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OPTIMIZATION OF FUROSEMIDE LIQUISOLID TABLETS PREPARATION PROCESS LEADING TO THEIR MASS AND SIZE REDUCTION

MATEUSZ KUREK*, KRZYSZTOF WOYNA-ORLEWICZ, MOHAMMAD HASSAN KHALID and RENATA JACHOWICZ

Chair and Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University, Medical College, Medyczna 9, 30-688 Kraków, Poland

Abstract: The great number of drug substances currently used in solid oral dosage forms is characterized by poor water solubility. Therefore, various methods of dissolution rate enhancement are an important topic of research interest in modern drug technology. The purpose of this study was to enhance the furosemide dissolution rate from liquisolid tablets while maintaining an acceptable size and mass. Two types of dibasic calcium phosphate (Fujicalin®/Emcompress®) and microcrystalline cellulose (Vivapur® 102/Vivapur® 12) were used as carriers and magnesium aluminometasilicate (Neusilin® US2) was used as a coating material. The flowable liquid retention potential for those excipients was tested by measuring the angle of slide. To evaluate the impact of used excipients on tablet properties fourteen tablet formulations were prepared. It was found that LS2 tablets containing spherically granulated dibasic calcium phosphate and magnesium aluminometasilicate exhibit the best dissolution profile and mechanical properties while tablets composed only with Neusilin® US2 was characterized by the smallest size and mass with preserved good mechanical properties and furosemide dissolution.

Keywords: liquisolid, dissolution rate, furosemide, solubility

Gastrointestinal absorption of a drug administered orally is affected by multiple parameters including drug dissolution rate, which is influenced by the drug solubility in gastrointestinal fluids. Water solubility of an active pharmaceutical ingredient (API) is the critical factor in the design of solid oral dosage forms. Nowadays, approximately 40% of the immediate release dosage forms administered orally contain active substances that are insoluble in water (1). Therefore, the low dissolution rate of poorly soluble drugs, i.e., belonging to the class II and IV of the Biopharmaceutical Classification System (BCS), still remains one of the major problems in the formulation of the dosage forms. Many strategies can be applied to improve drug dissolution properties, namely: micronization, formulation of solid dispersions, complexation with β-cyclodextrins or drug derivatization.

The liquisolid technique that has emerged in the last decade is a promising approach to the solubility improvement of poorly water soluble drugs. Its main advantages include simplicity of manufacturing, use of commercially available excipients, and application of well-known methods and equipment utilized for the manufacturing of conventional tablets.

Liquisolid systems (LCS) are described as dry, free flowing and compressible powder mixtures with absorbed solution or dispersion of drug substance in non-volatile solvent or liquid drug form (2). The liquisolid system is mainly composed of two groups of excipients: carriers and coating materials. Various grades of microcrystalline cellulose (MCC), dibasic calcium phosphate, pregelatinized starch and lactose are commonly used as carriers, while different types of silica dioxide are utilized as coating material (3). The factor limiting formulation of reasonable size and low mass liquisolid tablets is the solubility of the active substance in non-volatile solvents. Thus, the application of solvents characterized by high solubilizing capability could be a promising method of reducing tablet size and mass. The most commonly used solvents include propylene glycol, polyethylene glycol, polysorbate, Cremophor® EL or Synperonic™ PE/L61 (4).

Insoluble model drug substances such as carbamazepine, famotidine, furosemide, piroxicam and

* Corresponding author: e-mail: mateusz.kurek@uj.edu.pl; phone: +48 12 6205602, fax: +48 12 6205619

prednisolone have been used in the liquisolid technology development (3-7).

A crucial limitation factor in the application of LCS technology is the dose of drug substance. Javadzadeh et al. (6) suggested that the liquisolid method is suitable for dosages lower than 50 mg. Nevertheless, it was found that the application of polymeric additives, e.g., polyvinylpyrrolidone (PVP) might help to overcome this problem, and higher amounts of drugs can be used. In that study, 100 mg of carbamazepine was loaded into liquisolid tablets weighting from 583 mg to 1010 mg per unit, but there is a lack of information about the size of the tablets (6). The application of excipients with high absorption capacity is another possibility to decrease the mass of the tablets. It was shown that application of porous excipients such as magnesium aluminometasilicate instead of conventional tableting excipients resulted in an increased drug loading capacity of formulation (3). Despite the low dose of griseofulvin, 3 mg of the API had to be introduced in the form of 2 to 5 tablets with a diameter as big as 10 mm (8). The size and the mass of the tablets are the fundamental factors affecting patient compliance. In the case of liquisolid tablets, the attributes result from the dose of the API, its solubility in the solvent used, carrier and coating material absorptivity and their weight ratio as well as polymer additives to the formulation.

