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Research Article

Enhancement of the Oral Bioavailability of Fexofenadine Hydrochloride via Cremophor® El-Based Liquisolid Tablets

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Abstract

Purpose: The current work aimed to develop promising Fexofenadine hydrochloride (FXD) liquisolid tablets able to increase its oral bioavailability and shorten time to reach maximum plasma concentrations (T_{max}).

Methods: Eighteen liquisolid powders were developed based on 3 variables; (i) vehicle type [Propylene glycol (PG) or Cremophor® EL (CR)], (ii) carrier [Avicel® PH102] to coat [Aerosil® 200] ratio (15, 20, 25) and (iii) FXD concentration in vehicle (30, 35, 40 %, w/w). Pre-compression studies involved identification of physicochemical interactions and FXD crystallinity (FT-IR, DSC, XRD), topographic visualization (SEM) and estimation of flow properties (angle of repose, Carr's index, Hausner's ratio). CR-based liquisolid powders were compressed as liquisolid tablets (LST 9 – 18) and evaluated for weight-variation, drug-content, friability-percentage, disintegration-time and drug-release. The pharmacokinetics of LST-18 was evaluated in healthy volunteers relative to Allegra® tablets.

Results: Pre-compression studies confirmed FXD dispersion in vehicles, conversion to amorphous form and formation of liquisolid powders. CR-based liquisolid powders showed acceptable-to-good flow properties suitable for compaction. CR-based LSTs had appropriate physicochemical properties and short disintegration times. Release profile of LST-18 showed a complete drug release within 5 min.

Conclusion: LST-18 succeeded in increasing oral FXD bioavailability by 62% and reducing T_{max} to 2.16 h.

Introduction

The dissolution rate is considered as the rate-determining step for absorption of poorly water-soluble drugs formulated in orally administered solid dosage forms. Various techniques were explored to enhance the solubility and dissolution properties of such drugs including; micronization of drugs,[1] development of various nano-based systems,[2] use of solid dispersions,[3] addition of surfactants and co-surfactants,[4] changing the drug to an amorphous state,[5] development of inclusion complexes with cyclodextrins,[6] use of pro-drug and drug derivatization,[7] dispersion in a porous matrix,[8] loading on carriers having high surface area,[9] development of orodispersible tablets via incorporation of superdisintegrants or sublimable agents.[10] The liquisolid compaction technique was developed, as another promising approach, by Spireas et al. for promoting the dissolution characteristics of prednisolone[11] and hydrocortisone.[12]

The liquisolid compacts are regarded as acceptably flowing and compressible powdered forms of a liquid medication. The latter include liquid lipophilic drugs or solid water-insoluble drugs dissolved in suitable water-miscible non-volatile solvents. The liquisolid compacts are prepared by simple admixture of liquid medications with carrier and coating materials.[13] Initially, the liquid medication is dispersed into the porous carrier having high absorption properties. As the carrier got saturated with the liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. In the liquisolid system, the drug is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state.[14] Therefore, due to their significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble drugs are expected to enhance the drug release characteristics and consequently to improve oral bioavailability.[15,16]

The flowability as well as the compressibility of the investigated liquisolid compacts were addressed simultaneously according to the ''new formulation mathematical model of liquisolid systems" developed by Spireas and Bolton.[17] According to this model, the appropriate quantities of the carrier and coating materials for each liquid vehicle could be calculated following the estimation of certain fundamental powder properties; the flowable liquid retention potential (Φ-value) and the compressible liquid retention potential (Ψ-number).[18]

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Fexofenadine hydrochloride (FXD) is a non-sedating antihistamine with selective peripheral H_1-receptor antagonist activity adopted for the symptomatic relief of allergic conditions including seasonal allergic rhinitis and chronic idiopathic urticaria.[19] The slight solubility of FXD in water, its low passive permeability as well as the intestinal secretion promoted by P-glycoprotein efflux could account for the incomplete drug absorption (35%) following oral administration.[20]

In an attempt to overcome these problems in the current work, Cremophor® EL-based liquisolid tablets were developed as a promising more water soluble alternative. Cremophor® EL is a hydrophilic (HLB 12 – 14) non-ionic surfactant that was proved to inhibit P-glycoprotein by increasing the apical-to-basolateral permeability and decreasing the basolateral-to-apical permeability.[21] Consequently, CR-based liquisolid tablets of poor water soluble drugs, like FXD, are expected to improve their oral bioavailability due to the dual improved effect of both solubility/dissolution and intestinal absorption.[22] To confirm this suggestion, the drug pharmacokinetics were estimated following oral administration in healthy human volunteers to explore the potential of the best achieved formula (LST 18) relative to the immediate release Allegra® tablets (Sanofi-Aventis, NJ, US).

Materials and Methods

Materials

Fexofenadine hydrochloride (FXD) and Terbinafine hydrochloride (TER) (Internal Standard) were kindly donated by Alkan Pharma (Cairo, Egypt) and Hikma Pharmaceuticals (6th of October City, Egypt), respectively. Microcrystalline cellulose (Avicel® PH 102) and sodium stearyl fumarate (Pruv®) were procured from JRS, (Rosenberg, Germany). Colloidal silicon dioxide (Aerosil® 200) was purchased from FMC Co. (Philadelphia, PA, USA). Polyoxy-35-castor oil (Cremophor® EL) was obtained from BASF, (Ludwigshafen, Germany). Crosslinked sodium carboxymethyl cellulose (Croscarmellose sodium; Ac-di-sol®) was derived from FMC Corporation (Philadelphia, USA). Lactose was from Meggle GmbH (Wasserburg, Germany). Methanol (HPLC grade) and acetonitrile (HPLC grade) were purchased from Sigma-Aldrich Chemical Co. (St-Louis, MO, USA). Propylene Glycol (PG) was purchased from El-Nasr Pharmaceutical Chemicals Co. (Cairo, Egypt). A reference FXD market product (Allegra®, 60 mg) was purchased from Sanofi-Aventis (NJ, USA).

Application of the mathematical model for designing the liquisolid systems

Three variables were investigated at different levels to optimize FXD-loaded liquisolid systems, Table 1. These variables include; (i) type of liquid vehicle; Propylene glycol (PG) and Cremophor® EL (CR), (ii) the carrier (Avicel® PH 102) to coat (Aerosil® 200) ratio (R = 15, 20 and 25) and (iii) FXD concentration in the liquid vehicle (30, 35, and 40 %, w/w).

