

FORMULATION AND EVALUATION OF MELOXICAM LIQUISOLID COMPACT

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Received: 28 Aug 2014 Revised and Accepted: 29 Sep 2014

ABSTRACT

Objective: The aim of the present research was to improve dissolution of poorly soluble meloxicam a BCS (Biopharmaceutical Classification System) Class-II drug by utilizing liquisolid technique. Different liquisolid (LS) compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flow able and compressible admixture.

Methods: Liquisolid compact was prepared from; microcrystalline cellulose (Avicel PH 102) as carrier, colloidal silicon dioxide (Aerosil 200) and silica (cab-O-sil) as coating material, sodium starch glycol ate and cross povidon as superdisintegrants, PVP-K25 and HPMC E5 as additives to increase loading capacity, polyethylene glycol 400, propylene glycol and tween 80 as liquid vehicles. The ratio of carrier to coating material was kept constant in all formulations at 25:1, this ratio was chosen after testing the ratios 5:1, 10:1, 15:1, 20:1 and 25:1. The ratio 25;1 give optimal results relative to other ratios.

The prepared LS compacts were evaluated for their tab letting properties. Fourier transform infrared (FTIR) analysis, differential scanning calorimetry (DSC), scanning electron microscope (SEM) and X-ray powder diffraction (XRPD) were performed.

Results: The tab letting properties of the liquisolid compacts was within the acceptable limits. The drug release rates of the selected formulas (LS-3, LS-3A, LS-3AP and LS-3AH) of prepared liquisolid compacts were distinctly higher as compared to directly compressed tablets, and marketed tablets.

The DSC, XRPD and SEM were suggested loss of meloxicam crystallinity upon liquisolid preparation indicating that even though the drug existed in a solid dosage form, it is held within the powder substrate in a solubilized, almost molecularly dispersed state, which may be contributed to the enhanced drug dissolution properties.

The FTIR spectra showed disappearance of the characteristic absorption band of meloxicam (3290 cm⁻¹) in liquisolid formulation which might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle; this resulted in drug dissolution enhancement.

Conclusion: From this study it concludes that the LS technique is an effective approach to enhance the dissolution rate of meloxicam.

Keywords: Meloxicam, Liquisolid compacts, PEG 400, Dissolution rate.

INTRODUCTION

The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of new and possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success.

The technique of 'liquisolid compacts' is a new and promising addition towards such a novel aim. The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water-insoluble drugs are a major challenge for pharmaceutical formulation scientists. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i. e. the dissolution rate is often the rate-determining step in drug absorption. Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs [1,2].

Liquisolid system is novel developed technique which involves conversion of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with the use of carrier and coating materials. In case of water soluble drugs, the sustained release can be obtained. "liquisolid system" is formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water-insoluble solid

drugs in suitable non-volatile solvent systems, into "dry" (i. e., dry-looking), nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials[3,4].

MATERIALS AND METHODS

Materials

The following materials were used: Meloxicam (Sigma, Germany), Avicel PH 102 (FMC, USA), Aerosil 200 (Wacher HDK, Germany), Cab-O-Sil, SSG and Crosspovidon (Provizapharma, India), Propylene glycols (DOW, Germany), polyethylene glycol (PEG 400) (Chemfin chemical, india), Tween 80 (J. K. BAKAR, British), Methanol (ScharLab, Spain), Potassium dihydrogenortho-phosphate (BDH Chemicals, England), Magnesium stearate (Robert E. M. TILK, Germany) and Hydrochloric acid (BDH chemical, UK). All reagents used were of analytical grade.

Methods

Solubility studies

To select the best non-volatile solvent for dissolving or suspending of meloxicam in liquid medication, solubility studies of meloxicam were carried out in PG, PEG 400 and Tween 80. Also SGF pH 1.2, and SIF pH 6.8 were used to study solubility behavior of meloxicam. Saturated solution were prepared by adding excess of meloxicam to the vehicles and shaking on the shaker for 48 hr under constant vibration. Then the solutions were filtered through a 0.45 mm Millipore filter, diluted and analyzed by UV-spectrophotometer (Specord, Japan). Three carried out for each sample to calculate the solubility of meloxicam.

Application of mathematical model for designing lquisolid system

The flow ability and compressibility of lquisolid compacts are addressed simultaneously in the new formulation mathematical model of lquisolid systems, which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flow able liquid retention potential (Φ -value) and compressible liquid retention potential (Ψ -number) of the constituent powders[5]. The flow able liquid retention potential of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability [6].

The compressible liquid retention potential (Ψ) of a powder is the maximum amount of liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compact ability, to produce compacts of suitable hardness and friability, with no liquid squeezing out phenomenon during the compression process. The Φ value of powders may be determined using a new procedure, the lquisolid flow ability (LSF) test. The Ψ number of powders may be determined using a new method termed the lquisolid compressibility (LSC) test which employs the 'pacticity theories' to evaluate the compaction properties of liquid/ powder admixtures[5]. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, Where,

$$R = Q/q(1)$$

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible lquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible lquisolid system. i. e.

$$Lf = W/Q(2)$$

The powder excipients ratios R and liquid load factors Lf of the formulations is related as follows:

$$\Psi Lf = \Phi + \Phi(1/R)(3)$$

In order to calculate the required ingredient quantities, the flow able liquid retention potentials (Φ -values) of powder excipients were utilized. So to calculate the required weights of the excipients used, first, from Eq. (3), Φ and Φ are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus 1/R. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible lquisolid system could be calculated from equations (1) and (2).

Preparation of directly compressible tablet (DCT) and lquisolid compact

Directly compressible tablets (DCT) of meloxicam were prepared by direct compression using single tablet punch machine, each containing 15 mg meloxicam, 149 mg Avicel PH 102, 10 mg Aerosil 200, 5 % w/w sodium starch glycol ate as superdisintegrant, 20 mg PVP K25 and 1 % w/w magnesium stearate. Various LS compacts denoted (LS-1 to LS-3AH) containing 15 mg of meloxicam were prepared by dispersing in non-volatile vehicles (PG, PEG 400 and Tween 80). Then a bindery mixture of carrier of carrier (Avicel PH 102) and coating material (Aerosil 200 or Silica Cab-O-Sil) was prepared at a ratio of 25: 1 (trial and error methods were used, i. e. changing the carrier: coating material ratio (R) from 5, 10, 15, 20

and 25, until get good result (flow properties) is obtained. R 25 was used in all formulations since it gave the optimal flow property.

This binary mixture was added to the admixture of drug and vehicle. Finally 5 % SSG as disintegrant was added in above powder blend and mixed in all formulas except formula LS-3B which used crosspovidon. The final powder blend was subjected to compression.

Precompression studies of the prepared lquisolid powder system

Differential scanning calorimetry (DSC)[7]

DSC was performed in order to assess the thermo tropic properties and thermal behavior of pure meloxicam, Avicel PH 102, DCT and the lquisolid compact. DSC measurement performed on DSC 60 Shimadzu, Japan. Thermal behavior of the samples was investigated under a scanning rate of 10°C/min, covering a temperature range of 30 to 300°C under inert atmosphere flushed with nitrogen.

