FORMULATION AND EVALUATION OF ROFECOXIB LIQUISOLID TABLETS

Khalid M. El-Say, Ahmed M. Samy, Mohamed I. Fetouh.
Dept. of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University,
Nasr City, Cairo, Egypt.

ABSTRACT

The aim of our study was to improve the availability of Rofecoxib a practically insoluble non-steroidal anti-inflammatory drug, as a model drug by using liquisolid technique. The effect of powder substrate composition on the flowability and compressibility of liquisolid compacts were evaluated. Specifically, several liquisolid formulations, containing 25-mg Rofecoxib, which containing different carrier to coating ratios in their powder substrates and a fixed liquid medication, were prepared. The dissolution profiles of Rofecoxib liquisolid tablets were determined according to USP method. The obtained dissolution profiles were compared to that of a commercial product. In the present study, the formulated liquisolid systems exhibited acceptable flowability and compressibility. In addition, liquisolid tablets displayed significant enhancement of the dissolution profiles compared to this of commercial one.

Keywords: Liquisolid tablets, Rofecoxib, Formulation and evaluation.

INTRODUCTION

It is believed that better bioavailability of poorly soluble drugs could be achieved when drug is present in solution as in liquisolid formulations.[1] The concept of liquisolid compacts as defined by Spireas et al, (1998) can be used to formulate liquid medication such as oily liquid drug and solutions or suspensions of water-insoluble solid drugs in non-volatile vehicles, into acceptably flowing and compressible powders[2]. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by a simple blinding with selected powder excipients referred to as carrier and coating materials. Various grades of cellulose, starch, lactose, etc, may be used as the carrier, whereas a very fine particle size silica powder may be used as the coating material.

Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications, and they are industrially applicable. In addition, the term "liquid medication" does not only imply drug solutions, as in "powdered solutions", but also drug suspensions, emulsions, or liquid oily drugs. Therefore, in contrast to "powdered solutions", the term "liquisolid compacts" is more general and it may encompass for different formulation systems, namely, "powdered drug solutions", "powdered drug suspensions", "powdered drug emulsions", and "powdered liquid drug". Furthermore, the older term of "powdered solutions" seems to be inadequate even in describing the original systems, since it has not been proven that the remains in solutions in the liquid vehicle after its deposition on the extremely large powder surfaces of silica used[3].

Liquisolid compacts may be hampered by their poor and erratic flow and compaction properties. The flowability and the compressibility of liquisolid compacts have been addressed resulting in the new "formation model of Liquisolid systems", which enables one to calculate the appropriate quantities of ingredients required to produce acceptably flowing and compressible powders. According to the new theories[3], the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the powder excipient ratio, R, of the powder substrate which is the fraction of the weights of carrier (Q) and coating (q) materials present in the formulations (i.e., $R = Q/q$), there is a characteristic maximum liquid load on the carrier material, termed the liquid load factor, L_f, and defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system (i.e., $L_f = W/Q$), which must be possessed by an acceptably flowing and compressible preparation.

A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs can be formulated into liquisolid systems using the new formulation-mathematical model. It is well established that better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form. That is why soft gelatin capsules containing solubilized forms of such medications demonstrate higher bioavailability compared to conventional oral solid dosage forms. The same principle governs the mechanism of drug delivery from liquisolid systems, specifically, powdered drug solutions, and is chiefly responsible for the improved dissolution profiles exhibited by these preparations. In this instance, even though the drug is in a tabletted or encapsulated dosage form, it is held in a solubilized liquid state, which consequently contributes to increase drug-wetting properties, thereby enhancing drug dissolution.

The technique of liquisolid preparations was used to formulate hydrochlorothiazide, as a model drug in tablet form[4]. Drug solution in PEG 200 was blended with different common tablet excipients such as Avicel, Aerosil, Calcium phosphate, Magnesium oxide, and Magnesium carbonate. The dissolution rates of the liquisolid tablets were determined according to USP basket method.

Spireas and Sadu, (1998) concluded that, the new technique of liquisolid compacts appears to be a promising alternative for the formulation of water insoluble drugs such as prednisolone, into rapid release tablets which may

present improved oral bioavailability. As compared to conventional directly compressed tablets, the liquisolid compacts of prednisolone display significantly enhanced in-vitro release properties[5].

In another study of Spireas and Co-workers the new formulation technique of liquisolid compacts was used to convert liquid medication such as solutions or suspensions of hydrocortisone in propylene glycol, a nonvolatile liquid vehicle, into acceptably flowing and compressible powders by blending with selective powder excipients[5].

Also, Spireas et al, (1999) studied the effect of powder substrate composition on the dissolution properties of methyclothiazide, a practically insoluble diuretic agent, as the model drug. Liquisolid tablets of methyclothiazide containing a 5% w/w drug solution in polyethylene glycol 400 were prepared using powder substrates of different carrier: coating ratios in their powder substrates from 5 to 70[6].

Also, the maximum drug release was achieved when glibenclamide was dissolved in polyethylene glycol 400 originally incorporated onto the powder substrate of the liquisolid systems[7].