Table 1. The composition of the investigated fexofenadine hydrochloride (FXD) liquisolid powders

Formulae	Vehicle	Carrier to coat ratio "R"	FXD concentration in vehicle (w/w %)	Loading Factor "Lf"
LS 1	Propylene Glycol	15	30%	0.3806
LS 2	Propylene Glycol	15	35%	0.3806
LS 3	Propylene Glycol	15	40%	0.3806
LS 4	Propylene Glycol	20	30%	0.3255
LS 5	Propylene Glycol	20	35%	0.3255
LS 6	Propylene Glycol	20	40%	0.3255
LS 7	Propylene Glycol	25	30%	0.2924
LS 8	Propylene Glycol	25	35%	0.2924
LS 9	Propylene Glycol	25	40%	0.2924
LS 10	Cremophor® EL	15	30%	0.3300
LS 11	Cremophor® EL	15	35%	0.3300
LS 12	Cremophor® EL	15	40%	0.3300
LS 13	Cremophor® EL	20	30%	0.3150
LS 14	Cremophor® EL	20	35%	0.3150
LS 15	Cremophor® EL	20	40%	0.3150
LS 16	Cremophor® EL	25	30%	0.3060
LS 17	Cremophor® EL	25	35%	0.3060
LS 18	Cremophor® EL	25	40%	0.3060

According to the "new formulation mathematical model of liquisolid systems", the carrier and coat powders could retain only certain amounts of liquid while maintaining acceptable flow and compression properties.[11,12,17] The flow properties of the carrier and the coat materials loaded with the liquid vehicle could be evaluated by

calculation of the flowable liquid-retention potentials of the carrier (Φ_{CA}) and the coat materials (Φ_{CO}), respectively. As reported for PG, the Φ-values for Avicel® PH 102 and Aerosil® 200 were 0.16 and 3.31, respectively.[18] With CR, the Φ-values for Avicel® PH 102 and Aerosil® 200 were 0.27 and 0.90, respectively.[23] According to Spireas and Bolton,[17] the flowable liquid-retention potentials of the carrier (Φ_{CA}) and the coat materials (Φ_{CO}) as well as the carrier/coat ratio (R) are required to calculate the liquid load factor (L_f) so that the loaded amount of the liquid vehicle would not hinder the flowability and compressibility of the liquisolid system, Equation 1.

$$L_f = \Phi_{CA} + \Phi_{CO}(1/\mathrm{R}) \quad (1)$$

Based on the drug concentration in the liquid vehicle, the weight of liquid vehicle (W) could be estimated. Following, the weight of the carrier (Q) could be calculated, Equation 2.

$$L_f = \frac{W}{Q} \quad (2)$$

Finally, the weight of the coat (q) could be calculated according to the defined carrier / coat ratio (R), Equation 3.

$$\mathrm{R} = \frac{Q}{q} \quad (3)$$

Preparation of FXD-loaded liquisolid powders

Eighteen drug-loaded liquisolid powders (LS 1 – LS 18) were prepared by mixing FXD (60 mg) in a non-volatile liquid vehicle (PG or CR) for 10 min in glass mortar. To this liquid medication, the calculated amount of the carrier (Avicel® PH 102) was added by continuous mixing in the mortar. Finally, the coating material (Aerosil® 200) was incorporated and mixed until the system contents look like a dry powder.

Pre-compression studies on FXD-loaded liquisolid powders

Investigation of the physicochemical interactions and degree of crystallinity

The following studies were conducted on the powders of pure FXD, Avicel® PH 102, Aerosil® 200 as well as the developed liquisolid system (LS 18). For comparison, FXD: Avicel® PH 102: Aerosil® 200 physical mixture was prepared by mixing the liquisolid components, except the liquid vehicle, using a glass mortar for 10 min.

Fourier Transform Infra-Red (FT-IR) spectroscopy: To scrutinize possible chemical interactions between FXD and Avicel® PH 102 or Aerosil® 200, the FT-IR spectra of the samples were scanned using a FT-IR spectrophotometer (IR Affinity-1, Shimadzu, Kyoto, Japan) in the fundamental FT-IR spectrum region between 4000 cm^{-1} - 400 cm^{-1}. The samples were mixed with potassium bromide (1:10, w/w) and pressed to develop suitable discs for FT-IR spectroscopy. Since the potassium bromide has no absorption in the investigated spectrum region, only the FT-IR spectrum of the sample is obtained.[24]

Differential Scanning Calorimeter (DSC): To assess the thermal behavior of the samples as well as their degree of crystallinity, the DSC thermograms of the samples were recorded on a differential scanning calorimeter (DSC-60, Shimadzu, Kyoto, Japan) over the temperature range extending from 30 °C to 250 °C. The samples (3 – 4 mg) were hermetically sealed in aluminum pans and were heated at a constant heating rate of 10 °C/min under a nitrogen purge of 30 ml/min.

Powder X-ray diffraction (XRD): To confirm the powders' crystalline state in the developed liquisolid system, relative to their original state, the X-ray spectra of the samples were recorded on an X-ray diffractometer (PANalytical Empyrean, Almelo, The Netherlands) over a 2θ range extending from 5° to 60° at a scanning rate of 2°/min. The samples were exposed to Ni-filtered Cu-Kα radiation at a λ of 1.544 ˚A. The accelerating potential was set at 45 kV while the tube current was adjusted at 30 mA.

Topographic visualization via scanning electron microscopy (SEM)

The morphologic characteristics of the samples were examined using a JEOL scanning electron microscope (JXA-840A, Tokyo, Japan) under different magnification powers. The samples were fixed on aluminum stubs with double-sided tape, and coated with a thin layer (150 Aº) of gold for 2 min using a sputter coater (Edwards S-150A, England). Finally, the gold-coated samples were examined under an accelerating voltage of 30 kV, at a working distance of 8 mm.

Estimation of the flow and packing properties of the liquisolid samples

To allow selection of the promising compressible powders, the flowability and the packing properties of the developed liquisolid powders (LS 1 – LS 18) were estimated, in triplicate, via three parameters namely; the angle of repose, Carr's index and Hausner's ratio.

The fixed-height cone method was adopted to allow the estimation of the angle of repose.[25] The other parameters [Carr's index % and Hausner's ratio] are directly correlated to the tapped and the bulk densities of the powder. Twenty grams of each liquisolid powder were poured into a glass cylinder (50 mL) without compaction. The bulk volume (V_0) was recorded and the bulk density (P_0) was calculated. Then, the cylinder was tapped by raising it to a height of 12 – 14 mm and then allowed to fall under its own weight. The process was repeated until no change in volume was observed, where the powder is expected to reach the most stable arrangement. The tapped volume (V_f) was observed and the tapped density (P_f) was calculated. The Carr's index %[26] and Hausner's ratio[27] were calculated according to Equations 4 and 5, respectively.

$$\text{Carr's Index } \% = \frac{P_f - P_0}{p_f} \times 100 \quad (4)$$

$$\text{Hausner's ratio} = \frac{P_f}{p_0} \quad (5)$$

The smaller values of the C_i % and the Hausner,s ratio indicate better flow properties.