The aim of this study was to develop and optimize liquisolid tablets composition characterized by improved dissolution rate and possible small size and mass. Furthermore, the influence of various carriers and carrier to coating material ratio were studied in respect to the liquisolid tablets mechanical properties and model drug dissolution profile. Furosemide, in the dose of 40 mg which is registered on the market, was chosen as a model practically insoluble in water drug substance which belongs to biopharmaceutical classification system (BCS) class IV (9). So far, liquisolid formulations containing 20 mg of furosemide were studied by Akinlade et al. (7).

EXPERIMENTAL

Materials

Furosemide in the form of micronized powder (J.B. Chemicals and Pharmaceuticals, India) was used as a model drug. Microcrystalline cellulose of various grades (Vivapur® 102 and Vivapur® 12), anhydrous dibasic calcium phosphate - Emcompress® Anhydrous (JRS Pharma, Rosenberg, Germany) and spherically granulated anhydrous dibasic calcium phosphate Fujicalin® (Fuji Chemical Industries, Toyama, Japan) were used as carriers, magnesium aluminometasilicate Neusilin® US2 (Fuji Chemical Industries, Toyama, Japan) as a coating material, crospovidone - Kollidon® CL (BASF, Ludwigshafen, Germany) as a disintegrant and macrogol 400 (B.D.H. Chemicals) as a drug solvent.

Solubility studies

The solubility studies of furosemide were carried out in PEG 400 or in water. An excess amount of furosemide was added to 10 mL of solvent and shaken using a reciprocating shaker (IKA KS 130 BASIC, Germany) at 400 rpm for 24 h in room temperature to reach an equilibrium state. Then, the samples were centrifuged and filtered through a 0.45 μm Millipore filter, diluted and analyzed spectrophotometrically (Jasco V-530 UV/Vis spectrophotometer, Japan) at λ = 228 nm. All measurements were done in triplicate.

Excipients properties

The angle of repose was determined in accordance to Ph. Eur. 8.0 method by pouring the powder sample from the bottom sieve container mounted 70 mm above a round horizontal surface (60 mm dia.) until the cone was formed. The angle of repose was measured using measuring rod connected with the angular and metric scale. The angle of repose corresponds to the maximum angle between the slope of the formed cone and the horizontal surface. The attribute describes frictional forces in loose powder. Bulk and tapped density were measured according to the European Pharmacopeia using a W-1 volumeter (ZDM Polfa, Poland). Hausner ratio (HR) and Carr's index (CI) were calculated as follows:

$$CI = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \quad \text{(Eq.1)}$$

$$HR = \frac{Bulk\ density}{Tapped\ density} \quad \text{(Eq. 2)}$$

The moisture content was analyzed using a RadWag WPE 30S apparatus at 100°C and 15 s sampling time till the constant weight of the sample was achieved.

The flowable liquid retention potential (Φ) (Eq. 3) corresponds to the maximum amount of liquid that can be absorbed by the excipient, while preserving its good flowability (10). To obtain the liquisolid powder with good flow properties, the angle of slide of the excipients with admixture of increasing amounts of PEG 400 was investigated. The sample of powder (1.0 g) was placed on a polished metal plate which was gradually tilted until the

sample started to slide. In order to check physical properties of admixed ingredients the samples were examined 5 min and 24 h after preparation. Values of Φ were calculated for mixtures which slides down at the angle of plate inclination of 33°, which is considered to be optimal flow of the powder.

$$\Phi = \frac{W_{liquid}}{W_{powder}} \quad \text{(Eq. 3)}$$

where: W_{liquid} – weight of liquid, W_{powder} – weight of dry powder.