Fourier transform infrared spectroscopy (FTIR)[7]

Compatibility studies of pure drug and excipients were carried out using Fourier transformed infrared spectrophotometer (Shimadzu, Japan) in the range of 400-4000/cm by KBr disc method. A base-line correction was made using dried potassium bromide and then the spectrum of the pure meloxicam, DCT and lquisolid system were obtained.

X-ray diffractometry (XRD)

For characterization of the crystalline state, the X-ray diffraction (XRD) patterns are determined for drug meloxicam, excipient and for the prepared lquisolid system [8].

The results were recorded over a range of 0-50° (2 θ) using the Cu-target X-ray tube and Xe-filled detector. The operating conditions were: voltage 40 kV, current 30 mA, scanning speed 1/min [9], using Philips Analytical (PW3710).

Scanning electron microscopy (SEM)

SEM is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems. The samples were fixed on aluminum stubs with double-sided tape, gold-coated sputter and examined in the microscope using an accelerating voltage of 15 kV at a working distance of 8 mm [10].

The photomicrographs of pure meloxicam and lquisolid system were performed using VEGA easy probe (Germany) scanning electron microscopy.

Flow properties of lquisolid system

The flow ability of powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies otherwise high dose weight variations will occur.

Evaluation of Meloxicam Lquisolid Tablets

Friability and hardness tests

The friability test was done using Erweka friabilitor for 4 minutes at 25 rpm using 20 lquisolid tablets for each formula, weighing them all together (W initial) then placing all of them inside the friabilitor. After their revolution, they were clean from dust and weighed again (W final). The friability was calculated as the percentage according to equation (10)[11].

$$\% \text{Friability} = (W \text{ initial} - W \text{ final}) / W \text{ initial} \times 100 \%. (10)$$

The hardness of 3 tablets from each of the prepared formulas was measured individually. An anvil driven by electric motor presses the tablet at a horizontal position and constant load until the tablet breaks [12]. The hardness was measured in terms of kg using hardness tester TBH 100 (Erweka, Germany).

Content uniformity

Drug content was assessed for five randomly selected tablets. The tablets were crushed and total content of the five tablets was mixed

thoroughly. powder containing 15 mg of meloxicam was dissolved in 10 mL of methanol and volume was adjusted to 100 mL with pH 6.8 buffer. The solution was then filtered, and from this solution 1 mL was taken and phosphate buffer (pH 6.8) was added to complete the volume to 100 mL in standard volumetric flask. The amount of drug present in each tablet was determined spectrophotometrically at 360 nm using UV- spectrophotometer. The same procedure was followed for all the prepared formulas[13].

Disintegration test

The disintegration test was performed at 37±0.5 °C in 0.1N HCl(pH 1.2) for three tablets from each formula and three capsules from encapsulated formulas (LS3-A, LS-3AP and LS-3AH) using the USP tablet disintegration apparatus (Disintegration tester ZT 322, Erweka, Germany). The tablets were considered completely disintegrated as no residue remains on the screen. Generally, ideal tablet hardness should be produced without applying excessive compression force where rapid tablet disintegration and drug dissolution are maintained at the same time[9].

In-vitro dissolution studies of liquisolid tablets

The dissolution study was carried out using USP apparatus 1 paddle for the tablets and apparatus 11 basket for the capsules. The dissolution test was used to compare between liquisolid tablets, DCT, and marketed meloxicam tablet (mobic). And then compare the selected liquisolid formula with the same formula but in encapsulation form.

The dissolution media were either 900 mL of SGF 0.1 N HCl pH 1.2 and SIF phosphate buffer pH 6.8, at 37 ± 0.5° C, Meloxicam tablet and capsule were kept in the paddle and basket dissolution apparatus respectively, at 50 rpm. Sample of 5 mL were withdrawn at specific time intervals (5, 10, 20, 30, 45, 60 min) and filtered through a 0.45 µm filter then analyzed spectrophotometrically at 344 nm and 360 nm for HCl pH 1.2 and phosphate buffer 6.8, respectively (using Copley dissolution 8000 tester, Copley scientific, UK). The samples withdrawn were replaced by fresh buffer solution to maintain constant volume. Each preparation was tested in triplicate and the mean value were calculated [14].

Statistical Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one-way analysis of variance (ANOVA) at the level of (P < 0.05).

RESULTS AND DISCUSSION

Solubility studies

The solubility of MLX in different solvents is listed in table (1). As shown in the table, its solubility is very poor in 0.1 N HCl (pH 1.2) 0.1939 mg/ ml. phosphate buffer solution, pH 6.8, enhanced the solubility of MLX to the level of 0.5790 mg/ ml, due to partial ionization of the drug at this pH. In propylene glycol (PG), the solubility of MLX was found to be 0.3489 mg/ ml, which is slightly greater than that of HCl. This slight increase is probably through

hydrogen bonding. Meloxicam solubility in PEG was 40 fold higher than HCl 7.0014. PEG, with a large nonpolar part and several hydroxyl groups is responsible for the enhanced solubility. Thus, among the solvents tested, PEG 400 could be a better choice as solvent[15]. Tween 80 also enhanced the solubility of meloxicam 0.3907, indicating the micellar solubilization in concentration higher than its cmc. This suggested the nonpolar nature of MLX and its presence in the hydrophobic interior of the micelle [16].

The table also shows that an increase in pH resulted in an increase in the solubility of MLX; this is because MLX is acidic[17].

Table 1: Solubility of MLX in various solvents

Solvent/ vehicle	Solubility(%w/w)
SGF (pH 1.2)	0.1939
SIF (pH 6.8)	0.5790
PG	0.3489
PEG 400	7.0014
Tween 80	0.3907

Application of Mathematical Model for Designing the Liquisolid Systems

Meloxicam has poor aqueous solubility and wet ability, and exhibits poor dissolution in aqueous fluids especially in acidic medium. Such property poses difficulties not only in the design of pharmaceutical formulations but also results in biovariability. It is an ideal candidate for testing the potential of rapid-release liquisolid compact [18]. In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized. In PEG 400, the Φ-values of Avicel PH 102 and Aerosil 200 (or silica) were found to be 0.005 and 3.26 respectively[4]. On the other hand, in PG, the Φ-values of Avicel PH 102 and Aerosil 200 (or silica) were found to be 0.16 and 3.31 respectively[19].

While, In Tween 80, the Φ-value of Avicel PH 102 was found to be 0.16, while for Aerosil 200 the Φ-value used was equal to 3.33[20].

Mathematical model equations for Avicel PH 102 and Aerosil 200 (or silica) in PEG, PG and Tween 80 express according to values of Φ as given by spire as et al[4, 5]as follow:

Lf = 0.005+ 3.26 (1/25) for PEG 400

Lf = 0.16 +3.31 (1/25) for PG

Lf = 0.16 + 3.33 (1/25) for Tween 80

For R-value used 25, the corresponding Lf value can be calculated. As soon as the optimum liquid load factor of a given excipients ratio is established for each formula and W is calculated according to MLX concentration in liquid vehicle, the appropriate quantities of Avicel PH 102 (Qo) and Aerosil 200 (qo) required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, were calculated using Eqs. (1) and (2). The amount of superdisintegrant is equal to 5% of the tablet weight. Table 2 and 3 represents the exact qualitative and quantitative composition for each formula.