Preparation of FXD liquisolid tablets

The promising flowable liquisolid powders (LST 10 – LST 18) were compressed following the direct compression method to prepare FXD liquisolid tablets, Table 2. Briefly, the liquisolid powders were mixed with lactose (filler) and croscarmellose sodium (super-disintegrant) for 10 minutes in a glass mortar. Following, the mixtures were lubricated with sodium stearyl fumarate (Pruv®) for another 3 min. Finally, 1000 mg of each mixture was fed manually into the die of a single punch tablet press machine (Royal Artist, Bombay, India) fitted with flat faced punches (14 mm) to produce FXD liquisolid tablets; LST 10 – LST 18. The hardness values of the tablets were adjusted at 5 ± 0.5 kg/cm^2 using a hardness tester (Monsanto, St Louis, MO), respectively.

Table 2. The composition (mg) of the investigated fexofenadine hydrochloride liquisolid tablets

Formulae[a]	FXD	Cremophor® EL	Avicel® PH 102	Aerosil® 200	Lactose
LST 10	60.00	140.00	606.06	40.40	108.54
LST 11	60.00	111.43	519.48	34.63	229.46
LST 12	60.00	90.00	454.54	30.30	320.16
LST 13	60.00	140.00	634.92	31.75	88.33
LST 14	60.00	111.43	544.22	27.21	212.14
LST 15	60.00	90.00	476.19	23.80	305.01
LST 16	60.00	140.00	653.59	26.14	75.27
LST 17	60.00	111.43	560.22	22.41	200.94
LST 18	60.00	90.00	490.19	19.60	295.21

In vitro evaluation of FXD liquisolid tablets

Random tablets were selected from each batch and subjected to the following physicochemical tests including determination of tablet weight variation, drug content uniformity, tablet friability percentage, tablet disintegration time as well as drug release studies, relative to Allegra® tablets.

For the determination of the tablet weight variation, twenty tablets were selected, dedusted and individually weighed. The mean (± S.D.) tablet weight was calculated. The drug content uniformity within tablets was evaluated spectrophotometrically (Shimadzu UV 2401-PC, Kyoto, Japan) following drug extraction, from individually crushed tablets, using methanol. The filtered (cellulose acetate membrane filter; 0.45µm) solutions were measured at a predetermined wavelength of 259 nm and the results were expressed as mean (± S.D.) values of ten tablets.[10] The tablet friability test was conducted, on a weighed sample of twenty tablets, using a Roche-type friabilator (FAB-2, Logan Instruments Corp., NJ, USA) revolving at a speed of 25 rpm. By the end of 4 min, the tablets were dedusted, reweighed and the percentage loss in weight was related to the original sample weight. The time necessary for complete disintegration of the tablets was evaluated using a USP disintegration tester (DST-3, Logan Instruments Corp., NJ, USA). The tests were carried out in distilled water (800 ml) and the temperature was adjusted at 37 ± 0.5 °C. The results are expressed as mean (± S.D.) values of six tablets.

The tablet dissolution studies were conducted to compere the drug release profiles from the prepared liquisolid tablets (LST 10 – LST 18) and Allegra® tablets. The studies were conducted in a USP dissolution Tester, type-II (Hanson SR6, Chatsworth, CA, USA) at 37 ± 0.5 ºC. The dissolution medium was 0.1N HCl (pH 1.2, 900 ml).[18] The speed of the paddles was set at 50 rpm. At specific time intervals, aliquot samples (5 mL) were withdrawn from the dissolution medium and filtered using a cellulose acetate membrane filter (0.45 µm). The drug content was determined spectrophotometrically at 259 nm. An equivalent volume of the fresh medium was replaced at each time of withdrawal. The drug released percentages were plotted against the time and the results were expressed as mean (± S.D.) values of three tablets.[10] For setting a level of comparison between formulae, the drug released percentage (DR%) and the dissolution efficiency percentage (DE%) after 5 minutes from the beginning of the dissolution studies were estimated. The latter was calculated according to Equation 6 proposed by Khan[28] as follows;

$$\mathbf{DE\%} = \frac{\int_0^t \boldsymbol{C \times dt}}{\boldsymbol{C_{100} \times T}} \times \mathbf{100} \quad (6)$$

where C represents the drug released percentage as a function of time, t. T represents the total time of drug release and C_{100} represents the complete drug release (100%).

In vivo absorption studies in healthy human volunteers

Determination of FXD in human plasma by HPLC

The investigated HPLC procedure for the determination of FXD was previously adopted for the estimation of FXD following administration of FXD orodispersible tablets in healthy volunteers.[10] To summarize, the mobile phase was a mixture of methanol and potassium dihydrogen phosphate (0.7% (w/v) (70: 30, v/v). The pH (3.5) of the latter solution was adjusted using phosphoric acid. The mobile phase was eluted at a flow rate of 1 ml/min. The chromatographic separation between fexofenadine hydrochloride (FXD) and the internal standard terbinafine hydrochloride (TER) was performed on a reversed phase micro-particulate Agilent® HC-C_{18} column (4.6 x 250 mm, 5 µm) (Kansas, USA) with UV detection (UV-Vis SPD – 10 AVP, Shimadzu, Japan) at 220 nm.[29] The peak areas of FXD and TER were recorded (C-R6A chromatopac integrator, Shimadzu, Japan) and the FXD / TER peak area ratios were calculated. Under the described conditions, the retention times of FXD and TER were 5.2 and 7.8 minutes, respectively. A linear (r^2 = 0.998) standard curve over a FXD concentration range (25 – 600 ng/ml) was constructed by plotting the peak area ratios of (FXD/TER) against the corresponding FXD concentrations in plasma.

Study design

The study was conducted on six healthy male volunteers to compare FXD pharmacokinetics following oral administration of the best achieved liquisolid tablet (LST 18) and a reference market product (Allegra® tablets) at 60 mg doses. The study followed a two-period, two-treatment, randomized, crossover design with a two-week washout period.[30] The study protocol was submitted to and approved (PI – 24) by the Research Ethics Committee in the Faculty of Pharmacy, Cairo University (REC-FOPCU). The protocol complied with the declarations of Helsinki and Tokyo on the biomedical research investigations involving human subjects. The nature and the purpose of the study were fully explained and an informed written consent was obtained from each volunteer. The volunteers kept the right to withdraw during the study without any penalty.

Administration of treatments

On the study day, the fasted (10 h) volunteers were randomly assigned to one of two groups of equal size. Each group was supervised by a physician to answer their queries, ensure their safety and collect the blood samples during the study. On phase I, three volunteers received Allegra® tablets (Treatment A) and the remaining volunteers received LST 18 (Treatment B) with water (200 ml). On phase II, the reverse of randomization took place. All volunteers fasted 4 h post dosing and then received a snack, as per FDA guidelines.

Sample collection and preparation

Venous blood samples (5 ml) were collected into heparinized tubes at specified time intervals following oral administration of each treatment. The derived plasma samples were pipetted into labeled glass tubes and then frozen (- 20°C) until analyzed.