El-Adawy (2003) formulated nifedipine, a practically insoluble antianginal agent, in liquisolid tablets. Several liquisolid, 10 mg, tablet formulations containing different carrier/coat ratios in their powder substrate and different liquid medication of nifedipine in PEG 600, or Tween 80 was prepared. Avicel PH 200 and Cab-O-Sil were used as carrier and coating material, respectively, in different ratios and a standard 5% w/w of the disintegrant sodium starch glycolate (Explotab®) was added in all systems[8].

Nokhodchi et al, (2005) used the technique of liquisolid compacts to formulate and enhance the in-vitro release of piroxicam, which was formulated into 10mg liquisolid tablets consisting of similar powder excipients and Tween 80 with different drug concentrations in their liquid medications[9]. Also, Nokhodchi et al, (2005) utilized the liquisolid technique to increase dissolution rate of indomethacin and studied the effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug, indomethacin, from liquisolid compacts[10].

Enhancement of the in-vitro dissolution of piroxicam via liquisolid compacts was studied (Soliman, 2005). Several systems of liquisolid compacts were prepared according to the calculated liquid load factors and their flow properties were evaluated. In-vitro dissolution of piroxicam from the prepared liquisolid tablets and capsules were performed using simulated gastric fluid. The tested liquisolid tablets demonstrated a significant high drug release rates[11].

Rofecoxib is a nonsteroidal anti-inflammatory drug that exhibits, analgesic, and antipyretic activities. The mechanism of action of Rofecoxib is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (Cox-2)[12]. Rofecoxib is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water[13].

In this study, Rofecoxib a practically insoluble non-steroidal anti-inflammatory drug was formulated into 25 mg liquisolid tablets consisting of Avicel PH 101, Cab-O-Sil, and PEG 600 as the liquid vehicle. The in-vitro release of such preparations were assessed and compared to this of commercial counterpart using a USP dissolution apparatus II (paddle) in 900 ml 0.1N HCl pH 1.2 for 45 minutes.

MATERIALS AND METHODS

1. Materials

The following materials were used as received: Rofecoxib powder and Rhumacure® tablets 25mg from Egyptian International Pharmaceutical Industries Co. (Egypt), Amorphous fumed silica, Cab-O-Sil® M-5P from Cabot Corporation (North America, USA), Methanol from Honil Limited (London), Methylene chloride, Propylene glycol, Glycerol, and Magnesium oxide from El-Nasr pharmaceutical chemicals (Egypt), Microcrystalline cellulose (Avicel PH 101), PEG 400, PEG 600, Tween 40, Tween 80, Brij 35% solution, and Span 80 from Sigma chemical Co. (USA), Tween 20 from Aldrich chemical Co. Ltd. (England), Ac-Di-Sol® "modified cellulose gum NF" from FMC corporation (Philadelphia, Pennsylvania 19103, USA), Magnesium stearate from Prolabo (France), and Hydrochloric acid from Carloerba (Milano, Italy).

2. Equipment

Shaking water bath (Julabo SW-20C, Germany), Electric balance (Mettler AJ100, Switzerland), Ultraviolet spectrophotometer (Jenway 6305 uv/vis. UK), Single Punch tablet press (First Medicine machinery shanghai factory of Dongha Branch, Shanghai, China), Tablet Hardness tester (Pharmatest, Type PTB 301, Hainburg, Germany), Friability tester (Pharmatest, Type PTF1, Hainburg, Germany), Thickness (micrometer, M&W. Ltd, Sheffild; England), Disintegration tester (Pharmatest, Type PTZ3, Hainburg, Germany), Dissolution apparatus, six-spindle dissolution tester (Pharmatest Type PTWII, Germany).

3. Experimental

3.1. Solubility studies

The solubility studies of Rofecoxib were carried out as described by Spireas et al., (1998); Spireas and Sadu, (1998); Nokhodchi et al., (2005). In this study, the solubility of Rofecoxib was determined in different solvents including: PEG 600, PEG 400, Tween 80, Tween 40, Tween 20, Span 80, glycerin, Brij 35 solution, propylene glycol, and distilled water. Preparing saturated solutions of the drug in these solvents and analyzing its drug content spectrophotometrically performed the test.

Specifically, Rofecoxib was mixed in 10ml test tubes with such amounts of each of the above solvents in order to produce a system containing excess of the drug. The mixture was sonicated for 48 hours and then cooled to 25°C, at constant vibration. The obtained solutions were filtered through Millipore filter (0.45µm). After this period, an accurately weighed quantity of the filtered supernatant solution was further diluted with methanol and analyzed spectrophotometrically at 268 nm for its drug content.

3.2. Holding capacity of the excipients

The capacity of each excipient to hold liquid and behave like dry powder (holding capacity) was determined using the following simple technique[4]:

Different weights of PEG 600, from 0.446 g to 4.464 g were transferred to a mortar. The constant weight (10g) of powder excipient was added gradually and the mixture was triturated after each addition to help distributing the liquid throughout the powder particles. The addition of powder and the trituration was continued until mortar contents start to look like dry powder.

