IJPSR (2021), Volume 12, Issue 2 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 February 2020; received in revised form, 28 May 2020; accepted, 11 July 2020; published 01 February 2021

LIQUISOLID TABLET: AN EFFECTIVE APPROACH TOWARDS IMPROVEMENT OF DISSOLUTION RATE OF FAMOTIDINE AS POORLY SOLUBLE DRUGS

Majid Saeedi [1], Jafar Akbari [* 1], Reza Enayatifard [1], Katayoun Morteza-Semnani [2], Seyyed Mohammad Hassan Hashemi [2], Amirhossein Babaei [2], Sogol Arbab Mashhadi [2] and Mohammad Eghbali [2]

Department of Pharmaceutics [1], Department of Medicinal Chemistry [2], Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran.

Keywords:

Liquisolid compacts, Famotidine, Dissolution, DSC

Correspondence to Author:
Jafar Akbari

Professor,
Department of Pharmaceutics,
Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

E-mail: jafakbari@gmail.com

ABSTRACT: This paper examined the liquisolid compact method as one of the tools for greater dissolution of the practically water-insoluble drug famotidine (FM). Therefore, the model drug, FM, has been formulated as directly compacted tablets and liquisolid compacts and then investigated for *in-vitro* release properties at diverse dissolution circumstances. According to the method, it is possible to convert the liquid medications of water-insoluble drugs in the non-volatile liquid vehicles into reasonably compressible and flowing powders. The formulated systems have been evaluated in terms of the pre-compression factors like the Fourier-transform infrared spectroscopy (FTIR) analysis, flow features of the liquisolid system, differential scanning calorimetry (DSC), post-compression factors, including the content uniformity, hardness, friability and weight variation, disintegration test, *in-vitro* dissolution examinations, effects of the dissolution volume as well as pH on the drug release rate and approximation of the fraction of the molecularly dispersed drug in the liquid medication. Since, the liquisolid compacts revealed notably greater drug release rates in comparison to the direct compress tablets in diverse dissolution volumes and pH, it could be concluded that this would be an encouraging approach to the improvement of dissolving the weak water-soluble drugs and formulation of the immediate release solid dose forms.

INTRODUCTION: Increasing the dissolution rate of the in-soluble and or liquid lipophilic drugs for improving the absorption efficacy and bio-availability is a major objective of the drug professionals [1, 2]. A series of the widely used methods for achieving such an objective include the water-soluble salts as well as the polymorphic forms, forming water-soluble molecular complexes, lyophilization, drug micronization, solid dispersion, coprecipitation as well as micro-encapsulation; out of which, 'liquisolid compacts' has been considered a major assuring one [3-6].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(2).803-12

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(2).803-12

It is well-known that the liquisolid systems are relatively compressible, and flowing powdered forms of the liquid drugs like the liquid lipophilic drugs and or water-insoluble drugs dissolved inappropriate water-miscible non-volatile solvent systems. It is notable that in case of admixture of such kinds of liquid medication with certain powder excipients as the coating materials; that is, carrier, they could be converted into dry-looking, free-flowing, and no adherent powder.

Notably, the liquisolid forms had considerable wetting features and the drugs' available surfaces for dissolution enhanced, which has been caused by trapping the solid drug parts into the powder substrate in solution or nearly molecularly dispersed state. Consequently, because of the respective remarkably enhanced wetting features and the drugs' available surfaces for dissolution, the liquisolid compacts of the water-insoluble materials

could probably exhibit the increased drug release characteristics and better bio-availability [4, 5, 7]. It is widely accepted that FM has been allowed for active and maintenance therapies of different kinds of ulcers and hyper-secretory situations.

Moreover, mechanisms, pharmacological impacts, sites of actions and clinical utilizations have been considered similar to other H_2-receptor antagonists; however, reports showed that FM on the equimolar bases respectively had ~20 and ~7.5 times higher potency than cimetidine and ranitidine for the inhibition of the gastric acid secretion. In spite of the greater efficiency of FM, remarkable consequences have not been reported [8, 9].

Although FM applied the minimum first-pass effect, its oral bioavailability in the male decreased and has been variable in a range between 40 and 50% due to the weak aqueous solubility, higher polarity as well as gastric degradation [9]. Another study showed the rate-limiting step for bio-availability of the poorly water-soluble drugs such as FM would be the dissolution rate. Such a factor has been a function of solubility and the drug surface area. Hence, the dissolution rate would enhance in the case of the drug-enhanced solubility, and it would augment by enhancing the drug surface area [9].

According to this paper, FM has been considered one of the poorly water-soluble drugs formulated into the liquisolid tablets with the same powder excipients, the liquid vehicle, as well as diverse drug concentrations in their liquid medications. Moreover, we examined the effects of the dissolution media and their volume on the rate of in vitro drug release.

MATERIALS AND METHODS:

Materials: According to the research design, FM has been provided by Daru Pakhsh Pharmaceuticals, Tehran, Iran. In addition, FMC Pharmaceuticals, Irland has been selected to purchase Avicel PH 102 (microcrystalline cellulose, MCC). Moreover, Aerosil 200 (Colloidal silicon dioxide), polysorbate 80 (tween 80), Magnesium stearate (MgSt), propylene glycol (PG), Sodium hydroxide, Polyethylene glycol 400 (PEG 400), as well as Potassium dihydrogen orthophosphate have been provided through Merck Co (Germany).

Solubility Examinations: The paper also evaluated FM solubility in glycerol, polyethylene glycol 200 and 400. Then, the FM saturated solutions have been procured *via* addition of the drug in excessive amounts to the solvents and shaken into the shaker (Ika, Germany) at 25 °C at constant vibration (150 rpm) for 48 h. Then, it has been sampled for reaching the fixed content of solubility. Afterward, the samples have been filtered and examined by UV-spectro-photometer (Jasco v 630, Philippine) at the wavelength of 268 nm 3 times for all solvents.