The human plasma samples were prepared according to the protein precipitation technique.[31] Briefly, the thawed plasma samples (350 µl) were transferred to centrifuge tubes along with a fixed aliquot (20 µl) of TER solution in the mobile phase (1.0 µg/ml). The internal standard-loaded samples were treated with a mixture of methanol: acetonitrile (1:1, 1050 µL), vortexed and allowed to stand for 5 min to deproteinize. The precipitated proteins were removed by centrifugation and the supernatants were completely evaporated to dryness under vacuum. The residue was dissolved in the mobile phase (100 µl), mixed well and vortexed for 30 s. Aliquot samples (20 µl) were analyzed by HPLC.

Pharmacokinetic and statistical analyses

The pharmacokinetic parameters of the two treatments were estimated according to the non-compartmental analysis adopting WinNonlin® software (Scientific consulting, Inc., Cary, NC, USA) and the results were expressed as mean (± S.D.) values of six volunteers. The estimated parameters were the maximum drug concentration (C_{max}, ng/ml), the time to reach C_{max} (T_{max}, h), the area under the curve from zero to 12 h ($AUC_{(0–12)}$, ng h/mL) and the area under the curve from zero to infinity ($AUC_{(0–\infty)}$, ng h/mL). The relative bioavailability percentage was determined using Equation 7;

$$\text{Relative bioavailabilty (\%)} = \frac{AUC_{(0-\infty)}\ of\ LST18}{AUC_{(0-\infty)}\ of\ Allegra}\ X\ 100 \quad (7)$$

A two-way ANOVA test was employed to assess the significance of formulations, periods, sequences and subjects on the derived pharmacokinetic parameters at a *P*-value of 0.05.

Results and Discussion

The concept of liquisolid powder design

According to Spireas and Bolton hypothesis,[17] when the liquid medication (FXD in PG or in CR) is added to a porous carrier material, like Avicel® PH 102, both absorption and adsorption take place. More clearly, the liquid medication is initially absorbed (captured) in its closely matted interior fibers. Following their saturation, adsorption of the liquid medication onto the internal and external surfaces of the carrier occurs. The incorporation of a coating material, like Aerosil® 200, is necessary to impart the desirable flow characteristics to the designed liquisolid system due to its high adsorptive properties and large specific surface area.[18]

Pre-compression studies on the prepared liquisolid powders

Investigation of FXD-excipient interaction

FT-IR Spectroscopy: FT-IR spectra of FXD, Avicel® PH 102, Aerosil® 200, their physical mixture and liquisolid system were represented graphically in Figure 1. It is clear that the characteristic peak of FXD (a carbonyl

absorption band at 1725 cm^{-1} assigned to the carboxyl group) is maintained in the physical mixture. As previously reported,[22] the peaks corresponding to the functional groups in the drug will shift to different wave-numbers compared to spectra of the pure drug and pure excipients according to their interaction. On the other hand, the splitting of the characteristic peak of the drug into two peaks and the decrease in the intensities of the peaks, in the FT-IR spectrum of the liquisolid system could indicate the presence of drug – excipient interaction.

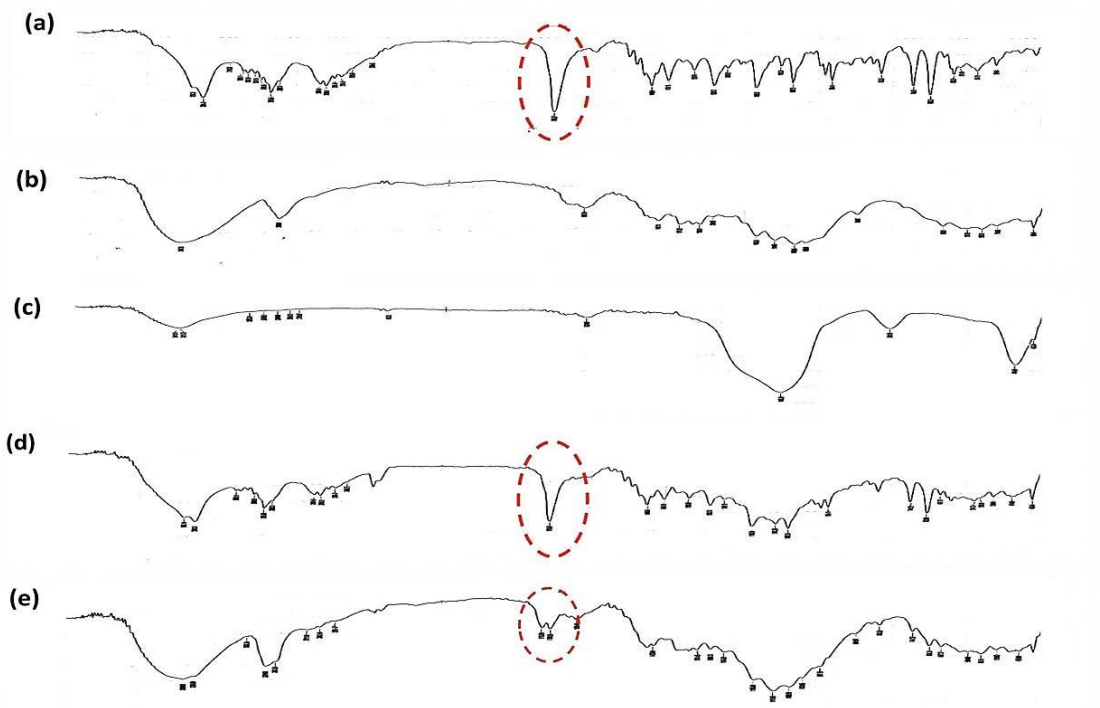

Figure 1. FT-IR spectra of FXD (a), Avicel® PH102 (b), Aerosil®200 (c), physical mixture (d) and liquisolid powder (e).

Differential Scanning Calorimeter (DSC): The crystallinity of FXD in the physical mixture and in the liquisolid system was compared to that of pure FXD via examination of the corresponding DSC thermograms, Figure 2. The pure FXD showed an endothermic characteristic peak with an onset at 193.39 °C with a peak maximum at 199.07 °C corresponding to the melting point of the drug. This sharp endothermic peak signifies that FXD used in pure crystalline state. The DSC thermogram of Avicel® PH 102 displayed one broad endothermic peak started at 56.53°C and ended at 108.30°C, corresponding to the evaporation of the adsorbed water. The absence of sharp peaks in the DSC thermogram of Aerosil® 200 dictates that the coating material was almost in an amorphous state.[18] The characteristic FXD peak was clearly observed in the DSC thermogram of the physical mixture, suggesting that the drug retained its crystalline nature when mixed with the excipients. On contrary, the disappearance of this peak in the DSC thermogram of the liquisolid system and the appearance of a new exothermic peak at 143.77 °C could indicate that drug was uniformly dispersed within the liquisolid matrix.[22] To confirm this suggestion, X-ray diffraction studies were conducted.