3.3. Evaluation of flowability and compressibility of liquisolid powders

The flowability of the obtained mixtures, after determining the holding capacity of the excipients, was calculated by measuring the angle of repose (direct method). Determination of bulk and tap densities of the obtained mixtures was used to calculate both the Hausner ratio and the Carr's index (indirect method).

The obtained mixtures were compressed into tablets and the compressibility of these tablets was determined by measuring the hardness of each tablet.

3.4. Determination of Liquid load factor (L_f)

Liquid load factor (L_f) is defined as the weight ratio of the liquid medication (w) and carrier powder (Q) in the system (i.e., L_f = W/Q), which must be possessed by an acceptably flowing and compressible preparation.

Constant weights of Avicel PH 101, the selected carrier according to the previous results, (10g) was placed in different mortars containing different weights of PEG 600 (0.446 - 4.464g) as a solvent, triturate well. The final mass was checked for their consistency, flowability, and compressibility properties and then compressed into tablets and their texture, hardness were detected. This procedure was repeated firstly, by addition of 5% Cab-O-Sil® and 2% of magnesium oxide in all mixtures and secondly, by increasing these percentages to 10% Cab-O-Sil® and 5% magnesium oxide to improve the flowability and the compressibility properties of the prepared mixtures.

3.5. Preparation of liquisolid tablets

Several liquisolid systems of Rofecoxib (denoted as LS-1 to LS-15) were prepared in 50 tablet batches and compressed into cylindrical tablets each containing 25 mg drug, using the single punch tablet press. All liquisolid formulations contained microcrystalline cellulose (Avicel® PH 101) as the carrier powder and silica (Cab-O-Sil® M5-P) as the coating material at different powder excipient ratio (R) using Box-Behnken design. Polyethylene glycol 600 was used as the liquid vehicle to prepare the liquid medications with a fixed 25 % (w/w) drug concentration. Different liquid load factor, L_f, 0.225, 0.275 and 0.325 were employed. Different percentage of magnesium oxide 2.5, 5, and 7.5 % (w/w) was used as a flow activator. Finally, standard 5% croscarmellose sodium (Ac-Di-Sol®) was used as a disintegrant and 1% magnesium stearate as a lubricant in all systems.

Liquisolid tablets were prepared as follows, Rofecoxib was dispersed in PEG 600 and the mixture of microcrystalline cellulose- silica and magnesium oxide were added to the mixture under continuous mixing in a mortar. Finally, Ac-Di-Sol® was mixed for a period 10 minutes and then adds magnesium stearate before compression.

3.6. Quality control tests of Rofecoxib liquisolid tablets

Quality control tests of Rofecoxib liquisolid tablets were examined. They include: weight uniformity, thickness uniformity, hardness, friability, HFR, disintegration time, and drug content uniformity.

3.7. In-vitro release of Rofecoxib from liquisolid tablets

The test was performed on the prepared Rofecoxib liquisolid tablets and commercial product according to the USP XXV dissolution procedures, apparatus 2[14]. Six individual tablets from each formula were tested. In all studies, the temperature of the dissolution medium was maintained at 37±0.5°C. The paddle rotated at 100 rpm. The dissolution medium was 900ml 0.1 N HCl pH 1.2 for 45 minutes. Samples of 5ml were withdrawn at regular time intervals 5, 10, 15, 20, 25, 30, 35, 40, and 45 minutes, filtered, and analyzed spectrophotometrically at 268nm. After their assay, the dissolution samples were recirculated to their original vessels. The spectrophotometric readings were converted into cumulative percent of drug released using the standard calibration curve of Rofecoxib previously constructed.

RESULTS AND DISCUSSION

Solubility studies

The solubility of Rofecoxib in the different solvents was studied. It was clear from the results according to Egyptian Pharmacopoeia (1984) that Rofecoxib was practically insoluble in water and very slightly soluble in both propylene glycol and Brij 35 solution[15]. The solubility of Rofecoxib was ascending increased to be a slightly soluble in glycerin, span 80, Tween 20, Tween 40, Tween 80 and PEG 400, While Rofecoxib is a sparingly soluble in PEG 600 (1.038% w/w). For this reason, PEG 600 was selected to be the suitable solvent for preparing Rofecoxib liquisolid compacts in this study. The results (Table 1) were extrapolated to determine the percent w/w of Rofecoxib in its saturated solution with the solvents under investigation.

Evaluation of flowability and compressibility of liquisolid powders

The powder has a good flowability; when the Hausner ratio is lower than 1.2, while if the ratio is more than 1.2 this indicates that the flowability is bad[16]. It was showed that powders with interparticle friction, such as coarse spheres, had ratios of approximately 1.2, whereas more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6. Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. A compressible material will be less flowable, and powders with compressibility values greater than 20-21 % have been found to exhibit poor flow

properties[17]. As a general guide, powders with angles of repose greater than 50° have unsatisfactory flow properties, whereas minimum angles close to 25° correspond to very good flow properties[18].

