Available online at **www. scholarsresearchlibrary.com**

Scholars Research Library

Der Pharmacia Lettre, 2021, 13 (8): 146-152
(http: //scholarsresearchlibrary. com/archive. html)

ISSN 0975-5071
USA CODEN: DPLEB4

Novel Application of Mixed Solvency Concept to Develop and Formulate Liquisolid System of a Poorly Water Soluble Drug, Furosemide and Their Evaluations

Simran Ludhiani [*], RK Maheshwari

Department of Pharmacy, Shri G.S Institute of Technology and Science, Indore, India

[*]***Corresponding author:*** *Simran Ludhiani, Department of Pharmacy, Shri G.S Institute of Technology and Science, Indore, India, Tel: +91 7999857440; Email: ludhianisimran007@gmail.com.*

ABSTRACT

In today's world of pharmaceutical research, the majority of newly developed drugs discovered are extremely water insoluble. It has issues with multiple developmental, manufacturing, and administration procedures, resulting in a high rate of failure in clinical trials due to poor pharmacokinetics. In the present research, liquisolid system of furosemide was prepared in two different solvent systems of propylene glycol and glycerin. Approximate solubility of furosemide in propylene glycol was found to be 25 mg/ml. In accordance with mixed solvency concept, various solid solubilizers in small quantities were dissolved in propylene glycol to enhance the solubility of drug. In the blend of 10% sodium caprylate and 10% sodium acetate in propylene glycol, the approximate solubility of furosemide was found to be 220 mg/ml. Likewise, solubility of furosemide in glycerin was found to be 3.5 mg/ml. In accordance with mixed solvency concept, various solid solubilizers in small quantities were mixed in glycerin to enhance the solubility of drug. In a blend of 5% sodium caprylate, 5% sodium citrate and 5% sodium acetate in glycerin, the approximate solubility of furosemide was found to be 120 mg/ml. In another blend of 2.5% sodium caprylate, 2.5% L-arginine, 2.5% sodium acetate, 2.5% niacinamide and 5% sodium benzoate in glycerin, the approximate solubility of furosemide was found to be 140 mg/ml. This is due to solubilizing power of solids. The prepared liquisolid systems gave fast dissolution of drug. Mixed solvency concept is a very useful to develop liquisolid systems of poorly water soluble drugs.

Keywords: Mixed solvency concept, Furosemide, Liquisolid system, Solid solubilizers, Solubility.

INTRODUCTION

Liquisolid systems

The liquisolid approach is a revolutionary and improved approach for improving the dissolution and solubility of pharmaceuticals and medications that are practically water insoluble. This technology was used to insert water-insoluble medicines into rapid-release solid dosage forms. This process involves turning a drug's liquid form (which has been solubilized in a non-volatile solvent) into a dry-looking, free-flowing, non-adherent powder which is readily compressible. Here you will discover that liquid medications, drug solutions, drug suspension and emulsion are converted into powder, which is free-flowing [1]. This is done by adsorbing the liquid on a carrier. Once a free-

flowing powder is obtained, addition of different excipients is done, which are required to make tablet or capsules. Figure 1 illustrates development of liquisolid system at molecular level (Figure 1).

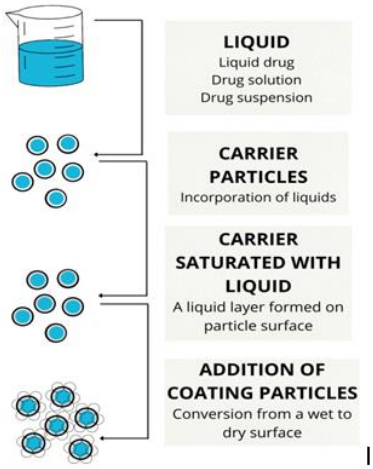

Figure 1: Development of liquisolid system at molecular level.

MATERIALS AND METHODS

Process of formulation of liquisolid systems

A drug that is weakly water soluble is dissolved in a non-volatile solvent and then absorbed into the carrier material's internal structure. The liquid solution or suspension is swiftly adsorbed onto a sufficiently fine coating material when the carrier material has been thoroughly saturated with liquid medicine, resulting in a dry, free-flowing, powdered liquid [2] (Figure 2).