Computation of the Loading Factor (L_f): It is notable that for calculating the loading factor, aerosil and avicel powder have been independently added to the liquid medication slowly and mixed for reaching a powder with adequate compressibility and flowability. Therefore, the above factors have been assessed by computing the Hausner's ratio (HR) and Carr's index (CI). In addition, CI and HR have been computed based on Eqs. (1) and (2):

$$\text{Carr's index} = 100 \times (\rho \text{ tapped} - \rho \text{ bulk}) / (\rho \text{ tapped}) \quad (1)$$

$$\text{Hausner ratio} = (\rho \text{ tapped}) / (\rho \text{ bulk}) \quad (2)$$

Applying $L_f = W/Q$ formula (W= the amounts of the liquid medication and Q= the amount of carrier (Ca) materials), values of the loading factor have been computed. **Table 1** reports the outputs.

Preparing the Liquisolid Compacts: Several FM-LS formulations have been procured in little batches between LS-1 and LS5 **Table 1**. The carrier (Ca) / coating (Co) ratio (R-value) equaled [10]. According to L_f, adequate contents of the excipients have been utilized for all formulations. Notably, ØCa and ØCo values for all specific solvents have been applied for calculating L_f (Equation 3) of a certain liquid vehicle.

According to (Lf), and content of the amounts of the carrier (Q), liquid medication (W) as well as the coating material (q) could be computed by re-arranging Equations [4, 5]. **Table 1** is a summary of the liquisolid formulations.

$$L_f = Ø\_Ca + Ø\_Co \times 1 / R \quad (3)$$

$$L_f = W/Q \quad (4)$$

$$R = Q / q \quad (5)$$

Thus, FM has been dispersed in a non-volatile solvent. The carrier and coating substances have been added to the liquid medication. Finally, MgSt has been added to the mix. Then, the resulting powder has been compressed into tablets with the use of the manual tableting machine.

Table 1 presents the composition of the examined formulations. As a result, the single punch compress machine has been adjusted for all formulas for reaching the optimal hardness of 50-70 N, though it has been impossible for some formulas.

Friability Testing and Hardness Test: According to the research design, an Erweka friabilator (Erweka, Heusenstamm, Germany) has been used to examine the tablet's friability at 25 rpm for four minutes. Before and following the examinations, the weight of ten tablets from all formulas has been measured, and percent friability has been computed by Eq. 6:

$$\% \text{ Friability} = (W_i - W_a) / W_i \times 100 \quad \text{.....(6)}$$

So that W_i and W are present the tablets weights before and following the examination. **Table 1** reports the outputs. In addition, Erweka hardness tester (Erweka, Heusenstamm, Germany) has been used to measure the force (N) necessary to crush the tablet. **Table 1** reports the outputs.

Content Uniformity: In this stage, 3 tablets from all batches have been randomly taken for examining its content uniformity. Then, they have been weighed and ground for obtaining separate powders. Afterward, the powders have been dissolved in1000 ml phosphate buffer at pH equal to 6.8 and have been filtered using the Whatman filter paper. Finally, based on the US Pharmacopeia, a UV spectrophotometer at 268 nm has been used to measure the content of the drug. **Table 1** reports the outputs.

Disintegration Test: According to the research design, disintegration has been tested at 37 ± 1 °C in the distilled water for six tablets from all formulations by means of Erweka disintegration tester (Erweka; Heusenstamm: Germany). These tablets have been regarded as entirely disintegrated so that any residues did not remain on the screen. In general, perfect tablet hardness would be obtained with no application of the excess compression force, in which fast drug dissolution and tablet disintegration were kept at a similar period [10].

Dissolution Examinations: It should be mentioned that USP dissolution apparatus No II (paddle technique) (Erweka: Germany) has been used to do in-vitro dissolution experiments on 3 tablets of each formulation.

Based on US pharmacopeia, dissolution tests for each tablet have been accomplished at 50 rpm in a 900 mL phosphate buffer at pH equal to 4.6 and 37 °C temperature for 20 min. Then, 5 ml of medium has been removed from each dissolution vessel at times 5, 10, 15, and 20 min and replaced by the fresh dissolution medium.

Afterward, a UV/visible spectrophotometer has been used to analyze the samples at 268 nm. For determining the effects of the pH and volume, dissolution has been examined for a chosen formulation in 900 mL, 300 mL, as well as 150 ml volumes and pH equal to 1.3, 4.6, and 6.8 for 20 min. Finally, each medium with a certain pH has been procured according to the US pharmacopeia.

Differential Scanning Calorimetry (DSC): In this stage, a Pyris 6, (Perkin Elmer, USA) has been used to record the DSC thermograms of the samples (FM, excipients & liquisolid formulations). Then, the 4-5 mg samples have been placed in the aluminum pans. Finally, thermal behaviors have been registered based on nitrogen gas at the scanning rate equal to 20 °C / min that had a temperature ranging between 30 and 300 °C [11].

FTIR Analyses: Here, the Perkin Elmer FT-IR spectrophotometer has been used to examine the FM, FM-LS5, and PEG 400. Then, potassium bromide (KBr) powder has been used to grind the samples. Afterward, KBr discs have been procured by compressing powders at the pressure of 5 tons in the hydraulic press for five minutes. Finally, FTIR spectra have been registered with 4 cm^{-1} resolution in the 4000-500 cm^{-1} region [12].

Statistical Analyses: Notably, outputs have been represented as the mean ± standard deviation (SD) of not less than 3 determinations (n = 3). Then, analysis of variance (ANOVA) and then the

Tukey's test has been utilized for the comparison of the treated groups with the controls. While comparing just 2 means, a t-test has been run. Statistical analyses have been run with SPSS 2021. Finally, a P-value of less than 0.05 has been significant.