Table 1: Solubility of Rofecoxib in different solvents

Solvent	Solubility(%w/w)
Polyethylene glycol 600	1.0382
Polyethylene glycol 400	0.9569
Tween 80	0.8018
Tween 40	0.7602
Tween 20	0.6883
Span 80	0.6346
Glycerin	0.2405
Brij 35 solution	0.0567
Propylene glycol	0.0435
Distilled water	0.0023

Table (2) revealed that all the tested liquisolid systems had a satisfactory flow according to the obtained results of measuring the angle of repose for each liquisolid system. The range was from 31.59 for LS-5 to 38.66 for LS-6. The prepared Rofecoxib liquisolid systems can be arranged in ascending order, regarding the angle of repose measurements as follows: LS-5< LS-9< LS-2< LS-12< LS-4< LS-8< LS-10< LS-11< LS-3 = LS-13< LS-1< LS-14 = LS-15< LS-7, LS-6.

The bulk and tap densities for Rofecoxib liquisolid powders were illustrated in Table 2, the mean densities of Rofecoxib liquisolid powders were found to be from 0.278 to 0.417 g/cm^3 for bulk density and from 0.4 to 0.5 g/cm^3 for tap density.

Hausner ratio and Carr's index were calculated from the density values. These results revealed that LS-12, LS-13, LS-14 and LS-15 had Hausner ratio of 1.14, 1.19, 1.19 and 1.19, respectively, which were less than 1.2 and this indication for good flowability of these formulae and the rest formulae had low flowability because it had Hausner ratio less than 1.6. The same formulae in addition of LS-10 and LS-2 had Carr's index less than 21% and this indicates that these formulae had a good flowability but the rest formulae had a bad flow properties.

It was found that, there is a relationship between powder excipient ratios (R) and the angle of repose of the liquisolid powders in the formulae having the same L_f. The powder excipient ratio (R) was directly proportional to the angle of repose of the liquisolid powders i.e., when the powder excipient ratio (R) increased the angle of repose of the liquisolid powders will increase. This finding was displayed from the following results: formulae LS-8, LS-1, and LS-7 were having the same L_f equal to 0.225 and (R) 5.44, 8.16, and 16.3, respectively, and the mean angle of repose of the liquisolid powders were 35.37, 36.87, and 37.95 degrees, respectively (r = 0.93078). Also, formulae LS-4, LS-13, and LS-6 having the same L_f 0.275 and (R) 5.23, 7.84, and 15.7 and the mean angle of repose of the liquisolid powders of them were 34.92, 36.62, and 38.66 degrees, respectively (r = 0.996739). And this finding was confirmed by the third example, formulae LS-5, LS-2, and LS-11 having L_f 0.325, and the mean angle of repose of the liquisolid powders of them were 31.59, 33.78, and 35.75 degrees, respectively (r = 0.950306). This can be explained by the fact that, increasing (R) of the formula leading to increase in the amount of the carrier powder used (Avicel PH 101) which is a highly porous material and decrease the amount of the coating material "Cab-O-Sil", which is a very fine particle size silica powder responsible for the flowability of the powder, and this subsequently, lead to the increase of the angle of repose of the powder.

Table 2: Physical properties of the prepared Rofecoxib liquisolid powders

Liquisolid powder	Angle of Repose	Densities (g/cm^3)		Hausner Ratio	Carr's Index
		Bulk Density	Tap Density		
LS – 1	36.87	0.357	0.455	1.27	21.52
LS – 2	33.78	0.385	0.476	1.23	19.12
LS – 3	36.13	0.357	0.500	1.40	28.60
LS – 4	34.92	0.313	0.435	1.39	28.05
LS – 5	31.59	0.313	0.435	1.39	28.05
LS – 6	38.66	0.286	0.417	1.45	31.41
LS – 7	37.95	0.295	0.417	1.41	29.26
LS – 8	35.37	0.313	0.400	1.28	21.75
LS – 9	32.62	0.345	0.455	1.32	24.18
LS – 10	35.75	0.345	0.417	1.21	17.27
LS – 11	35.75	0.278	0.400	1.44	30.50
LS – 12	34.61	0.417	0.476	1.14	12.97
LS – 13	36.13	0.400	0.476	1.19	15.97
LS – 14	37.60	0.400	0.476	1.19	15.97
LS – 15	37.60	0.400	0.476	1.19	15.97