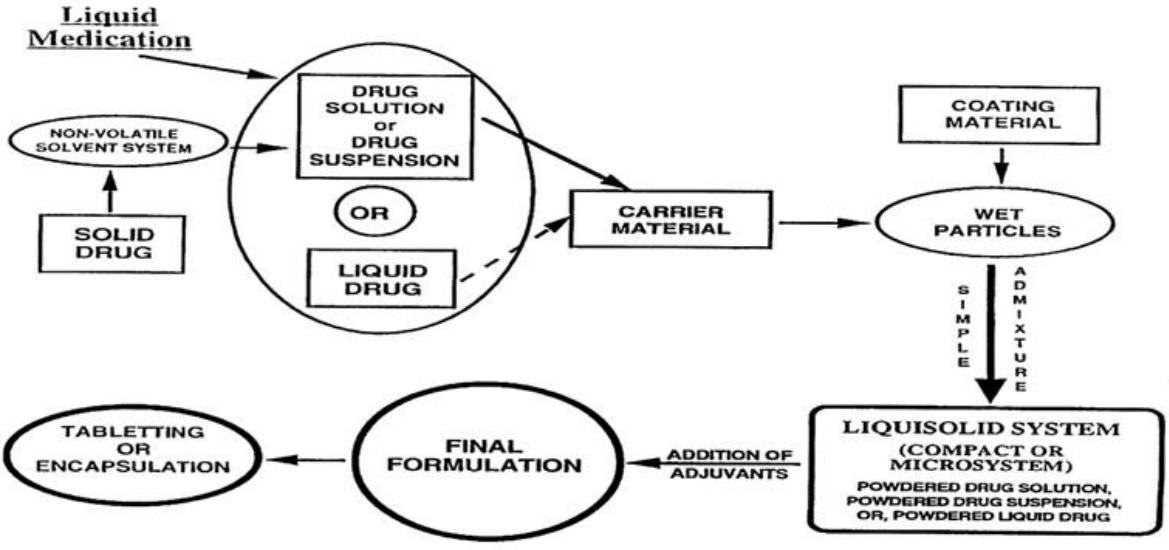

Figure 2: Process of formulation of liquisolid systems.

Formulation and development of liquisolid system of furosemide

Selection of solvent system: A non-volatile solvent solution was used for the formulation of the quick-release liquisolid system. Propylene glycol and glycerin were selected in the proposed research work. They are inert, have a high boiling point, non-volatile and are water-miscible. Solubility of furosemide in propylene glycol and glycerin were observed to be extremely poor. To improve the solubility of the drug, separate blends were created in each solvent system by dissolving various solid solubilisers (mixed solvency concept). Solid solubilisers in the solvent system were used to increase the solubility of the drug without significant increase in volume of solvent system.

In propylene glycol as a solvent, blends B1PG, B2PG, and B4PG showed good solubility of the drug. Likewise, in glycerin as a solvent, blends B11Gly, B12Gly, and B13Gly showed good solubility of the drug. So, all six blends were selected for further studies as they showed maximum drug solubility [3].

Selection of carrier and coating material

For blends prepared in propylene glycol: One ml of propylene glycol was taken in a mortar. To adsorb propylene glycol, 500 mg of MCC PH 200 (particle size 180 micron) was added and triturated. The mixture was still moist after adding 500 mg, therefore another 500 mg of MCC PH 200 was weighed and triturated again. This process was continued until 2 grams of MCC was utilized and powder was near to free flowing consistency [4]. Now, portions of 100 mg MCC PH 200 were added until they had absorbed all of the propylene glycol and the powder became free flowing. The same procedure was repeated taking di-calcium phosphate, $MgCO_3$ and talc Table 1 shows the results of amount of carrier adsorbed by 1 ml propylene glycol (Table 1).

S.No.	Carrier material	Propylene glycol	An approximate amount of carrier required to make powder free flowing
1	Avicel PH 200 (MCC)	1 ml	3500 mg
2	Di-calcium phosphate	1 ml	3200 mg
3	$MgCO_3$	1 ml	2500 mg
4	Talc	1 ml	4000 mg

Table 1: Approximate amount of carrier materials used to adsorb propylene glycol.