Table 2: Composition of different meloxicam liquisolid formulas prepared by using different liquid vehicles

Liquisolid system code	Liquid vehicle used	Drug conce. In liquid medication (% w/w)	Carrier: coating ratio (R)	Liquid load factor (Lf)	Liquid vehicle (mg)	Active ingredient meloxicam (mg)	Carrier (Q)Avicel PH 102(mg)	Coating (q)Aerosil 200(mg)	Disintegrant SSG (mg) 5 % w/w	Unit dose (mg)
LS-1	PEG	15	25	0.135	85	15	740.7	29.6	43.5	913.8
LS-2	PEG	22.5	25	0.135	51.6	15	493.3	19.7	28.9	608.5
LS-3	PEG	30	25	0.135	35	15	370.3	14.8	21.7	456.8
LS-4	PG	15	25	0.292	85	15	342.4	13.6	22.8	478.8
LS-5	PG	22.5	25	0.292	51.6	15	228	9.1	15.1	318.8
LS-6	PG	30	25	0.292	35	15	171.2	6.8	11.4	239.4
LS-7	TW 80	15	25	0.293	85	15	341.2	13.6	22.7	477.5
LS-8	TW80	22.5	25	0.293	51.6	15	227.3	9.09	15.1	318.1
LS-9	TW 80	30	25	0.293	35	15	170.6	6.82	11.3	238.7

Table 3: Composition of meloxicam liquisolid formulas prepared by using PEG 400 as liquid vehicle

Liquisolid system code	Liquid vehicle used	Drug conce. in liquid medication (% w/w)	Carrier: coating ratio (R)	Liquid load factor (Lf)	Liquid vehicle PEG 400 (mg)	Active ingredient meloxicam (mg)	Carrier Q Avicel PH 102 (mg)	Coating q silica (cab-o-sil) mg	Disintegrant 5 % w/w mg	Additives 10 % (45.6) mg	Unit dose (mg)
LS-1 A	PEG	15	25	0.135	85	15	740.7	29.6	SSG		913.8
LS-2 A	PEG	22.5	25	0.135	51.6	15	493.3	19.7	SSG		608.5
LS-3 A	PEG	30	25	0.135	35	15	370.3	14.8	SSG		456.8
LS-3 B	PEG	30	25	0.135	35	15	370.3	14.8	Crosspovidon		456.8
LS-3 A P	PEG	30	25	0.135	35	15	370.3	14.8	SSG	PVP-K 25	502.4
LS-3AH	PEG	30	25	0.135	35	15	370.3	14.8	SSG	HPMC E5	502.4

Precompression Studies of the prepared liquisolid powder systems

As the angle of repose (θ) is characteristic of the internal friction or cohesion of the particles, according to USP values, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive [21].

From the result show in table (4), conclude that, the increase in concentration of drug in vehicle (LS -1, LS-2 and LS-3 in PEG 400) and (LS-4, LS-5 and LS-6 in PG) cause reduction in the angle of repose and increase in flow ability of formula. Whereas, decrease in concentration of liquid vehicle used lead to increase in flow ability and decrease in angle of repose.

While, in (LS-7, LS-8 and LS-9 in Tween 80) show poor flow ability and in all concentration, may attributed to that tween 80 is poor liquid vehicle for meloxicam liquisolid system due to solubility of drug in that vehicle.

So, any formula which have poor flow were cancelled and not followed for further evaluation such as LS-4, LS-7, LS-8 and LS-9.

The formulas LS-1A, LS-2A and LS-3A show better flow ability than corresponding formulas LS-1, LS-2 and LS-3, this attributed to that silica (cab-O- sil) have good result in coating properties which lead to increase the flowbility and decrease the angle of repose, in spite of have similar surface area as Aerosil 200.

The formula LS-3B show increase in the angle of repose slightly than corresponding formula LS-3, due to nature of crosspovidon used which have low flow ability than sodium starch glyconate.

Both formula LS-3AP and LS-3AH show increase the flowbility and decrease the angle of repose corresponding to the formula LS-3A, this may be due to the usage of the PVP- K25 and HPMC E 5 to produce the micro system.

Also, these additives cause increase in the loading capacity of the carrier to liquid medication resulting in free flowble formula better than corresponding one. The formula of DCT give good flow ability.

The Carr's compressibility index and Hausner's ratio are measurements to find out tendency of powders to be compresses [22].

Formulas LS-1, LS-2, LS-3, LS-5, LS-6, LS-1A, LS-2A, LS-3A, LS-3B, LS-3AP, LS-3AH and DCT exhibited good flow, while the flow of the remaining liquisolid formulas were fair as show in table 4.

As presented in table (4), the formulas of the higher drug concentration in liquid vehicle showed lower Carr's index and Hausner's ratio (better flow ability) than the formulas of lower concentration.

Also the formulas LS-3AP and LS-3AH have lowest angle of repose, Carr's index and Hausner's ratio due to effect of additive (PVP and HPMC) which leade to increase the loading capacity of drug and give good flow ability.

Beside, the formulas of PEG as liquid vehicle better than PG, and these two are better than tween 80 as liquid vehicle, indicated that PEG is better solvent to MLX liquisolid system. The DSC showed the thermal behaviors of the pure components together with the thermal behavior of the final liquisolid system [23].

Figure (1) showed the thermal behaviors of the pure meloxicam. The MLX peak is clear, demonstrating a sharp characteristic endothermic

peak at 260 °C corresponding to its melting temperature. Such a sharp endothermic peak shows that the MLX used was in a pure crystalline state[24].

The thermo grams of Avicel PH 102 (figure 2) displayed a broad endothermic peak at 48.12°C, which might correspond to volatilization of the adsorbed water followed by melting decomposition with charring of the crystalline cellulose type material [23].

The thermo gram of DCT (figure 3) exhibited endothermic peak at 250°C, which is the peak of the drug, indicated that there is no interaction between the drug and excipients used in the formulation and the drug still in the crystalline form[22].

On the other hand, the liquisolid system (figure 4) showed that the characteristic peaks of MLX disappeared, this agrees with the formation of a solid solution in the liquisolid powdered system, i. e., the drug was molecularly dispersed within the liquid vehicle[25].

This disappearance of drug peaks upon formulation into a liquisolid system was in agreement with McCauley and Brittain[26]who declared that the suppression of all drug thermal features undoubtedly indicates the formation of an amorphous solid solution. In addition, Mura et al [27] found out that the disappearance of the drug melting peak indicates that drug amorphization had taken place.