Table 3: Formulation characteristics of prepared Rofecoxib liquisolid compacts

Liquisolid system [a]	Liquid load factor (L_f) [b]	Powder excipient ratio (R)[c]	Avicel PH 101 (Q)[d]	Cab-O-Sil (q)[e]	MgO[f]	Ac-Di-Sol[g]	Mg stearate[h]	Tablet weight
			Quantity in mg					
LS- 1	0.225	8.16	444.40	54.44	13.60	30.62	6.12	**649.19**
LS- 2	0.325	7.50	307.69	40.77	10.19	22.93	4.59	**486.17**
LS- 3	0.325	7.50	307.69	40.77	30.58	23.95	4.79	**507.78**
LS- 4	0.275	5.23	363.64	69.55	11.59	27.24	5.45	**577.47**
LS- 5	0.325	5.03	307.69	61.15	20.38	24.46	4.89	**518.57**
LS- 6	0.275	15.7	363.64	23.18	11.59	24.92	4.98	**528.31**
LS- 7	0.225	16.3	444.40	27.22	27.22	29.94	5.99	**634.77**
LS- 8	0.225	5.44	444.40	81.66	27.22	32.66	6.53	**692.47**
LS- 9	0.275	5.23	363.64	69.55	34.77	28.40	5.68	**602.04**
LS- 10	0.275	15.7	363.64	23.18	34.77	26.08	5.22	**552.89**
LS- 11	0.325	15.1	307.69	20.38	20.38	22.42	4.48	**475.35**
LS- 12	0.225	8.16	444.40	54.44	40.83	31.98	6.40	**678.05**
LS- 13	0.275	7.84	363.64	46.36	23.18	26.66	5.33	**565.17**
LS- 14	0.275	7.84	363.64	46.36	23.18	26.66	5.33	**565.17**
LS- 15	0.275	7.84	363.64	46.36	23.18	26.66	5.33	**565.17**

[a] All systems contain 25% w/w drug solution in polyethylene glycol 600 as their liquid medication.
[b] The liquid load factor is defined as $L_f = W/Q$ where W and Q are the weights of the liquid medication and carrier powder, respectively.
[c] The powder excipient ratio is defined as R = Q/q where Q and q are the weights of Avicel PH 101 and Cab-O-Sil, respectively.
[d] The weight of carrier powder.
[e] The weight of coating material.
[f] The weight of flow activator (adsorbent), magnesium oxide, in different percentage 2.5, 5, 7.5%.
[g and h] All systems contain 5% and 1% of disintegrant croscarmellose and lubricant magnesium stearate, respectively.

Table 4: Quality control tests of Rofecoxib liquisolid tablets

Liquisolid Tablets	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (g)	HFR	Disintegration (min.)	Content Uniformity (%)
LS-1	641.3	4.87	7.46	0.008	955.8	6.32	96.0
LS-2	480.7	3.77	3.29	0.009	357.1	3.57	100.1
LS-3	503.6	3.85	3.37	0.017	200.5	3.50	99.0
LS-4	575.0	4.34	5.92	0.007	911.1	12.5	95.8
LS-5	514.3	3.85	5.27	0.006	864.3	8.32	97.4
LS-6	523.9	3.99	3.10	0.012	258.1	1.47	95.6
LS-7	632.1	4.78	5.76	0.006	976.3	1.30	100.4
LS-8	689.6	5.02	10.97	0.014	772.5	17.0	99.5
LS-9	600.0	4.21	5.61	0.013	434.9	11.4	97.3
LS-10	548.8	4.11	3.08	0.008	394.2	1.35	95.8
LS-11	472.7	3.63	1.80	0.012	147.1	1.46	100.2
LS-12	675.9	4.95	7.36	0.006	1226.5	5.84	95.9
LS-13	562.3	4.30	4.32	0.012	356.6	4.33	95.8
LS-14	562.4	4.27	4.39	0.017	256.7	4.35	96.7
LS-15	561.6	4.32	4.20	0.015	281.5	4.31	97.4

Preparation of liquisolid tablets

The formulation characteristics of the prepared Rofecoxib liquisolid systems according to Box-Behnken design, as shown in (Table 3), gave 15 formulae with different variables.

Quality control tests of Rofecoxib liquisolid tablets

Table 4 showed the uniformity of weight of all investigated tablets. Most Pharmacopoeias include a simple weight test on a specified number of tablets, which are weighed individually, and the arithmetic mean weight is calculated. The permitted weight variations in USP, not more than two tablets differ from the mean by more than 5%, and none of the investigated tablets differ from the mean by more than 10%. In B.P., the permitted weight variations are essentially the same as that of the USP. It was clear from the obtained results that all the investigated tablets met with the requirements of USP and BP.

The thickness uniformity although being nonofficial, yet it could be considered as an additional control to tablet dimensions and increased reproducibility[19]. The obtained results showed that all the prepared Rofecoxib liquisolid tablets had the acceptable limits of thickness uniformity. All results of thickness were tabulated in Table 4.

The mechanical properties of the prepared Rofecoxib liquisolid tablets were investigated by testing their hardness as well as their friability and from the obtained values the hardness/friability ratio (HFR) was calculated for all investigated tablets.