For blends prepared in glycerin: One ml of glycerin was taken in a mortar. To adsorb glycerin, 500 mg of MCC PH 200 (particle size 180 micron) was added and triturated. The mixture was still moist after adding 500 mg [5]. Therefore another 500 mg of MCC PH 200 was weighed and triturated again. This process was continued until 2 grams of MCC PH 200 was utlized and powder was near to free flowing consistency. Now, portions of 100 mg MCC PH 200 were added until they had absorbed all of the glycerin and the powder became free flowing. The same procedure was repeated taking di-calcium phosphate, $MgCO_3$ and talc. Table 2 shows the results of amount of carrier adsorbed by 1 ml glycerin **(**Table 2).

S.No.	Carrier material	Glycerin	An approximate amount of carrier required to make powder free flowing
1	Avicel PH 200 (MCC)	1 ml	3300 mg
2	Di-calcium phosphate	1 ml	3000 mg
3	$MgCO_3$	1 ml	2300 mg
4	Talc	1 ml	3800 mg

Table 2: Approximate amount of carrier material used to adsorb glycerin.

Preparation of liquisolid system

Blend B1PG, B2PG and B4PG of propylene glycol were chosen. Approximate solubility of furosemide in blend B1PG was found out to be 250 mg/ml. For preparing a batch of 50 doses with 40 mg dose strength, 8.00 ml of blend was taken. Observed density of the blend was 1.02 g/ml, so the weight of the blend (8.00 ml), used to prepare the liquisolid system was 8.16 grams. Two grams of drug was dissolved in 8.00 ml blend and this solution was transferred in a clean and dried mortar. For adsorption of this solution, twenty-eight grams of MCC was used. The amount of aerosil used was 1.400 grams (5% of MCC). The solution of drug dissolved in blend was triturated with calculated amount of MCC. After adsorption of the solution of drug dissolved in blend, calculated amount of coating material was added to get a free flowing powder. Now the total weight of powder shall be 39.56 grams. A single dose of 40 mg furosemide consisted of 791 mg powder for liquisolid system of LSS-PG-01 [6].

Approximate solubility of furosemide in blend B2PG was found out to be 200 mg/ml. For preparing a batch of 50 doses with 40 mg dose strength, 10.00 ml of blend was taken. Observed density of the blend was 1.02 g/ml, so the weight of the blend (10.00 ml), used to prepare the liquisolid system was 10.2 grams. Two grams of drug was dissolved in the 10.00 ml blend and this solution was transferred in a clean and dried mortar. For adsorption of this solution, thirty-five grams of MCC was used. The amount of aerosil used was 1.750 grams (5% of MCC). The solution of drug dissolved in blend was triturated with calculated amount of MCC. After adsorption of the solution of drug dissolved in blend, calculated amount of coating material was added to get a free flowing powder. Now total weight of free flowing powder shall be 48.95 grams. A single dose of 40 mg furosemide consisted of 979 mg powder for liquisolid system of LSS-PG-02 [7].

Approximate solubility of furosemide in blend B4PG was found out to be 220 mg/ml. For preparing a batch of 50 doses with 40 mg dose strength, 9.10 ml of blend was taken. Observed density of the blend was 1.02 g/ml, so the weight of the blend (9.10 ml), used to prepare the liquisolid system was 9.28 grams. Two grams of drug was dissolved in 9.10 ml blend and this solution was transferred in a clean and dried mortar. For adsorption of this solution, thirty-eight point eight one grams of MCC was used. The amount of aerosil used was 1.575 grams (5% of MCC). The solution of drug dissolved in blend was triturated with calculated amount of MCC. After adsorption of the solution of drug dissolved in blend, calculated amount of coating material was added to get a free flowing powder. Now total weight of free flowing powder shall be 44.66 grams. A single dose of 40 mg furosemide consisted of 892 mg powder for liquisolid system of LSS-PG-03. Table 3 summarizes the quantity of carrier and coater used for a batch of 50 doses for blends in propylene glycol (Table 3).

S.No.	Batch number	Carrier material		Coating material		Blend	The blend used (ml)	Net weight (gm)
		Material	Amount used (gm)	Material	Amount (gm)			
1	LSS-PG-01	Avicel PH 200	28	Aerosil	1.4	B1PG	8	39.56
2	LSS-PG-02	Avicel PH 200	35	Aerosil	1.75	B2PG	10	48.95
3	LSS-PG-03	Avicel PH 200	31.815	Aerosil	1.575	B4PG	9.1	44.64

Table 3: Quantity of carrier and coater used for a batch of 50 doses (blends in propylene glycol).