RESULTS AND DISCUSSION:

Solubility Examination: We selected FM as the model drug due to its water-insolubility characteristics that made it a perfect alternative to be designed as the fast release liquisolid compact. According to the results, standard curves of FM solution have been linear in the concentration ranges between 5 and 30 µg/mL. Moreover, Table 2 presents FM solubility in propylene glycol (PG), Polyethylene glycol 400 (PEG400), and polysorbate 80. According to the table, FM had the greatest level of solubility in PEG 400. As the present research aimed at enhancing the drug dissolution rate, PEG 400 has been utilized as a non-volatile solvent to procure the liquisolid systems. It should be noted that choosing the liquid vehicle would be highly dependent on the research objective; that is, a liquid vehicle with a higher capability of solubilizing the drug would be chosen for the dissolution enhancement. However, if the objective has been the prolonged drug release, the liquid vehicle with the minimum capacity to solubilize the drug could be selected [13]. Besides the drug solubility in the liquid vehicle, a number of other physicochemical factors like polarity, viscosity, lipophilicity as well as chemical structure significantly influenced the drug release profiles [7].

Pre-Compression Examination of the Liquisolid System: Like several other drug delivery systems, factors with the ability to affect the features of the liquisolid powder system would be mechanical, environmental, and physical parameters. Carr's index up to 17.3 has been reasonable as the flow feature. Therefore, Hausner's ratio (HR) has been associated with inter-particle friction. In addition, powders with lower inter-particle friction possessed a ratio of nearly 1.21, presenting an acceptable flow. Finally, the FM-LS-5 system with HR of 1.21 and Carr's index (CI) of 17.3 has been regarded for future studies. **Table 1** presents each batch of the FM-LS compacts.

TABLE 1: COMPOSITION (MG) OF LIQUISOLID FORMULATIONS (CALCULATED FOR ONE TABLET), R-VALUE, LF, CARR'S INDEX (CI %), HAUSNER'S RATIO (HR), HARDNESS, DISINTEGRATION TIME, FRIABILITY AND CONTENT UNIFORMITY OF LIQUISOLID COMPACTS

Code	Formulation composition											Tablet characteristics			
Formulation	Liquid vehicle	Amount of Drug (mg)	Amount of vehicle (mg)	Aerosil (mg)	Avicel (mg)	MgSt (mg)	Tablet weight (mg)	R	Lf	CI	HR	Hardness N±SD	Disintegration time	% Friability	Content uniformity
FM-LS1	PEG400	20	0	17.14	171.4	1.56	210.13	10	0.11	17.3	1.21	59.3±0.57	342±41.63	0.31	97.55±2.54
FM-LS2	PEG400	20	20	34.28	342.8	3.12	420.27	10	0.11	17.3	1.21	58. 3± 0.57	284.66±42.85	0.23	96.45±3.34
FM-LS3	PEG400	20	40	51.42	514.2	4.69	630.40	10	0.11	17.3	1.21	62.33± 1.52	327.66±28.88	0.05	97.12±1.01
FM-LS4	PEG400	20	60	68.57	685.7	6.25	840.54	10	0.11	17.3	1.21	63.6± 3.51	521.66±9.01	0.23	101.74±2.69
FM-LS5	PEG400	20	80	85.71	857.1	7.82	1050.67	10	0.11	17.3	1.21	66±2	118±19.69	0.64	100.79±3.61

TABLE 2: SOLUBILITY OF FM IN VARIOUS SOLVENT

Solvent	Solubility (mg/100ml)
Polyethylene glycol 400 (PEG400)	309.4±1.21
Propylene glycol (PG)	270.6±3.18
polysorbate 80 (tween 80)	130.1±1.63

FTIR Analyses: For detection of all feasible interactions between the excipients and drug in the formulation as well as for the achievement of the structural information of the molecules, FTIR analysis was performed. **Fig. 2** depicts FTIR spectra of PEG 400, FM-LS 5, and FM. As seen, FTIR spectrum of FM exhibited the absorption bands at 3500 to 3100 cm^{-1} (NH_2 stretching), 1330 and 1146 cm^{-1} (SO_2 stretching) and 1690-1475 cm^{-1} (C=N & C=C stretching). In addition, the FTIR spectrum of PEG400 showed the absorption bands at 3348 cm^{-1} (O-H stretching), 1300-1100 cm^{-1} (C-O stretching), and 2873 cm^{-1} (C-H stretching). Finally, it has been observed that the FTIR spectrum of the chosen formulation contained the typical drug peaks.

DSC: According to studies, a classic application of the DSC analysis would be to determine probable interaction between the excipients and drug entity in its formulation. Therefore, the presence of incompatibility in the course of the pre-formulation phase would be highly prominent for ensuring the

successfulness of the consequent stability investigations [14].

Fig. 1 is a schema of the thermal behavior of the pure elements and thermal behaviors of the resulting liquisolid system. According to the figure, FM peaks have been evident in its DSC thermo-gram **Fig. 1**, which confirmed a sharp typical endothermic peak at 178 °C relatives to the respective melting temperature (Tm). This sharp endothermic peak signified that the utilized FM has been in the pure crystalline mode. Moreover, an exothermic peak has been observed at 204.92 °C that could be caused by the boiling or vaporization possibly after the drug decomposition. According to the thermo grams of Avicel PH 102 in **Fig. 1D**, 2 wide endothermic peaks have been observed at 90.18 and 342.78 °C, which could be relative to the absorbed water volatilization accompanied by the melting decomposition with charring the crystalline cellulosic materials. However, the thermal behaviors of Aerosil 200 in **Fig. 1c** showed no sharp peaks, which proved the amorphous state of the coating material. Put differently, the liquisolid system thermogram in **Fig. 1D** represented the full disappearance of the two typical peaks of FM, which agreed with forming the drug solution in the liquisolid powdered system; that is, the drug has been molecularly dispersed into the liquisolid matrix. Therefore, disappearing the medicine peaks by formulating the liquisolid system has been compatible with Mc Cauley and Brittain's [14] study, in which complete suppression of each drug thermal feature clearly indicated forming an amorphous solid solution. Furthermore, Mura *et al.* [15] showed drug amorphization by the total disappearance of the drug melting peak.