The mean hardness of the tablets ranged from 1.795 kg for LS-10 to 10.97 kg for LS-8. The mean of the hardness values were shown in Table 4. The Optimum hardness for each liquisolid tablet was calculated according to (Spireas, 2002) as follow: specific crushing strength of a tablet is the ratio of its crushing strength (hardness) over its weight, for instance, liquisolid tablets weighing 0.6 and 0.3 grams were compressed to hardness of 9 kg (i.e., 15 kg/0.6g) and 4.5 kg (i.e., 15kg/0.3g), respectively. It was found that LS-8 had the least deviation from the mean hardness (0.583) related to its weight, followed by LS-1, LS-5, while LS-11 had the worst hardness and the largest deviation from the mean (5.335)[20].

It was found that, there is a relationship between liquid load factor (L_f) and the hardness of the tablets in the formulae having approximately the same powder excipient ratio. The liquid load factor was inversely proportional to the hardness of the tablets i.e., when the L_f increased the hardness of the tablets will decrease, and this was obvious from the following results. Formulae LS-8, LS-4, and LS-5 were having L_f 0.225, 0.275, and 0.325, and the mean hardness of them was 10.97, 5.922, and 5.272 kg, respectively (r = -0.91341). Also, Formulae LS-12, LS-14, and LS-2 having L_f 0.225, 0.275, and 0.325, and the mean hardness of them were 7.359, 4.39, and 3.285 kg, respectively (r = -0.96684). And this finding was confirmed by the third example, formulae LS-7, LS-10, and LS-11 having L_f 0.225, 0.275, and 0.325, and the mean hardness of them were 5.67, 3.075, and 1.795 kg, respectively (r = -0.97971). This can be explained by that, increasing L_f of the formula increasing the amount of solvent used and decreasing the amount of powder excipient and this subsequently, decrease the hardness of the tablets.

Another finding was declared from the obtained results that there is a relationship between powder excipient ratios (R) and the hardness of the tablets in the formulae having the same L_f. The powder excipient ratio (R) was inversely proportional to the hardness of the tablets i.e., when the powder excipient ratio (R) increased the hardness of the tablets will decrease; this finding was cleared from the following results. Formulae LS-8, LS-1, and LS-7 were having the same L_f equal to 0.225 and had (R) equal to 5.44, 8.16, and 16.3, and the mean hardness was 10.97, 7.455, and 5.76 kg, respectively (r = -0.8872). Also, formulae LS-4, LS-14, and LS-10 having the same L_f 0.275 and had (R) equal to 5.23, 7.84, and 15.7 and the mean hardness of them were 5.922, 4.39, and 3.075 kg, respectively (r = -0.9474). And this finding was confirmed by the third example, formulae LS-5, LS-2, and LS-11 having L_f 0.325, and had (R) equal to 5.03, 7.5, and 15.1, and the mean hardness of them were 5.272, 3.285, and 1.795 kg, respectively (r = -0.93291). This can be explained by that, increasing (R) of the formula leading to increase the amount of the carrier powder (Avicel PH 101) used which is a highly porous material and the amount of the coating material "Cab-O-Sil" will decreased and this subsequently, lead the tablet to be friable and decreased the hardness of the tablets.

LS-7 showed the best result of friability test regarding to the loss of weight mean (0.0059 g) followed by LS-12, LS-5, while LS-14 had the largest weight loss mean (0.0171 g).

Combining the hardness and friability values of all the tested tablets and calculating obtained the HFR, a clear picture of the mechanical properties of the liquisolid tablets. It was found from the data of HFR that LS-12 had the largest HFR value (1226.7), followed by LS-7, LS-1, LS-4, while LS-11 had the smallest HFR value (150).

The disintegration time for the prepared Rofecoxib liquisolid tablets was shown in Table (3). It was found that, the mean of the disintegration times for all investigated tablets were less than 30 minutes, which met the Pharmacopoeial requirements. LS-7 was found to be the fastest formula to be disintegrated (1.296 minutes), followed by LS-10, LS-11, and LS-6, with disintegration time 1.352, 1.456, and 1.472, respectively. While, the slowest disintegrated formula was LS-8, which toke 16.95 minutes to disintegrate.

The same finding was obtained from the results of the investigation of the disintegration time of the tablets. It was found that, there is a relationship between liquid load factor (L_f) and the disintegration time of the tablets in the formulae having approximately the same powder excipient ratio. The liquid load factor was inversely proportional to the disintegration time of the tablets i.e., When the L_f increased the disintegration time of the tablets will decrease, and this was obtained from the following results. Formulae LS-8, LS-4, and LS-5 were having L_f 0.225, 0.275, and 0.325, and the mean disintegration time of them

were 16.95, 12.50, and 8.32 minutes, respectively (r = -0.99984). And this finding was confirmed by the second example, formulae LS-12, LS-14, and LS-2 having L_f 0.225, 0.275, and 0.325, and the mean disintegration time of them were 5.839, 4.353, and 3.569 minutes, respectively (r = -0.99557). That, increasing L_f of the formula increasing the amount of liquid used 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, can explain this finding.