The spectrum of pure MLX was represented in figure 15 and showed the characteristic peaks of the drug at[28]: N-H stretching: 3290.33 cm⁻¹, C-H stretching: 2966.62 cm⁻¹, S=O stretching: 1043.42 cm⁻¹, C=O stretching: 1618.17 cm⁻¹

Figure 6shows the FTIR spectrum of physical mixture (DCT) values as follows: N-H stretching: 3294 cm⁻¹, C-H stretching: 2976 cm⁻¹, S=O stretching: 1098 cm⁻¹, C=O stretching: 1670 cm⁻¹

There is no different between figure 5 and 6 in pure drug and DCT of the characteristic peaks of FTIR. Indicating that there was no interaction between drug-excipients used in the study and no hydrogen bond formation in DCT.

It is observed that the peaks of major function groups of MLX, which are present in spectrum of pure drug, were present in MLX liquisolid formula (figure 7) but the broadness of the characteristic peak of MLX with shifting to lower frequency might be due to formation of hydrogen bonding between the carboxylic group of MLX and the hydroxyl group of the PEG in liquisolid formula, this resulted in drug dissolution enhancement [29].

The crystallinities of pure MLX, excipients and liquisolid system were evaluated by XRD measurement. It has been seen that polymorphic changes of the drug are important factors, which may affect the drug dissolution rate and bioavailability[9]. The XRD results were in good agreement with the thermal analysis data. The X- ray diffract gram of pure MLX (figure 15) exhibited several sharp peaks at different angle (2θ) 13.00, 15.00, 18.50, 19.00, 20.50 and 26.00 suggested that the drug existed as crystalline material [30]. The liquisolid powder X-ray diffraction pattern in figure 10 showed only one sharp diffraction peak at 2θ angle of 22.5 belonging to Avicel PH 102 (figure 9), indicating that only Avicel PH 102 maintained its crystalline state[10]. Such absence of MLX specific peaks in the liquisolid X-ray diffract grams indicates that MLX has almost entirely converted from crystalline to amorphous or solubilized form, such lack of crystallinity in the liquisolid system was understood to be as

a result of drug solubilization in the liquid vehicle (PEG 400) i. e., the drug has formed a solid solution was absorbed into and adsorption onto the carrier Avicel PH 102. This X-ray data supported that the MLX formed a solid solution with in the carrier matrix. The amorphization or solubilization of drug in the liquisolid system may cause the marked improvement in the solubility and therefore the dissolution rate of the drug [31]. Morphological characteristics of drug and powder mass of liquisolid system were analyzed using SEM [30].

Figure 11 illustrated the photomicrograph of the pure drug (MLX). It showed the drug had crystalline nature as was proved previously by the DSC and XRD.

The photomicrograph of the liquisolid system showed the complete disappearance of MLX crystals (figure 12). Thereby supporting the transformation of drug from the crystalline to the amorphous state, this fact indicates that even though the drug is in solid dosage form, it is held within the powder substrate in solution or in solubilized, almost molecularly dispersed state which contributes to enhance drug dissolution property [32].

Table 4: flow ability parameters of MLX liquisolid powder systems.

LS system code	Angle of repose $\theta \pm S. D.*$	Compressibility% $\pm S. D.*$	Hausner's ratio $\pm S. D.*$
LS- 1	33.6 \pm 0.528	11.62 \pm 0.396	1.131 \pm 0.012
LS- 2	33 \pm 0.337	13.6 \pm 0.452	1.156 \pm 0.01
LS- 3	29 \pm 0.5323	11.89 \pm 0.384	1.136 \pm 0.012
LS- 4	39.2 \pm 0.649	16.3 \pm 0.473	1.2 \pm 0.011
LS- 5	34.5 \pm 0.584	14.68 \pm 0.447	1.172 \pm 0.011
LS- 6	31.14 \pm 0.482	12.24 \pm 0.357	1.14 \pm 0.011
LS- 7	Not flow	24.02 \pm 0.302	1.302 \pm 0.01
LS- 8	47 \pm 0.334	24.53 \pm 0.233	1.32 \pm 0.01
LS- 9	45 \pm 0.412	23.22 \pm 0.3	1.28 \pm 0.01
LS- 1A	32.8 \pm 0.263	14.64 \pm 0.495	1.167 \pm 0.01
LS- 2A	30.7 \pm 0.873	12.61 \pm 0.411	1.146 \pm 0.01
LS- 3A	26.5 \pm 0.742	14.65 \pm 0.299	1.172 \pm 0.02
LS- 3B	30.73 \pm 0.732	14.53 \pm 0.412	1.14 \pm 0.011
LS- 3AP	24.3 \pm 0.437	11 \pm 0.145	1.123 \pm 0.01
LS- 3AH	25 \pm 0.623	11.1 \pm 0.262	1.125 \pm 0.01
DCT	28.1 \pm 0.774	15.24 \pm 0.471	1.179 \pm 0.011

*S. D. standard deviation from mean. n=3.