Preparation of liquisolid tablets

The composition of tablets is presented in Table 1. The maximum amount of furosemide solution (liquid load factor L_f) which can be loaded into powder bulk was calculated according to equation 4 (10):

$$L_f = \Phi_{carr.} + \Phi_{coat}\ (1/R) \quad \text{(Eq. 4)}$$

where: – liquid load factor, $\Phi_{carr.}$, $\Phi_{coat.}$ – flowable liquid retention potential for carrier and coating material, respectively, R – carrier/coating material ratio.

Twelve liquisolid formulations with four type of carriers: Fujicalin® (LS1 – LS3), Emcompress® (LS4 – LS6), Vivapur® 12 (LS7 – LS9) and Vivapur® 102 (LS10 – LS12) were prepared. The each individual carrier was combined with different amount of coating material. In particular, the following carrier to coating material ratios were examined: 1 : 1, 5 : 1, 10 : 1. Tablets were prepared as follows, the carrier was placed in a mortar and mixed with 20% furosemide solution in macrogol 400 poured in the quantity equal to 40 mg dose of the API. The coating substance (Neusilin® US2) was gradually added and blended gently for 5 min. Then, 5% of Kollidon® CL was added and mixing was continued for the next 5 min. Final blends were compressed using a Korsch EK0 single punch tablet press (Germany). Two lots of tablets (LS13 and LS14) were prepared using magnesium aluminometasilicate in the function of carrier and coating material. The lots were differentiated by quantities of disintegrant as follows: 5% for the LS13 formulation and 10% for LS14.

Preparation of directly compressed tablets (DCT)

Control tablets containing 40 mg of crystalline furosemide were prepared with direct compression method. The furosemide powder was mixed with suitable amounts of considered carrier and coating material. Afterwards, 5% of Kollidon Cl was added as a disintegrant and mixed. Final blend was compressed using Korsch EK0 (Germany) eccentric tablet press.

Evaluation of tablet properties

Tablet mass uniformity, thickness and hardness

Ten tablets of each formulation were accurately weighed and measured. The hardness of the tablets was evaluated using a VanKel VK 200 hardness tester (USA).

Table 1. Composition of prepared liquisolid tablets calculated on 100 tablets batch.

Form.	Carrier (Q) quantity [g]		Coating material quantity [g]	20% furosemide solution [g]	Kollidon Cl amount [%]	R	L_f
LS1	Fujicalin	11.2	11.2	20.0	5%	1	1.793
LS2		33.2	06.6			5	0.602
LS3		44.2	4.4			10	0.453
LS4	Emcompress	11.9	11.9			1	1.678
LS5		41.1	08.2			5	0.487
LS6		59.1	5.9			10	0.338
LS7	Vivapur 12	12.7	12.7			1	1.574
LS8		52.2	10.4			5	0.383
LS9		85.4	8.5			10	0.234
LS10	Vivapur 102	13.2	13.2			1	1.510
LS11		62.7	12.5			5	0.319
LS12		117.5	11.8			10	0.170
LS13	Neusilin US2	13.4			5%	-	-
LS14		13.4			10%	-	-

Friability

The friability test was performed according to the European Pharmacopoeia 8.0 using PharmaTest PTF-E friabilator (Germany).

Disintegration time

Tablets disintegration time was determined using a disintegration test ElectroLab ED2 Sapo (India) apparatus in accordance with Ph. Eur. 8.0 method. Purified water kept at 37°C was used as a medium, six randomly selected tablets from each formulation were evaluated.

Furosemide content determination

Three randomly taken tablets of each formulation were accurately weighed and shaken with 200 mL of sodium hydroxide solution (4 g/L) over 24 h (IKA KS 130 Basic shaker, Germany). Afterwards, samples were centrifuged at 3600 rpm and filtered through 0.45 μm Milipore® filter. After dilution, drug concentration was assayed spectrophotometrically using a Jasco V-530 UV-Vis spectrophotometer (Japan) with a wavelength λ = 228 nm.

Dissolution studies

Drug dissolution studies were carried out using a Ph. Eur. 8.0 dissolution apparatus 2 (Hanson Research SR8 Plus Dissolution Test Station, USA) operated at 50 rpm. Tablets were placed in 900 mL of 0.1 mol/L hydrochloric acid solution (pH 1.2) at 37°C. Sample volumes of 5 mL were withdrawn from each dissolution vessel at 5, 10, 15, 30, 60 and 120 min and analyzed spectrophotometrically at λ = 228 nm. Every time vessel volumes were replen-

Table 2. Excipients parameters.