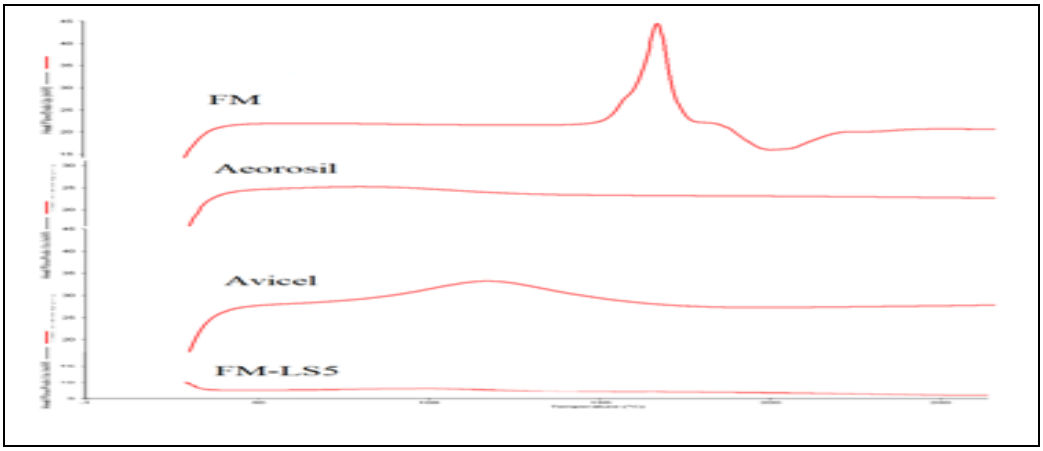

FIG. 1: DIFFERENTIAL SCANNING CALORIMETRY OF LIQUISOLID FORMULATIONS, EXEPIANT AND FM

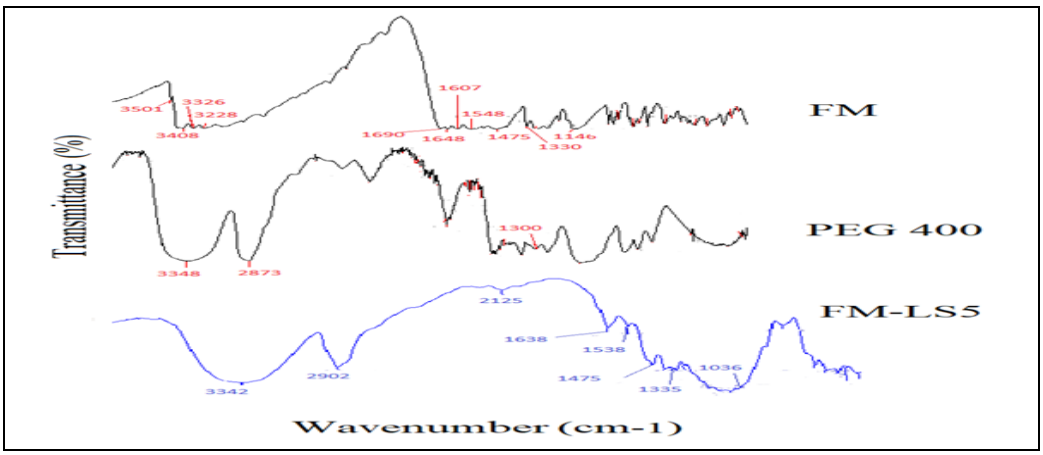

FIG. 2: THE FTIR SPECTRA OF FM, PEG 400 AND FM-LS5

Tablet Features (Content Uniformity, Hardness, Friability and Disintegration Tests): Each liquisolid tablet followed US pharmacopeia weight uniformity test. Moreover, each tablet satisfied the content uniformity criteria, as per US Pharmacopeia, where all contents ranged from 96% to 102% of the average content **Table 1**. According to the analyses, each FM-LS tablet has been

substantially passed the friability tests. However, the percentage had not been excessing 1% of the tablet weight, and any tablet has not been deformed or broken. As each procured formula satisfied the standard friability criteria, it showed reasonable toughness and tolerated the abrasion in the course of handling. Moreover, each procured batch exhibited hardness in the ranges between 55 and 70 kg/cm^2. In general, an acceptable hardness of the tablet has been concurrently regarded with the least compression force, fast disintegration as well as reasonable dissolution of the drug [15]. Generally, the formulation must be led to the optimization of the tablet hardness with no excess compression force so that it simultaneously assured the fast drug dissolution and tablet disintegration. Put differently; the tablets must have adequate hardness for resisting the breaking in the course of the normal handling and also have a suitable softness for proper disintegration following the swallowing [16].

Therefore, the mean hardness of each liquisolid formula has been specified in **Table 1**, which confirmed each liquisolid tablet formula, possessed a reasonable hardness. In addition, hydrogen bonds between the hydrogen groups over the neighboring cellulose molecules in the Avicel PH 102 could justify entirely cohesiveness and strength of the compacts based on Shangraw [17]. Furthermore, higher compactness and compressibility of Avicel PH102 could be accounted for by the nature of microcrystalline cellulose particles that have been linked by hydrogen bonds while compressing. These particles experienced plastic deformation, and a robust compact would be shaped because of the highly increased numbers of the contacted surfaces in the course of the plastic deformation and strength of the established hydrogen bonds [17]. Additionally, PEG400 molecule contained 2 terminal hydroxyl groups; hence, the formation of the hydrogen bonds with Avicel PH 102 would be probable. Finally, each procured batch possessed a disintegration interval of <600 s.

***In-vitro* Dissolution Examination (Effects of the Liquid Concentration, Dissolution Volume and pH):** It is notable that FM has been chosen as the model medicine in the present research because of it's' insolubility in water; therefore, it would be a perfect alternative to test the potentials of the fast-release liquisolid compacts.

Additionally, it could be readily assayed and determined its quantity in the solution with the use of spectrophotometric principles and processes. Moreover, the effects of the solvent like the drug ratio to drug release behavior have been examined in our research see **Fig. 3**.