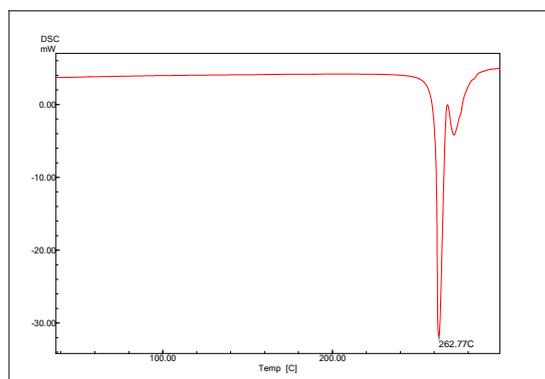


Fig. 1: The DSC thermogram of pure MLX

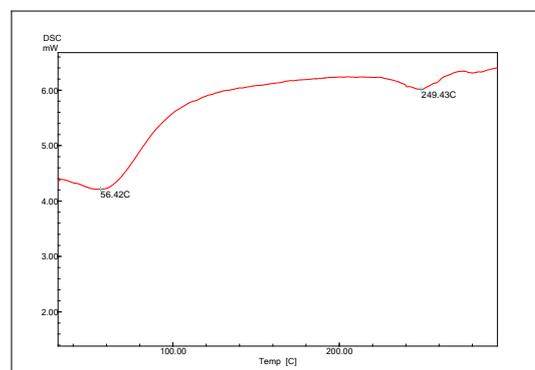


Fig. 3: DSC thermgram of DCT

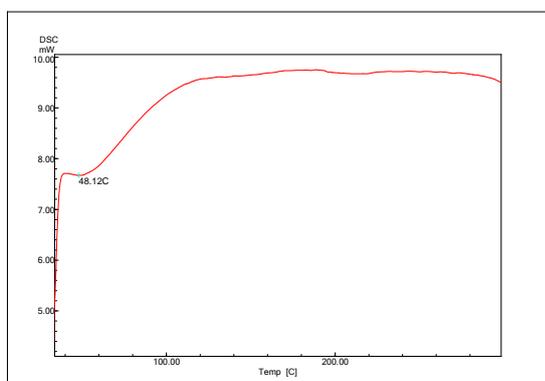


Fig. 2: DSC thermogram of Avicel PH 102

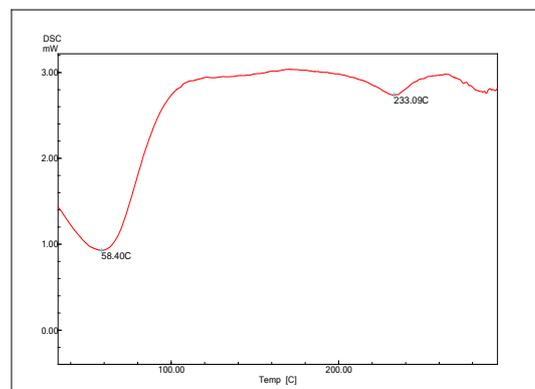


Fig. 4: DSC thermogram of MLX liquisolid system

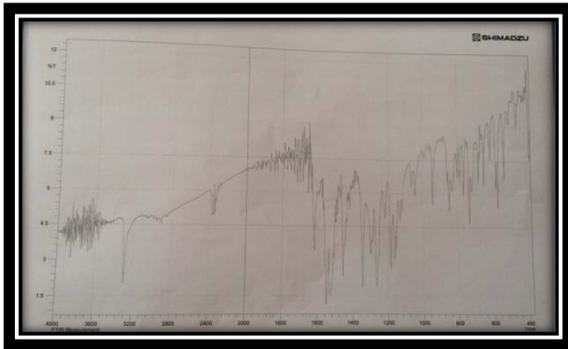


Fig. 5: FTIR spectrum of pure MLX

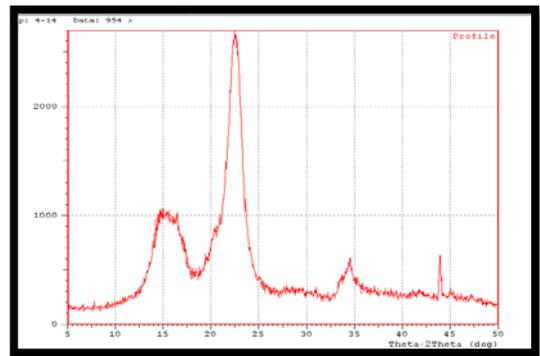


Fig. 9: X-ray diffraction of Avicel PH 102

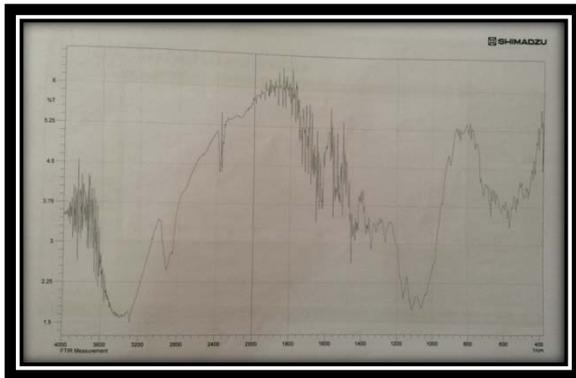


Fig. 6: FTIR spectrum of DCT

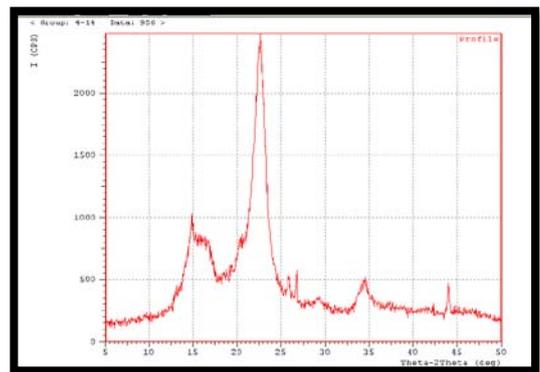


Fig. 10: X-ray diffraction of MLX liquisolid system.

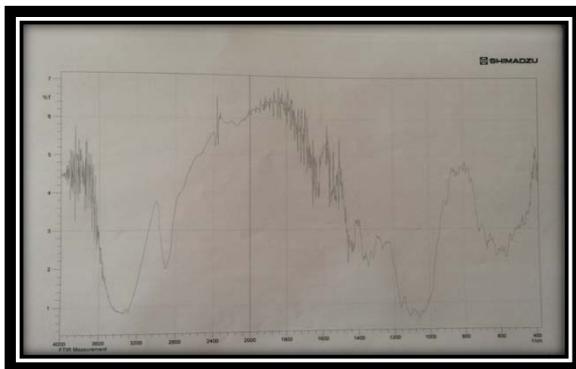


Fig. 7: FTIR spectrum of MLX liquisolid system

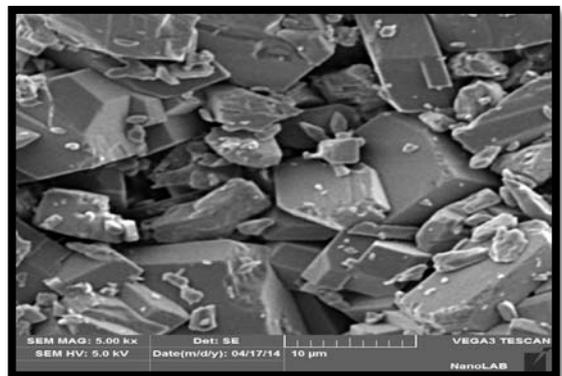


Fig. 11: SEM of pure drug MLX

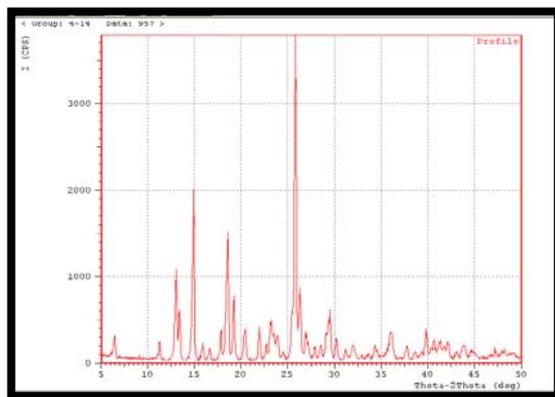


Fig. 8: X-ray diffraction of pure MLX

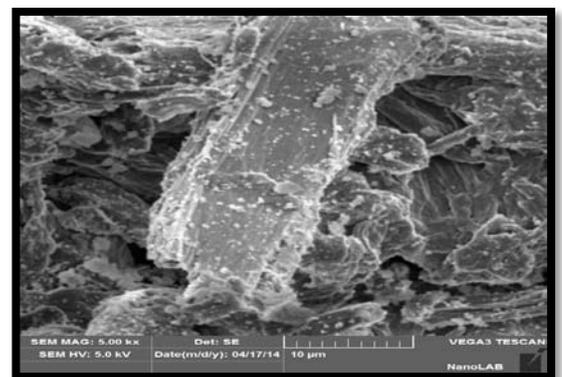


Fig. 12: SEM of liquisolid compact

Evaluation of meloxicam Lquisolid Tablets

Friability and hardness tests

All MLX lquisolid tablets exhibited acceptable friability as none of the tested formula had percentage loss in tablets weights that exceed 1%, also, no tablet was cracked, split or broken in all formulas. Since all the prepared formulas met the standard friability criteria, they are expected to show acceptable toughness and withstand abrasion during handling, packaging and shipment [29].