Excipient	Φ value	Humidity content (%)	Angle of repose (°)	Hausner ratio	Carr index (%)
Vivapur 102	0.021	4.7	45	1.38	27.7
Vivapur 12	0.085	2.5	38	1.39	28.3
Emcompress Anh.	0.189	0.6	34	1.21	17.0
Fujicalin	0.304	1.1	30	1.14	12.5
Neusilin US2	1.489	7.2	27	1.15	13.3

Table 3. Physical parameters, disintegration time and amount of drug dissolved of each formulation.

Form.	Tablet mass [mg] ± SD	Dia. [mm]	Thickness [mm]	Hardness [N] ± SD	Friability [%]	Average disintegration time	Amount of API dissolved after 2 h [%] ± SD
LS1	439.1 ± 8.6	10	4.07	45.6 ± 7.3	0.78	5 min 11 s	83.11 ± 5.77
LS2	627.7 ± 11.9	11	4.92	38.5 ± 2.4	0.13	1 min 58 s	92.93 ± 10.54
LS3	721.2 ± 6.3	12	4.25	48.4 ± 2.5	0.03	7 min 40 s	91.08 ± 7.29
LS4	463.7 ± 9.5	11	3.60	40.3 ± 5.5	0.31	9 min 07 s	85.17 ± 18.84
LS5	728.7 ± 8.1	11	4.68	51.3 ± 3.2	0.06	5 min 22 s	83.59 ± 14.06
LS6	833.8 ± 14.5	11	5.43	56.7 ± 9.1	0.08	1 min 26 s	84.79 ± 9.59
LS7	476.4 ± 8.7	15	3.74	40.6 ± 0.9	0.15	9 min 18 s	79.11 ± 15.53
LS8	870.0 ± 14.9	15	4.45	53.5 ± 9.3	0.15	29 s	69.27 ± 1.16
LS9	1200.0 ± 13.3	15	6.88	58.3 ± 4.5	0.97	26 s	71.09 ± 2.16
LS10	484.9 ± 5.8	12	3.68	48.2 ± 3.6	0.17	12 min 13 s	52.18 ± 17.66
LS11	1009.0 ± 11.2	15	5.75	53.6 ± 3.3	0.79	31 s	76.21 ± 0.49
LS12	1569.0 ± 34.1	20	4.93	48.5 ± 7.4	0.71	24 s	68.20 ±3.30
LS13	349.7 ± 5.6	10	3.88	36.2 ± 4.0	0.13	14 min 53 s	85.83 ± 6.55
LS14	360.0 ± 6.8	10	4.16	37.2 ± 5.7	0.14	7 min 51 s	95.86 ± 5.66
DCT	460.0 ± 7.1	12	4.21	58.35± 4.2	0.90	52 s	28.53 ± 2.30

ished automatically with fresh medium. The measurements were carried out in triplicate. There was no interference on the absorption spectrum of furosemide from liquid vehicles and other excipients.

RESULTS AND DISCUSSION

The solubility of furosemide in macrogol 400 (234.97 mg/mL) was approximately 10000 times higher than in water (26.9 μg/mL). Javadzadeh et al. (12) showed that the dissolution rate is directly proportional to the fraction of molecularly dispersed drug (F_M) and the use of drug solution causes that the F_M factor is as high as possible (F_M = 1). The high solubility of furosemide in macrogol 400 allows obtaining small tablets since less amount of liquid has to be adsorbed onto powder surface.