Powder X-ray diffraction (XRD): The XRD results of all samples were in line with their thermal analysis data. The X-ray diffractogram of FXD, Figure 3, revealed the presence of sharp distinct peaks having intensity reflection counts of 585.47, 482.72, 655.82, 738.50, 433.77 and 430.16 at 2Θ 5.88, 7.42, 14.07, 18.23, 19.90 and 23.48Aº, respectively. This pattern confirmed the presence of FXD in a crystalline state. Avicel® PH102 is crystalline in nature showing 2 diffraction peaks at 2Θ 16 and 22.5. The X-ray diffractogram confirmed the amorphous nature of Aerosil® 200. The X-ray diffractogram of the physical mixture was a summation of the individual peaks at their corresponding 2Θ positions confirming that physical mixing has no influence of the drug and/or excipient crystallinity. The decrease in the intensity reflection count of the peaks could be related to the dilution effect.[24] The X-ray diffractogram of the liquisolid system supported the conversion of FXD to the amorphous form. Such lack of drug crystallinity was understood to be as a result of FXD solubilization in the liquid vehicle that was absorbed into and adsorbed onto the carrier material (Avicel® PH 102) and coated with the coating (Aerosil® 200). These results were in line with those reported for famotidine[18] and domperidone[32] liquisolid compacts.

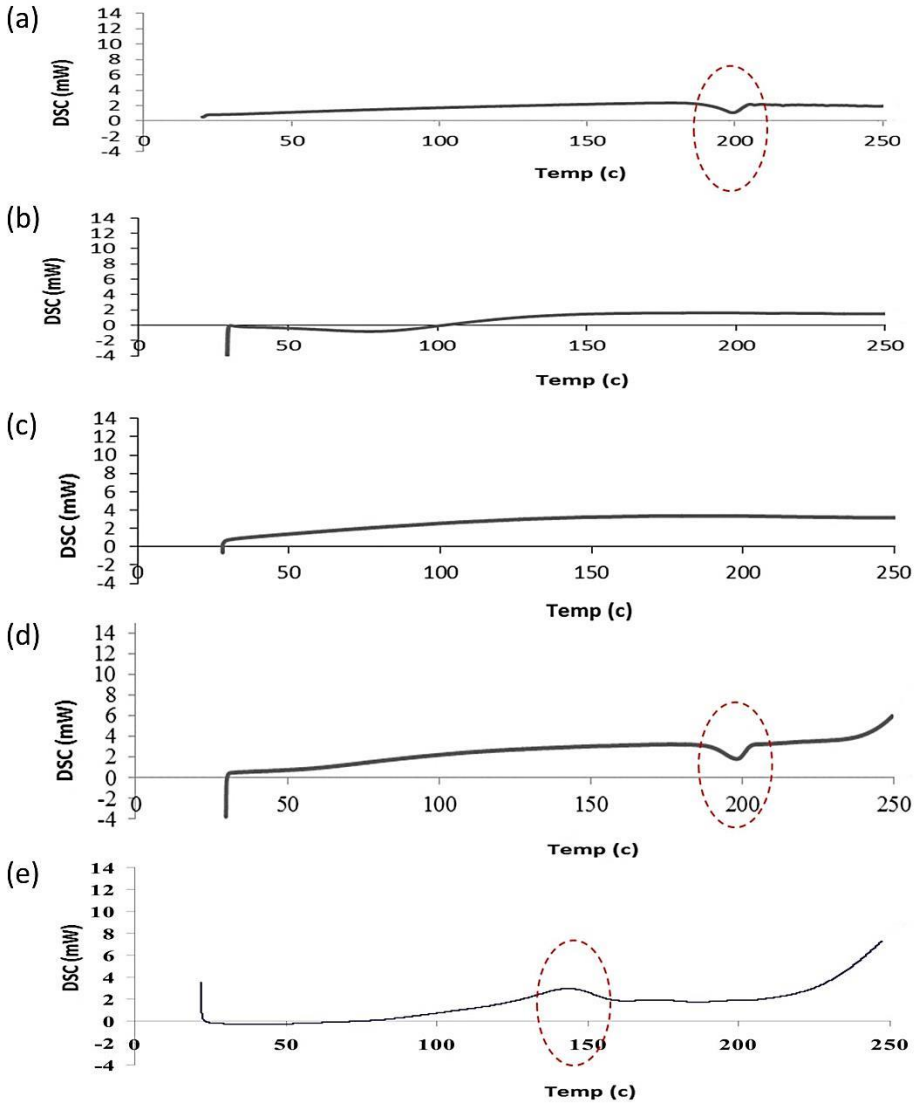

Figure 2. DSC Thermograms of FXD (a), Avicel® PH 102 (b), Aerosil® 200 (c), physical mixture (d) and liquisolid powder (e).

Visualization via scanning electron microscopy (SEM)

The SEM micrographs of pure FXD, Avicel® PH 102, Aerosil® 200 and the liquisolid system (LS 18) were presented in Figure 4. The crystalline rod-shaped particles of FXD were clearly observed, as proved by the DSC and XRD studies. Avicel® PH 102 is partially depolymerized cellulose that occurs as microcrystalline powder composed of porous particles.[33] Aerosil® 200 is an amorphous anhydrous colloidal silicon dioxide powder. The inability to differentiate FXD crystals in the developed liquisolid system suggested the complete drug solubilization and/or dispersion in almost molecularly dispersed state.

Determination of the flow properties of the prepared powders

Powder flow properties influence many handling and processing operations in the tablet production process-train like flow from hoppers, mixing and compression. Obtaining reliable and uniform flow out of the hoppers represent one of the major challenges in handling poor-flowing powders as this might affect the uniform tablet weight and drug content.[23]

In the current work, Avicel® PH 102 was adopted as a porous carrier and compactible filler. When compacted, these microcrystalline cellulose particles are deformed plastically so that a strong compact is formed due to the extremely large surfaces brought in contact during the plastic deformation and the strength of hydrogen bonds formed between the adjacent cellulose molecules.[34] Aerosil® 200 was used as a coating material to adsorb excessive liquid and a glidant to enhance powder flowability. Due to the subjective nature of the individual indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio, Table 3. All of these parameters reflect the degree of inter-particle friction and cohesion. As per the British Pharmacopeial specifications,[35] the lower values of these indicators indicate better powder flowability. It is clear that PG-based liquisolid powders (LS 1 – LS 9) showed poor to very poor powder flow characteristics and were not

compactible into tablets. On the other hand, the CR-based liquisolid powders (LS 10 – LS 18) showed acceptable-to-good flow characteristics and were compactible into tablets; LST 10 – LST 18.