In general, formulation should be directed at optimizing tablet hardness without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution. In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing [33]. The mean hardness of each lquisolid formulas was determined and is presented in table (5) proving that all the lquisolid tablet formula had acceptable hardness.

The compactness of tablets may be due to hydrogen bonding between Avicel PH 102 molecules [34]. Avicel PH 102 compressibility and compactness characteristics can be explained by the nature if crystalline cellulosic particles themselves which are held together by hydrogen bonds which when compressed, are deformed plastically and a strong compact is formed due to the extremely excessive number of surfaces brought into contact during the plastic deformation, and the strength of the hydrogen bonds are formed[10]. In addition, both PG and PEG 400 molecules contain two terminal hydroxyl groups, thus there is also a probability of forming hydrogen bonds with Avicel PH 102[35].

It was seen that as the amount of Avicel goes on increasing, hardness also increases. This low hardness could be attributed to the less amount of added Avicel and poor compressibility of Aerosil [36].

The disintegration time for the prepared MLX lquisolid tablets and capsule was shown in table (5). It was found that, the mean of the disintegration times for all investigated tablets were less than 2 minutes(except for LS-3B), which fulfill the pharmacopoeial requirement. Also the capsule prepared showed disintegration time between 25- 35 minutes. LS-3AP, LS-3AH and LS-1 showed short disintegration time (38, 43 and 52 second; respectively). whileLS-3B, LS-3 and LS-3A showed the slowest disintegration time that equal to 1500, 82 and 78 second; respectively. These results can be explained as increasing the amount of liquid used in formulas with short disintegration time and significantly increased wetting properties and surface area of the drug and increasing the availability of the drug to be easily disintegrated from its solution or suspension, and this subsequently; decrease the disintegration time of the tablets. Also high Avicel PH 102 content where Avicel PH 102 functions as a swell able disintegrant [37].

In addition, the highly hydrophilic characteristic of Avicel PH 102 could increase the wetting of MLX and this subsequently, lead the tablet to be disintegrated quickly and decreased the disintegration time of the tablets [38].

Moreover, the disintegration time for DCT was approximately less than 7 minutes, while for capsules prepared from lquisolid formulas (LS-3A, LS-3AP and LS-3AH) showed 30, 35 and 28 minutes; respectively.

Be sided, the use of superdisintegrant (sodium starch glycol at) accelrated the disintegration of the tablets by virtue of its ability to absorb a large amount of water when exposed to an aqueous environment[39].

From the table 5 of disintegration time showed SSG better disintegrant than crosspovidon.

Table 5: Hardness, Friability and disintegration percentage of MLX lquisolid formulation

LS system cod	Hardness (Kg/cm ²)±S. D.* N=3	% Friability (W/W)	Disintegration time (sec) Mean ± S. D. n=3
LS-1	6.39 ± 0.22	0.23	52 ± 4.23
LS-2	6.13 ± 0.24	0.33	72 ± 4.1
LS-3	5.93 ± 0.54	0.42	82 ± 3.12
LS- 5	5.57 ± 0.33	0.46	73 ± 4.47
LS-6	5.41 ± 0.55	0.29	77 ± 4.6
LS-1A	6.2 ± 0.44	0.38	58 ± 3.26
LS-2A	6.15 ± 0.34	0.27	72 ± 3.11
LS-3A	6.10 ± 0.31	0.38	78 ± 3.42
LS-3B	6.27 ± 0.37	0.44	1500 ± 4.48
LS-3AP	6.41 ± 0.42	0.40	38 ± 2.28
LS-3AH	6.28 ± 0.43	0.35	43 ± 3.58
LS-3A CAP			1800 ± 5.2
LS-3AP CAP			2120 ± 6.86
LS-3AH CAP			1680 ± 7.09
DCT			385 ± 6.86

Content uniformity

The drug content of the prepared lquisolid tablets were found to be in the range of 92 -101 % which is due to acceptable uniformity of content of prepared lquisolid tablets.

In-vitro dissolution studies

In-vitro drug release studies were performed in two different dissolution media (0.1N HCl pH 1.2 and phosphate buffer pH 6.8) for the prepared lquisolid formulas and were compared with that of DCT and marketed tablet.

The graphs showing drug release profile for all formulas were shown in the figures 13, 14, 15, 216 and 17.

The percent of MLX released from lquisolid compacts containing varying amounts of carrier and coating material (from LS-1 to LS-6) was found to vary from 30.38 % to 80.38 % in 0.1N HC1 (pH 1.2) and from 56.10 % to 81.16 % in phosphate buffer (pH 6.8) in the first 20 min (figures 13).

All the formulas of lquisolid compact prepared with PEG solvent showed better release than PG prepared lquisolid compact, due to fact that the solubility of MLX higher in PEG than PG as show in table (1), so the preparation of MLX lquisolid compact good with the PEG solvent.

The percent of MLX released from formula LS-3B is low corresponding to formula LS-3 which replaced the SSG with crosspovidon as superdisintegrant, this attributed to the disintegration time of formula LS-3B slower than LS-3, so the release slower than lquisolid formula LS-3,as show in figure 14.

The formulas LS-1A, LS-2A and LS-3A showed higher percent release of MLX in first 20 minutes corresponding to LS-1, LS-2 and LS-3, this attributed to coating effect which related to used the silica (Cab-O-sil) instead of Aerosil, which indicate that silca is good coating material than Aerosil which facilitate the release drug fastely than Aerosil. Unless, these tow coating material have same surface area, as showed in figure 14.

The used of additives PVP and HPMC gave the formula release of drug higher than other formula in first 20 minutes. This showed in formulas LS-3AP and LS-3AH, this attributed to increase the loading efficiency of the drug through the carrier Avicel that related to used additives, as show in figure 15.

The comparism of selected formula LS-3A, LS-3AP and LS-3AH with corresponding same formulas but, encapsulated in shell capsule by dipping method showed that release profile of MLX from the liquisolid tablets was higher and faster than same formula in capsule form. This attributed to that disintegration time of tablet occur with seconds to few minutes than capsules which need more than 25 minutes to opening of shell of capsule and then release its content slowly until complete rupture of the shell and release its content to media, as show in figures 16, 17 and 18.

All the liquisolid batches derivative from LS-3 (LS-3, LS-3A, LS-3AP and LS-3AH) showed higher drug release profile than the DCT and the marketed tablet. The enhanced dissolution rates of liquisolid compacts compared to DCT and marketed tablet may be attributed to the fact that the drug is already in solution in PEG, while at the same time it is carried by the powder particles (microcrystalline cellulose and silica)[8].