Another finding was displayed from the obtained results that there is a relationship between powder excipient ratios (R) and the disintegration time of the tablets in the formulae having the same L_f. The powder excipient ratio (R) was inversely proportional to the disintegration time of the tablets i.e., when the powder excipient ratio (R) increased the disintegration time of the tablets will decreased, this finding was cleared from the following results. Formulae LS-8, LS-1, and LS-7 were having the same L_f equal to 0.225 and had (R) equal to 5.44, 8.16, and 16.3, and the mean disintegration time were 16.95, 5.839, and 1.296 minutes, respectively (r = -0.88487). Also, formulae LS-4, LS-14, and LS-10 having the same L_f 0.275 and had (R) equal to 5.23, 7.84, and 15.7 and the mean disintegration time of them were 12.50, 4.353, and 1.352 minutes, respectively (r = -0.85655). And this finding was confirmed by the third example, formulae LS-5, LS-2, and LS-11 having L_f 0.325, and had (R) equal to 5.03, 7.5, and 15.1 and the mean disintegration time of them were 8.32, 3.569, and 1.456 minutes, respectively (r = -0.87546). This can be explained by that, increasing (R) of the formula leading to the high microcrystalline cellulose content where Avicel PH 101 functions as a swellable disintegrant (Patel et al, 1994). In addition, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of Rofecoxib and this subsequently, lead the tablet to be disintegrated quickly and decreased the disintegration time of the tablets[21].

It was clear from Table 4, that all the investigated liquisolid tablets complied with the pharmacopoeial requirements as regard their content uniformity, which was found to lie within the range 95-105% with a coefficient of variation percent less than 0.019156%. LS-2 showed the lowest deviation from the 100% (0.05%), while LS-6 showed the highest deviation (4.375%).

In-vitro release of Rofecoxib from liquisolid tablets

The in-vitro release of Rofecoxib from the formulated liquisolid tablets were performed and the dissolution profiles of them from the prepared liquisolid tablets in 0.1N HCl pH 1.2 were graphically represented in figure 1. It was found that, all the prepared liquisolid tablets released more than 90% of their Rofecoxib content after 45 minutes.

After five minutes in the dissolution apparatus, the percent released from Rofecoxib liquisolid tablets was found to range from 12.25% (formula LS-5) to 44.13% (formula LS-7). The percent released was increased in continuous pattern from five minutes until twenty minutes. This continuous increase of Rofecoxib liquisolid tablets ranged from 78.2% (formula LS-5) to 90.5% (formula LS-7). After this period, the percent release was increased in slow performance until reach 89.15% for formula LS-5 (the smallest release) and 96.25% for formula LS-7 (the largest release).

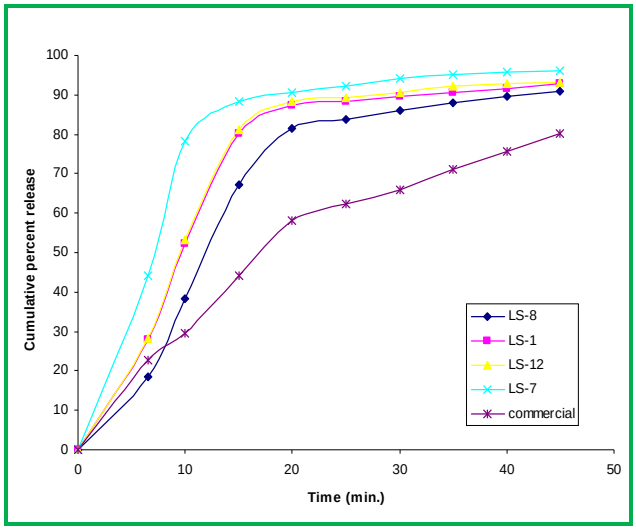

Figure 1: Dissolution profile of Rofecoxib liquisolid and commercial tablets

From the obtained results, it was displayed that there is a relationship between the powder excipient ratio and the in-vitro release of Rofecoxib from liquisolid tablets. The powder excipient ratio was directly proportional to the in vitro release i.e., when the powder excipient ratio increased the release will increase. This finding was declared from the following results. Formulae LS-8, LS-1, and LS-7 were having the same L_f equal to 0.225 and had (R) equal to 5.44, 8.16, and 16.3, and the cumulative percent released were 90.89, 92.75, and 96.25%, respectively (r = 0.994419). Also, formulae LS-9, LS-13, and LS-6 having the same L_f 0.275 and had (R) equal to 5.23, 7.84, and 15.7 and the cumulative percent released of them were 90.49, 92.43, and 95.83%, respectively (r = 0.992168). Also, formulae LS-4, LS-14, and LS-10 having the same L_f 0.275 and had (R) equal to 5.23, 7.84, and 15.7 and the cumulative percent released of them were 90.36, 92.42, and 95.73%, respectively (r = 0.989038). And this finding was confirmed by the fourth example, formulae LS-5, LS-2, and LS-11 having L_f 0.325, and had (R) equal to 5.03, 7.5, and 15.1 and the cumulative percent released of them were 89.15, 92.35, and 95.42%, respectively (r = 0.955918).