According to the flowability results obtained for raw materials it was stated that Neusilin® US2 possesses the best flow properties (Table 2). Its flow characteristic can be expressed as excellent based on the angle of repose lower than 30° and good according to the compressibility index (11-15%) and Hausner ratio (1.12 – 1.18). The results of the liquid sorption capacity show that the values of flowable liquid retention potential (Phi, Φ) were correlated with the angle of repose of raw material and it increases with lower angle of repose values. The Phi-values were in the range from 0.021 for Vivapur® 102 up to 1.489 for magnesium aluminometasilicate, which corresponds with the highest angle of repose of Vivapur® 102 (45°, passable flow - may hang up) and the lowest for Neusilin® US2 (27°, excellent flow) from all of tested excipients. The high humidity content of Neusilin® US2 is due to its large specific surface area reaching up to 300 m^2/g (11), but absorbing capacity was not affected by the humidity content, because Φ-value was the highest and reached up 1.49. The comparison of Emcompress® and Fujicalin® shows better flow properties of the spherically granulated dibasic calcium phosphate (Fujicalin®). The difference between those excipients is in their specific surface area and shape. Fujicalin® is composed of spherically granulated particles with a porous surface which results in a high specific surface area, i.e., over 32 m^2/g while Emcompress® Anhydrous has 20.7 m^2/g (11) which resulted in approx 1.6-fold lower liquid sorption capacity. Also the microcrystalline cellulose Vivapur® 12 with a larger particles, of median size 180 μm, has a higher value of flowable liquid retention potential in comparison to Vivapur® 102 with an average particle size of 100 μm. Based on the comparison of obtained results it can be stated that the spherically granulated anhydrous dibasic calcium phosphate is the most suitable carrier.

The characteristics of all kinds of tablets are presented in Table 3. Among the evaluated physical properties such as mass, thickness, hardness, friability and disintegration time for liquisolid formulations, the differences has been identified particularly in tablet mass and disintegration time. A relationship between the excipients properties and the tablets mass and diameter was identified. Tablets prepared with high absorption capacity substances such as magnesium aluminometasilicate (LS13, LS14) and spherically granulated anhydrous dibasic calcium phosphate i.e. formulations LS1–LS3 have the lowest mass among of the studied formulations prepared with different types of carriers. When Emcompress® was used as a carrier the increase of tablet mass was estimated while disintegration time was elongated only for two formulations (LS4, LS5). Tablets with microcrystalline cellulose PH102 were characterized by the highest mass exceeding 1569 mg and use of punches with 20 mm in diameter (LS12). Similar results were obtained by Hentzschel et al. while replacing microcrystalline cellulose and silica with Neusilin® US2 causing the griseofulvin unit dose mass reduction from 2026 to 600 mg (8).

The tablets parameters also depend on carrier/coating material ratio. The increase of Neusilin® US2 amount in the formulation results in the tablet mass and size decrease due to its high sorption capacity. For example, the mass of LS1 tablets containing 112 mg of Neusilin® US2, with the carrier to coating ratio 1 : 1, was 439 mg and 10 mm in diameter while in the case of LS3 tablets, in which the amount of Neusilin® US2 was three times lower, the tablet mass was 721 mg and diameter was 12 mm. The same relationship was identified for tablet formulations prepared with other carriers. Based on Ph. Eur. 8.0 monograph all of the tablets met the pharmacopeial friability requirement because the loss of weight after the friability test did not exceed 1%. The average disintegration time ranged from 24 s (LS12) to 14 min 53 s (LS13). Compared the average disintegration times for tablets containing microcrystalline cellulose with different amount of Neusilin® US2 i.e., LS7 – LS12 tablets, it was stated that high quantity of Neusilin® US2 in formulation significantly affect the disintegration time. This was confirmed by long disintegration times for tablets composed only with this coating material. LS13 tablets do not comply with the pharmacopeia

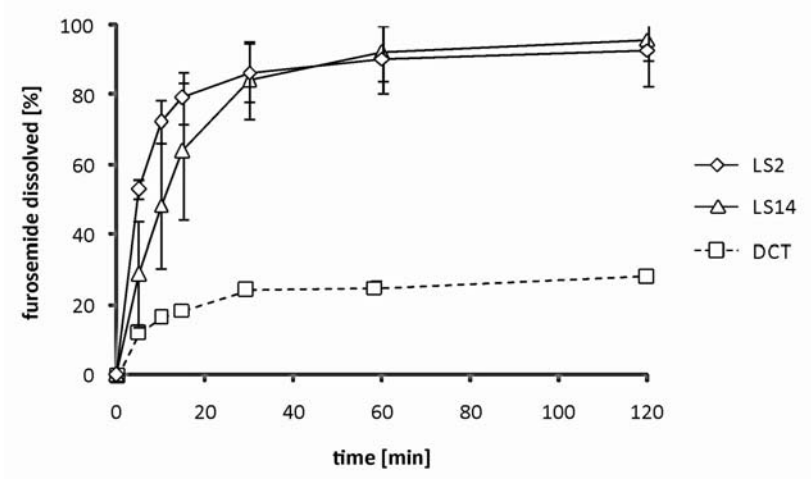

Figure 1. Comparison of furosemide dissolution profiles for the best liquisolid tablets and direct compressed control tablets