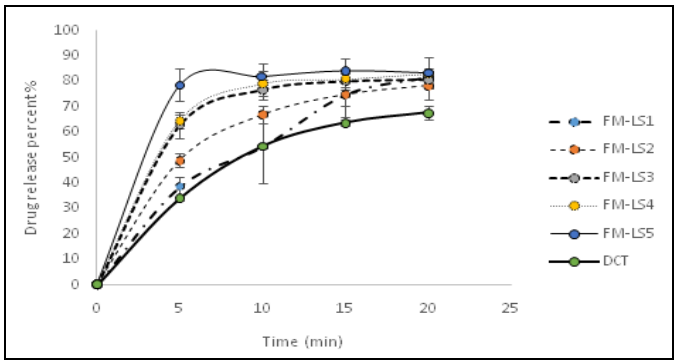

FIG. 3: DISSOLUTION PROFILE OF FM LIQUISOLID COMPACTS IN 4.6 pH

Earlier studies indicated that as the solvent concentration in the liquisolid systems increased, the drug release rate enhanced. Hence, the ratio of solvent-drug in formulations containing PEG400 did not significantly influence the dissolution rate ($P>0.05$). Outputs showed FM dissolution profiles from the liquisolid compacts as well as the directly compressed tablet. Furthermore, the liquisolid compacts produced a greater dissolution rate as compared to the direct compression tablet ($p<0.000$). The liquisolid method would have widespread utilization for improving the dissolution rate of the low-dose insoluble medicines like prednisolone [18], famotidine [14], valsartan [19], ketoprofen [20], raloxifene hydrochloride [21], clonazepam [22], clofibrate [23,] and so on regarding the increased dosage of water-insoluble drugs; that is, carbamazepine, the researchers addressed the possibility of the liquisolid procedure.

For example, Javadzadeh *et al.* [24] indicated the possibility of the contribution of the liquisolid method to the incorporation of the increased dose water-insoluble medicines into the liquisolid systems via the addition of a number of additives like HPMC, polyethylene glycol 35000, as well as PVP as the mentioned additives, had been capable of increasing the liquid adsorption capacities of the carrier and coating substances. In another study, Hentzschel *et al.* [25] showed one of the other potent approaches for loading the increased dosage of the weakly water-soluble medicines into the liquisolid

system *via* the new carriers like Neusilin® with greater specific surface area value and greater adsorption capacities. Moreover, Pezzini *et al.* [26] examined the feasibility of the use of the mentioned method for preparing the liquisolid pellets to enhance the felodipine dissolution. Researchers showed the formation of a liquisolid micro-environment with soft structures and higher porosity, favoring disintegration and dissolution processes of the felodipine liquisolid pellets. Findings suggested feasibility for adopting the liquisolid pellets as the new drug delivery systems for improving the dissolution rate of the weakly water-soluble medicines. Notably, Khan *et al.* [27] comparatively studied the feasibility of the liquisolid method for increasing dissolution rate of the hydro-chlorothiazide as compared to the solid dispersion procedure. According to the outputs, the liquisolid systems augmented the drug dissolution rate to 95%, whereas it just enhanced by 88% for the solid dispersion. Hence, the liquisolid method has been shown to have higher efficiency in comparison to the solid dispersion method for the improvement of the extent and rate of the drug release. Consequently, multiple studies dealt with *in-vivo* profiles of the liquisolid tablets. As an instance, Khaled *et al.* [28] assessed the *in-vivo* function of the hydro-chlorothiazide liquisolid tablets in 6 male Beagle dogs with the use of a 2-way crossover design. Therefore, hydro-chlorothiazide liquisolid tablets displayed 15% higher bioavailability in comparison to the commercial oral dose form. Experts in the field introduced 3 probable mechanisms of dissolution increase for the liquisolid systems; that is, greater drug surface areas, greater drug solubility, and higher wetting features. Although this medicine has been in a solid dose form, it has been provided in a solubilized or dispersed state. Hence, the surface area of the medicine accessible for dissolution has been notably augmented [14, 29, 30]. Besides the earlier mechanism, it is possible to increase the solubility of the drug in the aqueous diffusion layer.

Moreover, a little liquid vehicle found in the liquisolid system could be inadequate for increasing total drug solubility in the dissolution medium. Nonetheless, in the micro-environment of diffusion layer between individual liquisolid primary particle and dissolution medium, the liquid vehicle could function as a co-solvent and would diffuse out of the primary particle with the medicine that could be enough for increasing the drug solubility [4, 14, 31]. In addition, as a result of the surface activities of the liquid vehicles, inter-racial tension between the tablet surface and dissolution media could be declined, causing the better wettability of the hydrophobic drugs [31, 32]. Recent authors enhanced the dissolution of tadalafil that is a poorly water-soluble drug using the liquisolid method. Furthermore, the increased dissolution mechanism has been examined. According to the outputs, reducing the particles' sizes and crystallinity and increasing the wettability has been the basic mechanisms for greater dissolution rate of tadalafil [7].