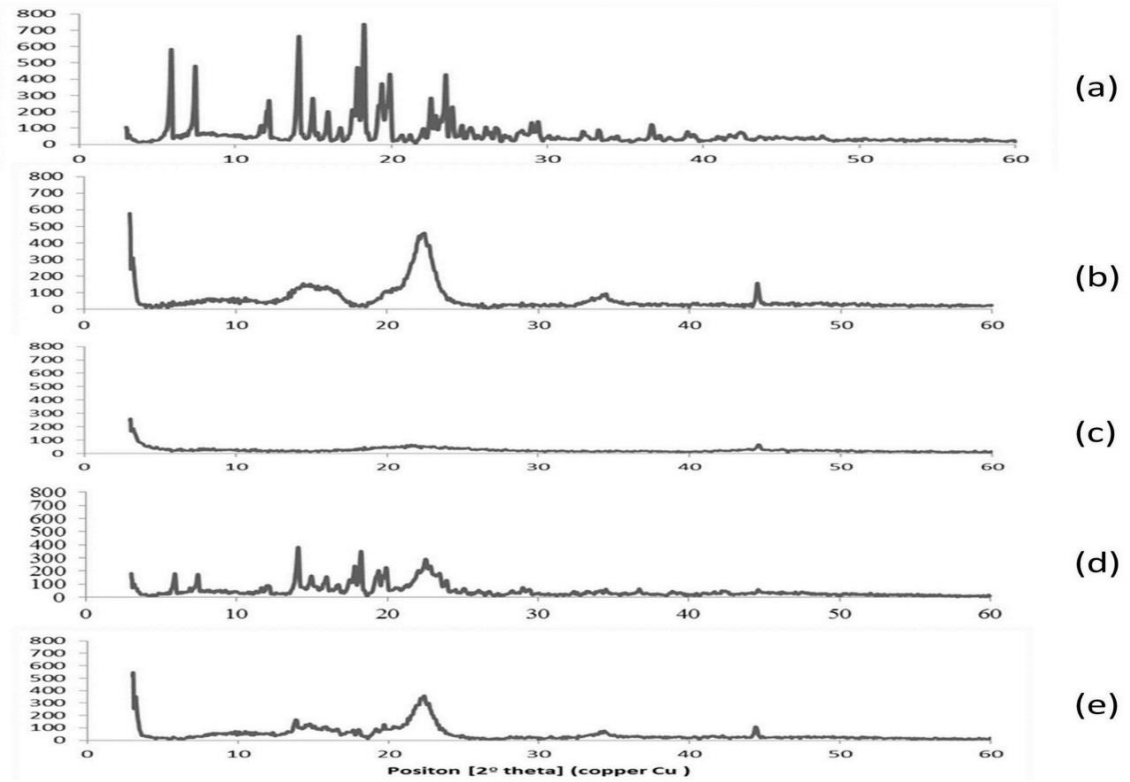

Figure 3. X-ray diffractograms of FXD (a), Avicel® PH 102 (b), Aerosil® 200 (c), physical mixture (d) and liquisolid powder (e).

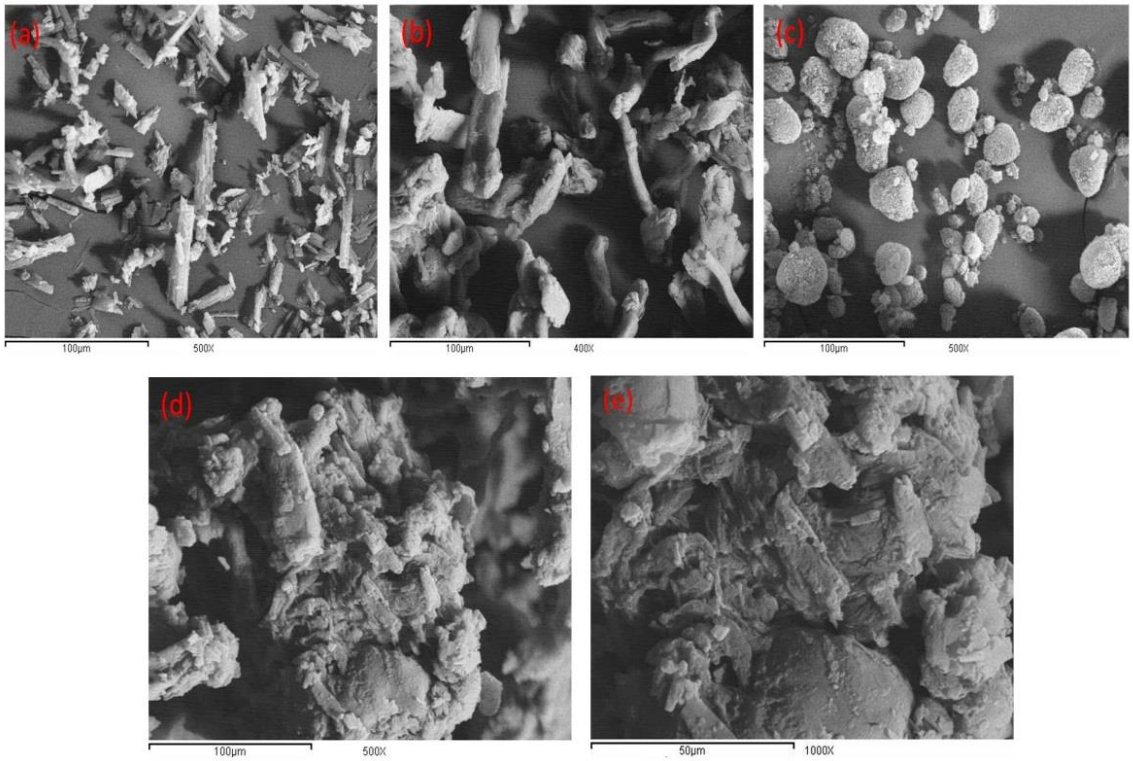

Figure 4. SEM micrographs of FXD (a), Avicel® PH 102 (b), Aerosil® 200 (c), liquisolid powder at different magnifications [500×(d) and 1000×(e)]

Table 3. The flow properties of fexofenadine hydrochloride liquisolid powders (mean ± s.d., n = 3).

Formulae	Angle of repose (Θ)	Carr's index (%)	Hausner's ratio
LS 1	39.57 ± 1.25	35.61 ± 2.17	1.58 ± 0.24
LS 2	39.45 ± 0.95	33.63 ± 1.05	1.54 ± 0.21
LS 3	37.00 ± 1.05	34.62 ± 0.67	1.51 ± 0.17
LS 4	36.53 ± 1.44	33.28 ± 2.05	1.48 ± 0.27
LS 5	36.59 ± 1.07	32.45 ± 1.67	1.47 ± 0.18
LS 6	35.21 ± 0.88	30.77 ± 1.44	1.44 ± 0.13
LS 7	34.04 ± 1.43	30.22 ± 0.78	1.41 ± 0.17
LS 8	33.74 ± 0.96	28.72 ± 1.08	1.39 ± 0.08
LS 9	33.40 ± 1.14	27.2 ± 1.44	1.37 ± 0.07
LS 10	30.93 ± 2.17	23.15 ± 1.27	1.29 ± 0.11
LS 11	30.82 ± 1.40	22.61 ± 0.49	1.26 ± 0.04
LS 12	30.03 ± 0.55	21.82 ± 1.04	1.26 ± 0.06
LS 13	30.54 ± 1.35	22.15 ± 0.78	1.28 ± 0.04
LS 14	30.09 ± 0.63	21.54 ± 1.06	1.27 ± 0.37
LS 15	30.23 ± 1.28	20.61 ± 0.71	1.26 ± 0.04
LS 16	30.11 ± 0.45	21.15 ± 0.58	1.28 ± 0.03
LS 17	30.36 ± 0.86	20.61 ± 0.43	1.26 ± 0.02
LS 18	29.50 ± 1.04	19.96 ± 0.24	1.25 ± 0.03