This may be attributed to the high microcrystalline cellulose content where Avicel PH 101 functions as a swellable disintegrant[22]. In addition, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of Rofecoxib and enhance its dissolution[21].

CONCLUSION

From the previous results, it was concluded that, addition of 10% Cab-O-Sil® and 5% magnesium oxide improved both the flowability and the compressibility of the tested Rofecoxib powders. These two substances change the flowability from bad flow to satisfactory flow. Rofecoxib

liquisolid tablets showed higher dissolution profiles than the three studied commercial tablet. There is a relationship between the powder excipient ratio and the in-vitro release of Rofecoxib from liquisolid tablets having the same liquid load factor. The powder excipient ratio was directly proportional to the in vitro release of Rofecoxib from their formulations. Finally, Liquisolid technique can be used to improve the availability, and the in-vitro release of Rofecoxib as a model for a practically insoluble drug.

REFERENCES

1. Spireas, S., Bioavailability improvement of clofibrate using liquisolid compact technology, APHA Annual Meeting, 142, 161 (1995).
2. Spireas, S., and Sadu, S., Enhancement of prednisolone dissolution properties using liquisolid compacts, Int. J. Pharm., 166, 177-188 (1998).
3. Spireas, S.S., Theoretical and Practical Aspects of liquisolid compacts. Ph.D. Thesis, St. John's University, New York, (1993).
4. Khaled, A.K., Formulation and evaluation of hydrochlothiazide liquisolid tablets, Saudi Pharm. J., 6 (1), 39-46 (1998).
5. Spireas, S., Sadu, S., and Grover, R., In vitro release evaluation of hydrocortisone liquisolid tablets, J. Pharm. Sci., 87, 867-872 (1998).
6. Spireas, S., Wang, T., and Grover, R., Effect of powder substrate on the dissolution properties of methchlorothiazide liquisolid compacts, Drug Dev. Ind. Pharm., 25,163-168 (1999).
7. Inas, A.D., and Amal, H.El., Dissolution enhancement of glibenclamide using liquisolid tablet technology, Acta. Pharm., 51, 173 (2001).
8. El-Adawyl, A.I.S., (2003) in "Preformulation, in-vitro evaluation, and bioavailability studies of a poorly water-soluble drug in solid dosage form", Ph.D. Thesis, faculty of pharmacy for girls, Al-Azhar University, Cairo, Egypt.
9. Nokhodchi, A., Javadzadeh,Y., Siahi-Shadbad, M.R., and Barzegar-jalali, M., Enhancement of dissolution rate of piroxicam using liquisolid compacts, Il Farmco., 60, 361-365 (2005).
10. Nokhodchi, A., Javadzadeh, Y., Siahi-Shadbad, M.R., and Barzegar-jalali, M., The effect of type and concentration of vehicle on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts, J. Pharm. Sci., 8(1), 18-25 (2005).
11. Soliman, I.I., Enhancement of the in-vitro dissolution of piroxicam via liquisolid compacts, Egypt. J. Biomed. Sci., 17, 61-74 (2005).
12. Martindale, (2005), The Complete Drug Reference, Sweetman, S.C., (ed.), London, The Pharmaceutical Press, Electronic version.
13. Physicians Desk Reference, PDR®, Electronic library, version 6.1.301 a-2004. 1.
14. USP 25 and NF 20; US Pharmacopoeia 25 and National Formulary 20, US Pharmacopoeial Convention Inc.; Rockville; MD; (2002), p. 1388.
15. Egyptian Pharmacopoeia, (1984), Third Edition, vol. 1, p. 9.
16. Fonner, D.E., Banker, G.S., and Swarbrick, J., J. Pharm. Sci., 55, 181 (1966).
17. Carr, R.L., Chem. Eng., 72, 2, 163-168 (1965).
18. Martin, A., Bustamante, P., and Chun, A.H.C., (1993) in "Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences", 4th Ed., Martin, A. (ed.), Lea and Febiger, Philadelphia, pp. 284-323.
19. Khattab, I., (1989) in "The use of direct compression vehicles for the manufacture of certain medicinal tablets", Ph. M. Thesis, Faculty of pharmacy, Al-Azhar University, Cairo, Egypt.
20. Spireas, S., Liquisolid systems and methods of preparing the same. Pharmaceutical patent, 6423339, July 23, (2002).
21. Petrovick, P.R., Jacob, M., Gaudy, D., and Bassani, V.L., Influence of adjuvents on the in vitro dissolution of hydrochlorothiazide from hard gelatin capsules, Int. J. Pharm., 76, 49-53 (1991).
22. Patel, N.K., Upadhyay, A.H., Bergum, J.S., and Rier, G.E., An evaluation of microcrystalline cellulose and lactose excipients using an instrumented single station tablet press, Int. J. Pharm., 110, 203-10 (1994).
23. Martin, A., Bustamante, P., and Chun, A.H.C., (1993) in "Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences", 4th Ed., Martin, A. (ed.), Lea and Febiger, Philadelphia, pp. 423-452.

****