In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, whereas the directly compressed compacts are merely exposed micronized drug particles. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the directly compressed compacts [40], as show in figure 15.

According to Noyes and Whitney [41], the drug dissolution rate (D_r) is directly proportional not only to the concentration gradient ($C_s - C$) of the drug, but also to its surface area (S) available for dissolution (eq 4). Moreover, since all dissolution tests for MLX preparations were carried out at a constant rotational paddle speed (50rpm/min) and identical dissolving media, it is assumed that the thickness (h) of the diffusion layer and the diffusion coefficient (D) of the drug molecules transported through it remain almost identical under each set of dissolution conditions. Therefore, the significantly increased effective surface area of the molecularly dispersed MLX in the liquisolid compacts may be principally responsible for their observed higher dissolution rates [29].

Thus, its release is accelerated due to its markedly increased wet ability and surface area available to the dissolution medium. The wet ability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts [42].

The consistent and higher dissolution rate displayed by liquisolid compacts will improve the absorption of drug from the GIT[43].

$$D_r = \{D \times S \times (C_s - C)\} / h \text{ eq (4)}$$

Where,

D_r = Rate of dissolution.

S = Surface area available for dissolution.

D = Diffusion coefficient of the compound.

C_s = Concentration of the drug in the diffusion layer.

C = Concentration of drug in the dissolution medium at time t .

h = Thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound[44].

From drug release profiles, it was found that the formula LS-3 (higher drug concentration in PEG) showed the highest drug release when compared to the formulas LS-1, LS-2, LS-5 and LS-6, while the formula LS-5 (lower drug concentration in PG) had lowest release profile among these above liquisolid formulas.

Also, when replaced the Aerosil 200 coating material with Silica give higher result in release profile as showed in formulas LS-1A, LS-2A

and LS-3A. The release of LS-3B formula showed lower than corresponding LS-3 due to disintegration time of superdisintegrant.

Beside, it can be concluded from figure 15 that the percentage drug release is increase with used of additives PVP K-25 and HPMC as show in formulas LS-3AP and LS-3AH.

In figure (15), the optimized formulation (LS-3A, LS-3AP and LS-3AH) was compared with marketed tablet and DCT. The results showed that there was no significant different ($P > 0.05$) between the release profile of these formulas with both DCT and marketed tablet in both dissolution media.

The percentage drug release (MLX) in 20thmin from DCT and marketed tablets were: 53.14 % and 61.64 %, respectively in 0.1 N HCl (pH 1.2); 77.89 % and 75.98 %, respectively in phosphate buffer (pH 6.8). while the percentage drug release of MLX in 20th min. from LS-3, LS-3A, LS-3AP and LS-3AH showed 80.28, 84.95, 90.96 and 94.58 %, respectively in 0.1 N HCl (pH1.2); and 81.16, 89.92, 92.01 and 94.82 %, respectively in phosphate buffer (pH 6.8) (figures 13, 14 and 15). This is because, in the case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means, is much greater than that of MLX particles delivered by the plain or directly compressed tablets. Significantly increased effective surface of the molecularly dispersed MLX in the liquisolid tablets may be chiefly responsible for their observed higher and consistent drug dissolution rates[33].

Variables Affecting the Dissolution Rate of meloxicam Liquisolid Tablets

The effect of liquid vehicle type

As shown in table (1), MLX has a higher solubility in PEG 400 compared to PG; therefore, the liquisolid tablets formulated with PEG 400 (LS-3 or its derivatives) should have a better dissolution rate than those formulated with PG (LS-5 and LS-6)[32,45,46]. Its clearly shown in figure (13A) that first 20 min., MLX dissolution from LS-3, LS-5 and LS-6 in SGF was 80.28, 34.70 and 39.87 %, respectively. Similar sequence was shown in SIF, meaning that liquisolid tablets which are formulated with PEG 400 show higher dissolution rates than those formulated with PG. In essence, the drug may be in a partly dissolved state in the liquid medications of LS-5 and LS-6 compact. On the other hand, the drug is completely in solution in the LS-3 compact, thereby presenting improved dissolution properties.

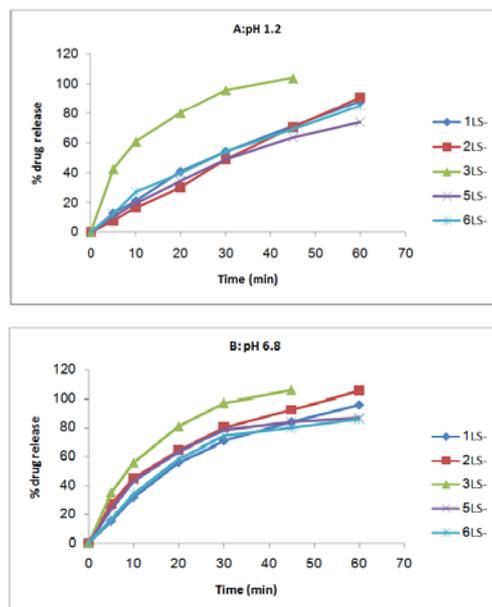


Fig. 13: Dissolution profile of liquisolid compact (LS-1, LS-2, LS-3, LS-5 and LS-6) in A: 0.1N HCl (pH 1.2), and B: phosphate buffer (pH 6.8) at 37° C.

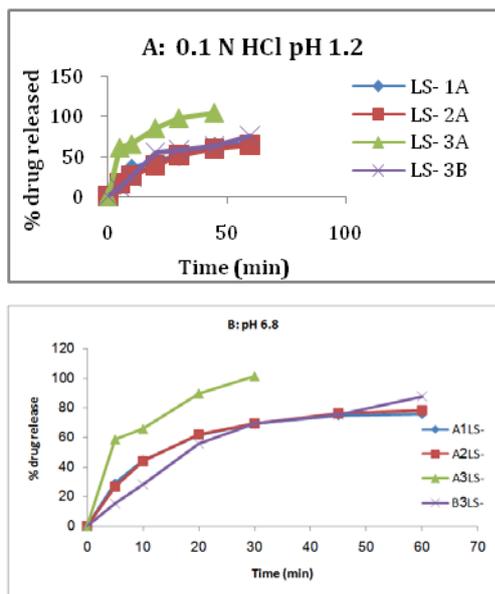


Fig. 14: The percentage release of MLX liquid-solid compacts (LS-1A, LS-2A, LS-3A and LS-3B) in A: 0.1 N HCl (pH 1.2), and B: phosphate buffer (pH 6.8) at 37°C.

The effect of liquid vehicle concentration

The concentration of drug in liquid medication is an important aspect in the formulation of liquid-solid compacts. As it was shown in figure 13, the increase in drug concentration in liquid medication, increase drug release rate [47].

Thus, formulation with highest drug concentration in PEG 400 (LS-3) showed higher drug release than lowest drug concentration (LS-1 and LS-2) 80.28, 41.07 and 30.38 %, respectively in first 20 min in SGF pH 1.2. Also, the formula LS-6 which has high drug concentration in PG than LS-5, showed high drug release than lowest drug concentration LS-5 by 39.87 and 34.70 %, respectively in first 20 min in SGF pH 1.2, and these two formula in PG showed lowest drug release than formulas with PEG 400.