In vitro evaluation of FXD liquisolid tablets

The physicochemical properties of FXD liquisolid tablets (LST 10 – LST 18) and Allegra® tablets are summarized in Table 4. All the investigated formulae complied with the British Pharmacopoeial specifications[35] for weight uniformity "a deviation less than ± 5% of the average weight", drug content uniformity "a deviation less than ± 15% of the average content", friability test "a deviation less than 1% in weight" and disintegration time "a complete disintegration in less than 30 min". A narrow range of weight variation was observed among the investigated batches of liquisolid tablets, extending from 1.00 ± 0.02 g (LST 18) to 1.08 ± 0.01g (LST 14). A uniform drug distribution was observed (inter-batch; a deviation less than ± 5% and intra-batch; S.D. values less than ± 2%). This uniformity could be related to the uniform adsorption of the liquid formulation onto the carrier. The friability test revealed that the loss in weight was less than 1%. Common physical defects like splitting or cracking were not observed, indicating good mechanical resistance enough to withstand different conditions during handling, packaging and transportation. The mean disintegration time of all liquisolid formulae did not exceed 4 min. A very short disintegration time (0.35 min) was observed with formula LST 18. For comparison, the disintegration time of Allegra® tablets was 7.10 min.

Table 4. Physicochemical characteristics of fexofenadine hydrochloride liquisolid tablets and Allegra® tablets.

Formulae	Tablet weight (g)	Drug content (%)	Tablet friability (%)	Disintegration time (min)	Drug Released[a] (%)	Dissolution Efficiency[a] (%)
LST 10	1.03 ± 0.04	97.95 ± 0.99	0.10	2.62 ± 0.23	64.42 ± 3.53	33.88 ± 1.25
LST 11	1.01 ± 0.04	97.22 ± 1.20	0.31	1.91 ± 0.49	79.61 ± 1.63	39.88 ± 2.33
LST 12	1.03 ± 0.01	96.89 ± 0.94	0.30	1.63 ± 0.12	84.80 ± 0.81	53.34 ± 3.47
LST 13	1.00 ± 0.03	95.99 ± 1.60	0.62	3.13 ± 0.14	86.15 ± 1.08	56.51 ± 2.35
LST 14	1.08 ± 0.01	98.50 ± 0.55	0.81	3.47 ± 0.24	86.60 ± 8.05	57.84 ± 3.16
LST 15	1.05 ± 0.02	97.33 ± 0.63	0.61	2.15 ± 0.12	95.18 ± 04.08	64.20 ± 2.46
LST 16	1.00 ± 0.03	96.20 ± 0.94	0.41	1.12 ± 0.23	56.92 ± 5.98	24.82 ± 1.35
LST 17	1.01 ± 0.05	98.09 ± 0.94	0.32	0.81 ± 0.13	69.80 ± 2.45	43.78 ± 2.33
LST 18	1.00 ± 0.02	99.10 ± 0.94	0.40	0.35 ± 0.12	100.09 ± 0.41	64.66 ± 2.77
Allegra®	0.21 ± 0.01	99.57 ± 1.06	0.25	7.10 ± 1.17	45.38±2.17	32.09 ± 1.24

[a] Determined after 5 min from the beginning of the dissolution studies

The *in vitro* drug release profiles of the investigated liquisolid tablets as well as Allegra® tablets in 0.1 N HCl (pH 1.2) are graphically illustrated in Figures 5. The drug released percentages (DR %) and the dissolution efficiency percentages (DE %) after 5 min were shown in Table 4. It is clear that the developed liquisolid formulae had significantly ($P < 0.05$) higher DR percentages than Allegra® tables. In a parallel line, the DE percentages of all formulae, except LST 10 and LST 16, were significantly ($P < 0.05$) higher.

According to the ''Noyes–Whitney" equation, the drug dissolution rate is directly proportional to the surface area available for dissolution and the drug concentration gradient in the stagnant diffusion layer.[36] FXD particles in the developed liquisolid formulae were dispersed in CR, a hydrophilic liquid vehicle having a HLB value of 14. Consequently, the wetting properties of the drug particles

were increased allowing for a tremendous increase in the drug surface area available for dissolution. On contrary, the surface area exposed for dissolution in the liquid medication-free Allegra® tablets is limited due to the hydrophobicity of the drug particles.[23] Furthermore, the liquisolid tablets are expected to increase the saturated solubility of FXD at the microenvironment incorporating the solid/liquid interface between individual liquisolid particles and the dissolution medium. The expected clinging of minute quantities of the latter onto the former would allow for the formation of a stagnant diffusion layer. Within this microenvironment, it is quite possible that the liquid vehicle could diffuse, along with FXD molecules, in adequate amounts enough to enhance FXD solubility by acting as a co-solvent with the aqueous dissolution medium. Such a possible increase in FXD saturated solubility might result in a larger drug concentration gradient and this is expected to increase the drug dissolution rate.[37,38] Practically, CR-based liquisolid tablets improved the wettability and consequently the dissolution rate of some drugs like griseofulvin[22] and naproxen.[23]

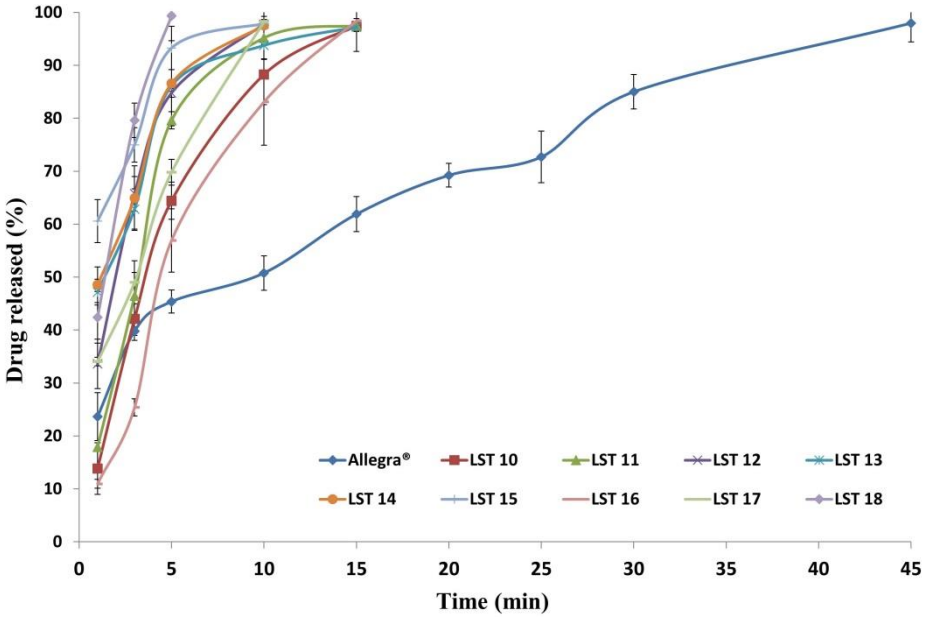

Figure 5. In vitro drug release from Cremophor® EL-based liquisolid tablets in 0.1 HCl at 37±0.5°C