requirement, despite that the average time was below 15 min but three of the six tablets had a disintegration time over 15 min. Two-fold higher amount of the disintegrant in the LS14 formulation with respect to the LS13 tablets resulted in reduction of disintegration time by half (Table 3).

The effect of the excipients used in tablet formulations on furosemide release profile was investigated. As shown in Table 3, there were large differences in drug dissolution between fourteen types of tablets. The amount of furosemide dissolved after 2 h was in the range from 52.18% to 95.86%. Taking into account tablet formulations prepared with both kinds of the excipients i.e., carrier and coating material (LS1 – LS12), the highest amount of the drug (92.93%) was released from LS2 liquisolid tablets containing spherically granulated anhydrous dibasic calcium phosphate (Fujicalin®) as a carrier. In the case of Emcompress®, independently of excipients quantity the amounts of furosemide released after 2 h were similar 83.6% – 85.2% (formulations LS4 – LS6). The release profiles of furosemide for microcrystalline cellulose based formulations varied depending on the physical properties of the carrier, and Vivapur® to Neusilin® US2 ratio (Table 3).

The dissolution profiles of furosemide from tablets with 1 : 1 carrier/coating ratio (LS1, LS4, LS7) were similar independently from the kind of the carrier i.e., Fujicalin®, Emcompress® and Vivapur® 12. The only exception was the formulation with Vivapur® PH102 (LS10). This kind of tablets differs in the physical properties and dissolution of furosemide. They were characterized by long disintegration time, exceeding 12 min and the lowest amount of furosemide dissolved after 2 h (52.2%). High quantity of Neusilin® US2 with its large specific surface area significantly influenced furosemide dissolution profile.

From these results it can be assumed that liquisolid tablets with Fujicalin® and Neusilin® US2 are recommended to enhance the dissolution rate of furosemide. Two formulations LS2 and LS14 fully met the formulation expectations. The similar amount of furosemide was released from both LS2 and LS14 formulations after 2 h i.e., 92.93 and 95.86%, respectively. The mass of LS2 tablets was 627 mg, disintegration time 1 min 58 s. In comparison, the mass of the LS14 tablets was the smallest one i.e., 366 mg but the disintegration time was 4-fold longer. As it is presented on Figure 1, the amount of dissolved drug after 2 h from liquisolid tablets was over 3-times greater than in control tablets (DCT).

CONCLUSION

This study showed that liquisolid technique is a promising strategy in the pharmaceutical technology. The formulation of liquisolid tablets enhances the dissolution rate of furosemide when compared with direct compressed control tablets. Typically used dose of furosemide is 40–120 mg a day but there was no study on 40 mg furosemide liquisolid tablets. The results of investigations demonstrate that by selection of suitable excipients 40 mg furosemide tablets with acceptable size and mass with fast and entire drug dissolution could be prepared. Spherically granulated dibasic calcium phosphate (Fujicalin®) and magnesium aluminometasilicate (Neusilin® US2) as carrier and coating materi-

al, respectively, are suitable for liquisolid technique. The optimized formulations LS2 and LS14 showed 86.5 ± 8.6% and 84.3 ± 11.4% drug release within first 30 min and 92.9 ± 10.5% and 95.9 ± 5.7% after 2 h, respectively. The improvement in the furosemide dissolution characteristics from liquisolid tablets is mainly due to utilization of solution of the API. It was also stated that the dissolution profiles are affected by the amount of highly absorptive excipients such as Neusilin® US2. Other physical parameters such as hardness, friability and disintegration time were also satisfactory. The mass of both formulations was also reduced. It is an important factor that should be considered in aspect of patient compliance.

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