LS-3, the liquid-solid formula of highest drug concentration in PEG 400 (30 % w/w), showed the highest dissolution rate among all other liquid-solid compact. This because as increase of drug concentration lead to decrease amount of non volatile solvent used in formula[48]. PEG 400 facilitated wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface [49].

Effect of dissolution media (pH):

Comparing the dissolution of MLX in SGF and SIF dissolution media, it was found that the drug exhibited higher dissolution rate in SIF as a dissolution medium compared to that in SGF as show in figure 13, 14 and 15. This can be explained on the basis that MLX is a weak acid (pKa =1.1) which displays pH-dependent solubility and dissolution. The weak acids react with bases in SIF and then exist as ions that are ordinarily soluble in water. In the other words, the concentration of the drug is high when the drug is mostly ionized. Therefore, its dissolution rate increased markedly with increasing the pH [50].

The effect of additives on dissolution profile:

figure (15) show the effect of additive materials that added to liquid-solid formula as PVP K25 and HPMC E5 this comparison with selected formula to show release profile of MLX, the high release of formula LS-3AP and LS-3AH compared to LS-3 showed no significant difference (P > 0.05), due to increase loading capacity of carrier to MLX under effect of these additives and give high release than original formula.

The effect of encapsulation process on dissolution profile:

The in-vitro dissolution profiles of MLX (figures 16, 17 and 18) showed that there was significant differences (P < 0.05) between release rate

of selected formulas (LS-3A, LS-3AP and LS-3AH) and its capsule formulated of the same formula in SGF dissolution media pH 1.2. Figure (16) show the delay release of MLX from capsule first 25 minutes in comparison with same formula liquid-solid tablet which give rapid release action. This due to the release from the capsule dosage form need to dissolve or lyses of the shell of capsule firstly then release it content to media, and this need time to take place which refer to disintegration time, as showed in table (5) need more than 25 min to completely release it content. While, the liquid-solid tablets give the release with the rapidly, due to disintegration time of tablets.

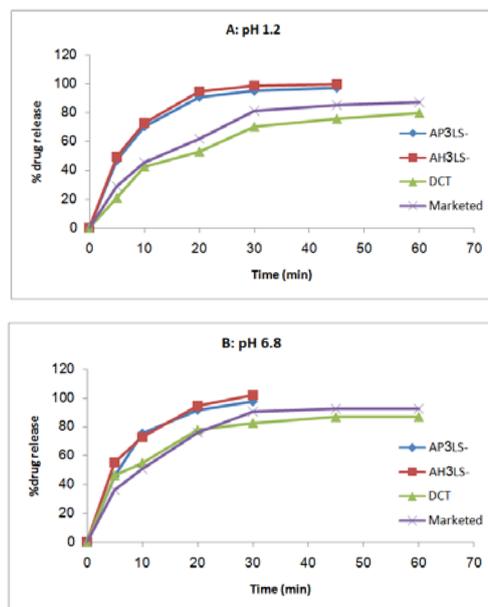


Fig. 15: Dissolution profile of liquid-solid compact (LS-3AP and LS-3AH), DCT and marketed tablet in A: 0.1 N HCl (pH 1.2), and B: phosphate buffer (pH 6.8) at 37°C.

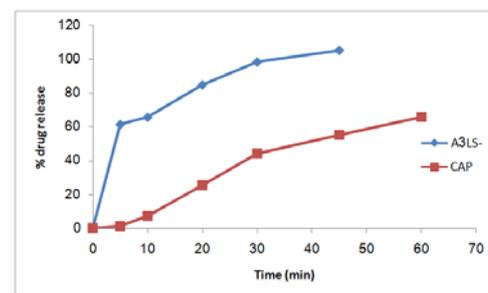


Fig. 16: Comparison of the percentage release of MLX liquid-solid compact (LS-3A) with same formula in encapsulation form in 0.1 N HCl pH 1.2.

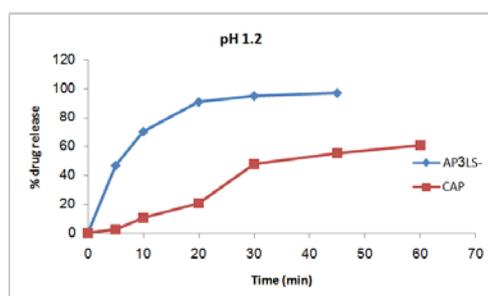


Fig. 17: Comparison of the percentage release of MLX liquid-solid compact (LS-3AP) with same formula in encapsulation form in 0.1 N HCl pH 1.2.

Selection of the best formula

The liquisolid tablet formulated with the PEG 400 at drug concentration of 30 % w/w (30 % drug and 70 % PEG 400) with excipient ratio (R) =25 is the best formula (LS-3) among all the batches of liquisolid tablets; in term of good flow properties, rapid disintegration, superior dissolution behaviors and acceptable tablet properties. While, the replacement of Aerosil 200 coating material with Silica (cab-O-sil) improved these properties as showed in formula LS-3A. Whereas, the addition of PVP K 25 as in LS-3AP or HPMC E5 as in LS-3AH lead to further improvement in properties and dissolution.

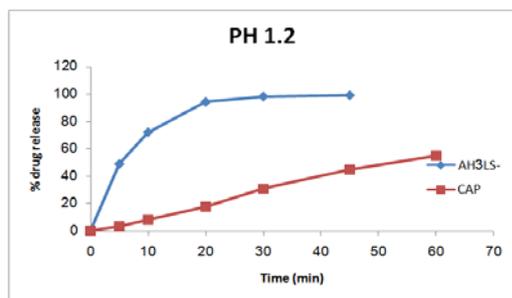


Fig. 18: Comparison of the percentage release of MLX liquisolid compact (LS-3AH) with same formula in encapsulation form in 0.1 N HCl pH 1.2.

So, the selected formula is LS-3 and its derivatives (LS-3A, LS-3AP and LS-3AH).

LS-3 (having the highest concentration in PEG 400 and R 25) and its derivatives showed higher drug release than reference preparation equivalent to 15 mg of MLX (mobic 15 mg Boehringer®) in both dissolution media as was shown in figure (15).

One-way ANOVA was used to verify the differences between the mean dissolution rates obtained for the selected liquisolid formula (LS-3 and its derivatives), DCT and marketed tablet. It is clear that, according to ANOVA, there were no significant differences (P> 0.05) between the mean dissolution rates obtained for selected LS formula with both DCT and mobic® 15 mg tablets in different dissolution media.

CONCLUSION

The liquisolid compacts technique can be a promising alternative for the formulation of water insoluble drugs, such as meloxicam into rapid release tablets. The higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability due to the increased wetting properties and solubility of drug in the liquid vehicles. it has been shown that the solubility of the drug in the liquid medication of the liquisolid compacts is directly proportion to their meloxicam dissolution rates.

CONFLICT OF INTERESTS

Declared None

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