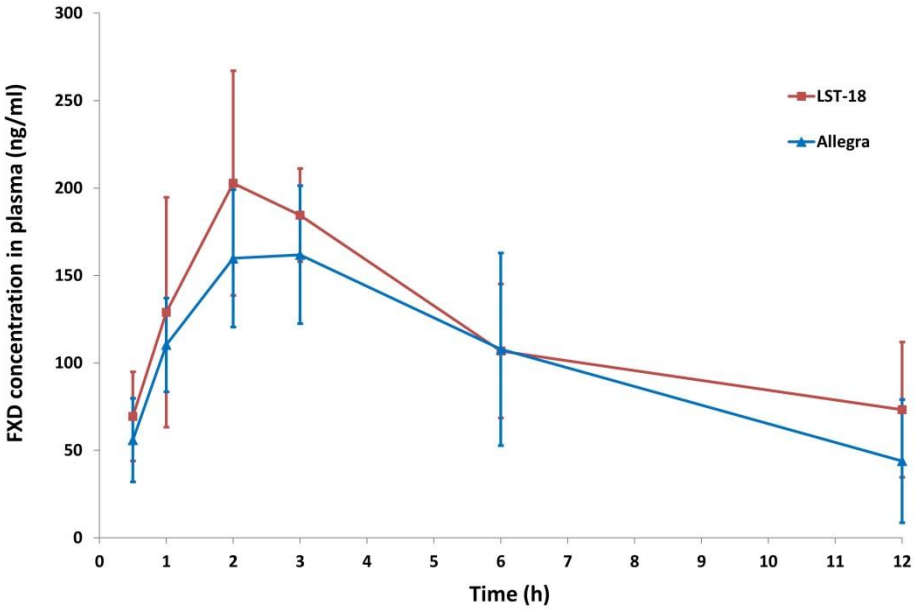

Figure 6. Plasma-concentration time curve of FXD following oral administration of Allegra® tablets and LST-18 liquisolid tablets in healthy human volunteers (mean ± s.d., n=6).

It is obvious that the investigated dissolution parameters (DR% and DE%) of the developed CR-based FXD liquisolid tablets were influenced by the carrier to coat ratio (R = 15, 20 or 25) and FXD concentration in the liquid vehicle (30, 35 or 40 %, w/w).

A direct correlation was observed the carrier to coat ratio and the dissolution parameters. Javadzadeh et al.[39] related this behavior to the nature of Avicel® PH 102 and Aerosil® 200. Avicel® PH 102 is well known disintegrant that acts by wicking effect allowing the dissolution medium to enter the tablet matrix via capillary pores, and consequently break the hydrogen bonding between adjacent bundles of cellulose microcrystals.[22] On contrary, Aerosil® 200 is a hydrophobic coat that might retard the drug dissolution rate. Liquisolid tablets with higher R-values would contain higher amounts of Avicel® PH 102 and lower amounts of Aerosil® 200. As suggested, higher Avicel® PH 102 concentrations would overcome, to a certain extent, the retarding effect of Aerosil® 200.[11,12]

The increase in FXD concentration in the liquid vehicle has been associated with an increase in the dissolution parameters of the investigated liquisolid tablets, probably due to possible increase in the drug concentration gradient in the stagnant diffusion layer. This finding was in accordance with that reported for famotidine liquisolid tablets.[18] To sum up, the best achieved formulae (LST 18) succeeded in releasing 100% of FXD within 5 min, while Allegra® tablets released the same drug content within 45 min. Consequently, LST 18 was selected for further *in vivo* studies.

In vivo absorption studies in healthy human volunteers

The mean (± S.D.) FXD plasma concentrations following oral administration of Allegra® tablets and LST 18 tablets in six healthy volunteers are graphically represented in Figure 6. Marked differences in the rate and extent of FXD absorption were observed following oral administration of the two treatments. The maximum FXD plasma concentrations, $C_{max,}$ for Allegra® tablets and LST 18 were 179.083 (± 27.064) and 221.950 (± 34.880) ng/ml, respectively. The time periods to reach the peak plasma concentrations, t_{max}, for the same treatments were 2.666 (± 0.516) h and 2.166 (± 0.408) h, respectively. The differences between the two treatments for C_{max} and t_{max} were proved to be statistically significant ($P < 0.05$). The success of the best designed formulae LST 18 to increase the C_{max} and shorten the t_{max} could be related to the rapid disintegration and the enhanced dissolution rate following oral administration of LST 18.

Traditional FXD oral dosage forms suffer from low oral bioavailability (35%) due to many factors like the limited water solubility, low passive permeability and intestinal secretion promoted by P-glycoprotein efflux.[20] In the current work, the estimated $AUC_{0-\infty}$ value of Allegra® tablets was 1628.622 (± 928.477) ng h/ml. The corresponding value for LST 18 [2640.193 (± 1830.06) ng.h/ml] was proved to be significantly ($P < 0.05$) higher. It could be concluded that the best achieved formula (LST 18) succeeded in increasing the extent of drug absorption and consequently the relative oral bioavailability of FXD by 62%. This significant increase could be related to several factors; (i) the conversion of the drug from the crystalline to the amorphous state, (ii) the increase in the surface area of drug particles available for absorption, (iii) the enhanced wettability of the drug particles, as well as (iv) the inhibition of intestinal P-glycoprotein efflux via increasing the apical-to-basolateral permeability and decreasing the basolateral-to-apical permeability.[21,40]

Conclusion

FXD-liquisolid powder systems were successfully prepared by dispersion of FXD in propylene glycol or Cremophor® EL and loading to Avicel® PH102 as porous carrier and adoption of Areosil® 200 as a coating material. Nine Cremophor® EL-based liquisolid systems (LS 10 – LS 18) showed acceptable flow properties with regards to the angle of repose, Hausner's ratio and Carr's index. Six batches of tablets (LST 13 - LST 18) showed rapid disintegration times ranging from 2.6 to 0.35 min. The best achieved Cremophor® EL-based liquisolid tablet (LST 18) showed a complete drug release within 5 min. Compared to Allegra® tablets, the pharmacokinetic studies in healthy volunteers proved the ability of LST 18 to increase the maximum FXD concentration, reduce the time for maximum FXD concentration (t_{max}), increase the extent of FXD absorption ($AUC_{0-\infty}$) and increase the relative bioavailability by 62%.

Ethical Issues

Not applicable.

Conflict of Interest

The authors declare that they have no conflict of interest.

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