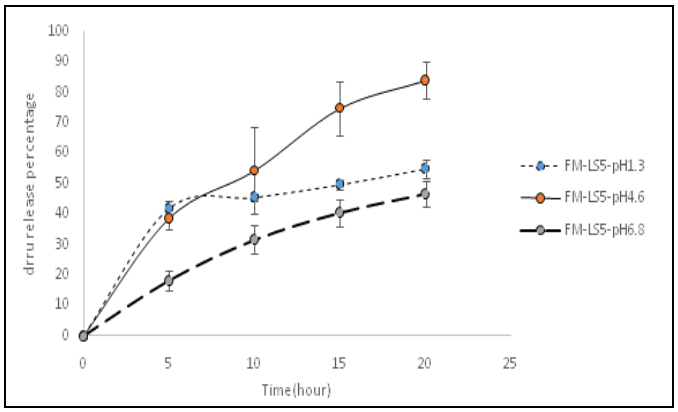

FIG. 4: EFFECT OF pH OF DISSOLUTION MEDIUM ON DRUG RELEASE FROM LIQUISOLID FORMULATIONS IN 900 mL

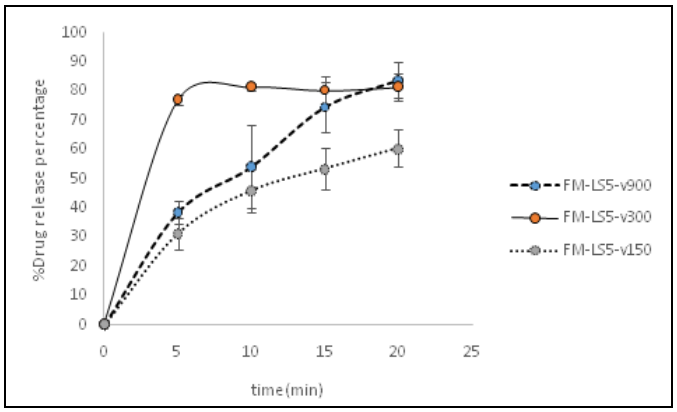

FIG. 5: *IN-VITRO* DISSOLUTION STUDIES AND EFFECT OF DISSOLUTION VOLUME ON DRUG

Fig. 4 demonstrates the dissolution profile of the liquisolid compact of FM-LS5 at 1.2 pH and 4.6. Moreover, 6.8. Liquisolid compact LS-5 generated a greater dissolution at 4.6 pH ($P < 0.05$). **Fig. 6** shows profiles of the drug dissolution from the liquisolid compacts (FM-LS5) and the directly

compacted tablets (DCT-1) of the micronized FM. In the case of the use of 900 mL (in each vessel) of distinct pH solution as the dissolving, the liquisolid tablets ha highly superior *in-vitro* release features in comparison to the tablets of the directly compacted counterparts. According to the studies, the solubility of poor bases and acids depended on the compound ionization constant (pKa) as well as the local environment pH. Hence, the bio-availability and dissolution of the above drugs have been highly affected by the pH of the gastrointestinal fluids. In addition, such a situation resulted in the increased degree of the inter-and intra-variability in the drug bio-availability and treatment impacts [33, 34].

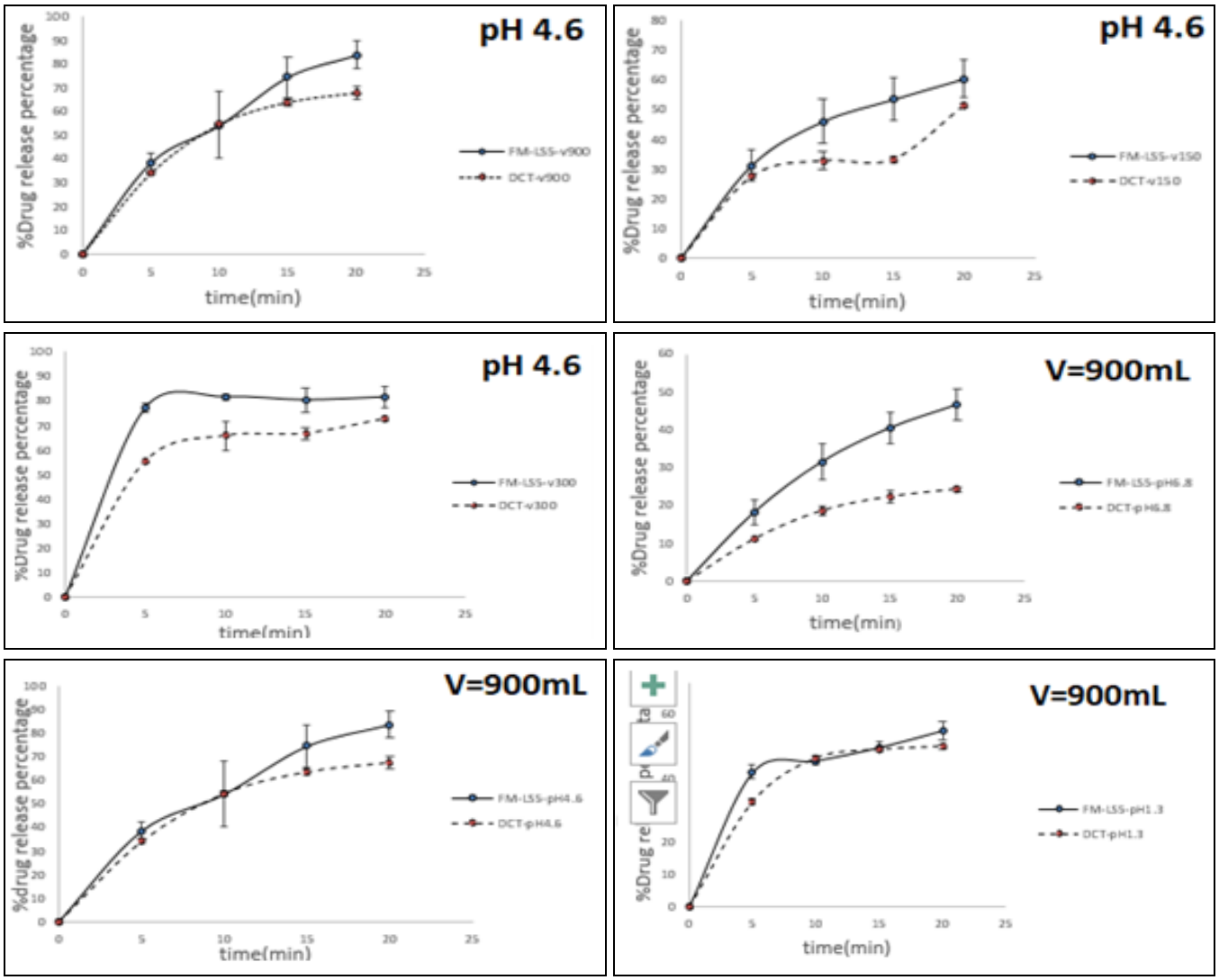

FIG. 6: COMPARISON OF DISSOLUTION PROFILE DISPLAYED BY THE LIQUISOLID COMPACT (FM-LS5) AND CONVENTIONAL TABLET IN DIFFERENT DISSOLUTION VOLUME AND DIFFERENT pH

