefixime trihydrate, which might significantly improve its absorption via the oral route leading to increase its bioavailability and might reduce its dose intake.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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