In their study, El-Hammadi *et al.*, [35] initially examined the feasibility of the use of the liquisolid method for minimizing the influences of pH variations on releasing loratadine. A number of liquisolid formulations have been procured with the use of MCC as a carrier, silica as a coating material and propylene glycol as a liquid vehicle. Therefore, the dissolution profile of the procured liquisolid tablets has been examined in 3 buffered media, respectively at pH-values equal to 1.2, 2.5, and 5. According to the outputs, the dissolution rate of the liquisolid tablets has been considerably greater and partially influenced by pH variations as compared to the directly compacted and marketed tablets (Clarityn®). Thus, the liquisolid method has been considered as an encouraging device for the minimization of the influences of pH variations on the dissolution rate of the weakly water-soluble drugs. Notably, the same outputs have been published in Chella *et al.*, [36] studies so that the optimum liquisolid formulation has been achieved with a notable enhancement in the dissolution and

lower pH-dependent release profile in comparison with the drug itself or the respective commercial formulation. The other research published by Badawy *et al.* [33] revealed the robustness of the mosapride citrate (a weakly soluble base) liquisolid tablets that minimized effects of the pH variations on the drug release along the gastrointestinal tract with the relevant media. **Fig. 5** depicts profiles of the drug dissolution from the liquisolid compacts (FM-LS5); since 900 mL of 4.6 pH solution has been chosen as the dissolving medium, the liquisolid tablets exhibited partly more acceptable in-vitro release features in comparison to the additional volume dissolution media. Nonetheless, in the case of the use of more little contents like 150 and 300 mL of dissolution media, liquisolid tablets showed notably lower drug dissolution characteristics ($p < 0.05$).

Fig. 6 represents the effects of the volume dissolution medium on FM dissolution profiles from the liquisolid compacts and the directly compressed tablet. According to the figure, the liquisolid compacts produced a greater dissolution rate than that of the direct compression tablet ($P<0.000$). Apparently, the drug dissolution rate of the liquisolid compacts would be highly more rapid than the rate of plain tablets and did not depend on the volume of the dissolving liquid. In addition, the declined dissolution volumes caused a relative decline of *in-vitro* drug release rates exhibited by the directly compacted pills [10]. Based on the dissolution theories of the 'diffusion layer model', the drug dissolution rate has been in direct proportionate with its concentration gradient ($\Delta C=Cs-C$) in the stagnant diffusion layer established by the dissolving liquid surrounding the drug particles. In fact, Cs refers to the drug saturation solubility in the dissolution medium. Therefore, it would be a fixed typical feature of the drug and the engaged dissolving liquid. Put differently, C represents the drug concentration in a bulk of the dissolving medium that increased as the dissolution fluid content enhanced. Hence, ΔC-values in 3 distinct dissolution content of this study experiments decreased as the dissolution medium declined [10].

CONCLUSION: This paper principally aimed at enhancing the dissolution of the weakly water-soluble FM using the liquisolid compact procedure. Moreover, the liquisolid tablets formulated with PEG400 at 80% w/w drug concentration has been the most acceptable formulation amongst each batch of the liquisolid tablets procured with regard to more rapid disintegration time, greater dissolution profile as well as reasonable tablet features.

In addition, it has been observed that PEG400 would be an encouraging liquid vehicle for the formulation of the liquisolid formulations of FM. In fact, liquid vehicles played a prominent and conducive role in the improvement of the dissolution profiles of a weak water-soluble drug in the liquisolid formulations in addition to select a proper liquid vehicle based on the respective viscosity as well as the HLB-value. Thus, a major phase for the formulation of a successful liquisolid tablet would be to determine optimum flowable liquid retention potential (ϕ-value). Actually, factors like the content of the solvent and carrier basically influenced the dissolution rate. Finally, the drug release rate with the liquisolid system has been altered via the medium volume and pH.

ACKNOWLEDGEMENT: This study was funded by a grant from the research committee of Mazandaran University of Medical Sciences.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

REFERENCES:

1. Dias RJ, Mali KK, Ghorpade VS, Havaldar VD and Mohite VR: Formulation and evaluation of carbamazepine liquisolid compacts using novel carriers. Indian J Pharm Educ Res 2017; 51(2): 69-78.
2. Khan A, Iqbal Z, Ullah A, Khadra I, Sherazi M and Zeb N: Discriminatory dissolution testing for liquisolid compacts containing a poorly water-soluble drug hydro-chlorothiazide. Dissol Tech 2019; 26: 46-54.
3. Spireas S: Liquisolid systems and methods of preparing same. United State Patent 6423,339 B1, 2002.
4. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR and Barzegar-Jalali M: The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci 2005; 8(1): 18-25.
5. Javadzadeh Y, Siahi-Shadbad M, Barzegar-Jalali M and Nokhodchi A: Enhancement of dissolution rate of piroxicam using liquisolid compacts. Il Farmaco 2005; 60(4): 361-5.
6. Suliman AS, Anderson RJ and Elkordy AA: Preparation of novel optimum liquisolid compacts via incorporating water granulation process to enhance the powder characteri-zations and dissolution behavior of a poorly soluble drug: Norfloxacin. Powder Technology 2019; 354: 259-70.

7. Lu M, Xing H, Jiang J, Chen X, Yang T, Wang D and Ding P: Liquisolid technique and its applications in pharmaceutics. Asia J of Pharma Scie 2017; 12(2): 115-23.
8. Bosela AA, El Maghraby GM and Mahrous GM: Design of programmable release formulations for combined therapy. Indo-Global J of Pharmaceut Sciences 2011; 1(2): 173-85.
9. Fahmy RH and Kassem MA: Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *in-vitro* and *in-vivo* evaluation. Eur J Pharm Biopharm 2008; 69(3): 993-1003.
10. Kapure VJ, Pande VV and Deshmukh PK: Dissolution enhancement of rosuvastatin calcium by liquisolid compact technique. Journal of Pharmaceutics 2013; 2013: 9.
11. Saeedi M, Akbari J, Morteza-Semnani K, Enayati-Fard R, Sar-Reshteh-Dar S and Soleymani A: Enhancement of dissolution rate of indomethacin: Using liquisolid compacts. Iran J of Pharma Rese IJPR 2011; 10(1): 25-34.
12. Akbari J, Saeedi M, Morteza-Semnani K, Kelidari HR, Sadegh Moghanlou F, Zareh G and Rostamkalaei S: The effect of tween 20, 60, and 80 on dissolution behavior of sprionolactone in solid dispersions prepared by peg 6000. Advanced Pharmaceutical Bulletin 2015; 5(3): 435-41.
13. Pavani E, Noman S and Syed IA: Liquisolid technique based sustained release tablet of trimetazidine dihydrochloride. Drug Invention Today 2013; 5(4): 302-10.
14. Fahmy RH and Kassem MA: Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *in-vitro* and *in-vivo* evaluation. European Journal of Pharmaceutics and Biopharmaceut 2008; 69(3): 993-1003.
15. Mura P, Faucci MT and Parrini PL: Effects of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties. Drug Development and Industrial pPharmacy 2001; 27(2): 119-28.
16. Allen L and Ansel HC: Ansel's pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins; 2013: 270.
17. Shangraw RF: Compressed tablets by direct compression. Pharmaceutical dosage forms. Tablets 1989; 1: 195-46.
18. Spireas S and Sadu S: Enhancement of prednisolone dissolution properties using liquisolid compacts. International Jou of Pharmaceutics 1998; 166(2): 177-88.
19. Chella N, Shastri N and Tadikonda RR: Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. Acta Pharmaceutica Sinica B 2012; 2(5): 502-8.
20. Vittal GV, Deveswaran R, Bharath S, Basavaraj B and Madhavan V: Formulation and characterization of ketoprofen liquisolid compacts by box-behnken design. International J of Pharmace Investigation 2012; 2(3): 150.
21. Komala DR, Janga KY, Jukanti R, Bandari S and Vijayagopal M: Competence of raloxifene hydrochloride loaded liquisolid compacts for improved dissolution and intestinal permeation. J of Drug Deli Sci and Tech 2015; 30: 232-41.
22. Sanka K, Poienti S, Mohd AB and Diwan PV: Improved oral delivery of clonazepam through liquisolid powder compact formulations: *in-vitro* and *ex-vivo* characterization. Powder Technology 2014; 256: 336-44.
23. Bonthagarala B, Sai P and Venkata S: Enhancement of dissolution rate of clofibrate (bcs class–ii drug) by using liquisolid compact technology. Int J Biomed Adv & Res 2015; 6: 288-98.
24. Javadzadeh Y, Jafari-Navimipour B and Nokhodchi A: Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). International J of Pharmaceutics 2007; 341(1-2): 26-34.
25. Hentzschel CM, Sakmann A and Leopold CS: Suitability of various excipients as carrier and coating materials for liquisolid compacts. Drug Development and Ind Pharm 2011; 37(10): 1200-7.
26. Pezzini BR, Beringhs AO, Ferraz HG, Silva MAS, Stulzer HK and Sonaglio D: Liquisolid technology applied to pellets: Evaluation of the feasibility and dissolution performance using felodipine as a model drug. Chemical Engineering Research and Design 2016; 110: 62-9.
27. Khan A, Iqbal Z, Shah Y, Ahmad L, Ullah Z and Ullah A: Enhancement of dissolution rate of class ii drugs (hydrochlorothiazide); a comparative study of the two novel approaches; solid dispersion and liqui-solid techniques. Saudi Pharmaceutical J 2015; 23(6): 650-7.
28. Khaled KA, Asiri YA and El-Sayed YM: *In-vivo* evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs. International J of Pharmace 2001; 222(1): 1-6.
29. Elkordy AA, Tan XN and Essa EA: Spironolactone release from liquisolid formulations prepared with capryol™ 90, solutol® hs-15 and kollicoat® sr 30 d as non-volatile liquid vehicles. European Journal of Pharmaceutics and Bopharmaceutics 2013; 83(2): 203-23.
30. Suliman AS, Anderson RJ and Elkordy AA: Norfloxacin as a model hydrophobic drug with unique release from liquisolid formulations prepared with peg 200 and synperonic pe/l-61 non-volatile liquid vehicles. Powder Technology 2014; 257: 156-67.
31. Yadav V and Yadav A: Liquisolid granulation technique for tablet manufacturing, an overview. Journal of Pharmacy Research 2009; 2(4): 670-4.
32. Javadzadeh Y, Siahi MR, Asnaashari S and Nokhodchi A: An investigation of physicochemical properties of piroxicam liquisolid compacts. Pharmaceutical Development and Technology 2007; 12(3): 337-43.
33. Badawy MA, Kamel AO and Sammour OA: Use of biorelevant media for assessment of a poorly soluble weakly basic drug in the form of liquisolid compacts: in-*vitro* and *in-vivo* study. Drug delivery 2016; 23(3): 808-17.
34. Ramenskaia G, Shokhin I, Savchenko A and Volkova E: The dissolution test in biorelevant media as a prognostic tool for modeling of drug behavior *in-vivo*. Bio-meditsinskaia Khimiia 2011; 57(5): 482-9.
35. El-Hammadi M and Awad N: Investigating the use of liquisolid compacts technique to minimize the influence of pH variations on loratadine release. Aaps Pharmscitech 2012; 13(1): 53-8.
36. Chella N, Narra N, Rama Rao T. Preparation and Characterization of Liquisolid Compacts for Improved Dissolution of Telmisartan. Journal of Drug Delivery. 2014; 2014: 692793.

How to cite this article:
Saeedi M, Akbari J, Enayatifard R, Morteza-Semnani K, Hashemi SMH, Babaei A, Mashhadi AS and Eghbali M: Liquisolid tablet: an effective approach towards improvement of dissolution rate of famotidine as poorly soluble drugs. Int J Pharm Sci & Res 2021; 12(2): 803-12. doi: 10.13040/IJPSR.0975-8232.12(2).803-12.