RESULTS AND DISCUSSION

Evaluation

The evaluation tests performed on LSS-PG-03, LSS-Gly-02, and LSS-Gly-03 are

- Weight variation.
- Determination of drug content of liquisolid formulation.
- Disintegration time of tablets of liquisolid formulation.

- Comparative dissolution profile.
- Friability.
- Hardness.

Weight variation

As per I.P., twenty tablets from LSS-PG-03 were taken and weighed individually. The average weight of all the tablets was calculated. Individual tablet weight was compared with the average weight. The same procedure was repeated for tablets of LSS-Gly-02 and tablets of LSS-Gly-03 [8]. None of the tablets from any of the batch went beyond the accepted range of ± 5 %. Hence, the test was passed by all the three batches.

Drug content determination

Five tablets of LSS-PG-03 were taken. All the tablets were weighed and average weight was calculated. The tablets were triturated to get a fine powder and powder containing equivalent to 40 mg of drug was placed in a 1000 ml volumetric flask to determine drug content. The volumetric flask was filled with 700 ml of D.M. water, shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Filtration was done of the solution. The absorbance was then measured at 333 nm against a blank of D.M. water [9].

Similarly, five tablets of LSS-Gly-02 were taken. All the tablets were weighed and average weight was calculated. The tablets were triturated to get a fine powder and powder containing equivalent to 20 mg of drug was placed in a 1000 ml volumetric flask to determine drug content. The volumetric flask was filled with 700 ml of D.M. water, shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Filtration was done of the solution. The absorbance was then measured at 333 nm against a blank of D.M. water.

Similarly, five tablets of LSS-Gly-02 were taken. All the tablets were weighed and average weight was calculated. The tablets were triturated to get a fine powder and powder containing equivalent to 20 mg of drug was placed in a 1000 ml volumetric flask to determine drug content. The volumetric flask was filled with 700 ml of D.M. water, shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Filtration was done of the solution. The absorbance was then measured at 333 nm against a blank of D.M. water [10].

Disintegration time studies

Six tablets of LSS-PG-03 were individually put into disintegration tubes. In the disintegration beaker, 900 ml of 0.1 N HCl was filled and the disintegration test was conducted at 37 $^{\circ}$C ± 2 $^{\circ}$C, at 28-32 cycles per minute frequency. Similarly, tablets of LSS-Gly-02 and LSS-Gly-03 were tested [11].

Comparative dissolution profile

Dissolution profile of tablets of LSS-PG-03 and marketed tablet Lasix 40 mg was studied and compared. One tablet of LSS-PG-03 (40 mg) was taken and compared with one tablet of Lasix 40 mg. For dissolution, 900 ml of 0.1N HCl was taken as dissolution media and the paddle rotation speed was kept at 50 rpm at 37 ± 0.5 ° C. After 2 minutes, twenty ml sample was withdrawn from dissolution media for analysis, and equal quantity of media was replaced. Similar procedure was repeated after different time intervals. Table 3 shows the comparative analysis [12]. The comparative dissolution profile in 0.1 N HCl of tablet LSS-PG-03 and pure drug is illustrated in Figure 3.

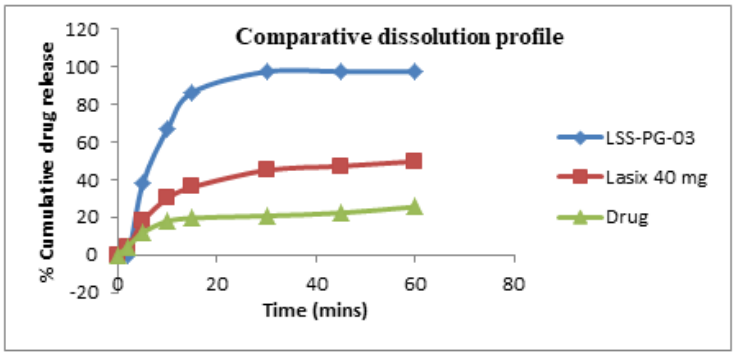

Figure 3: Comparative dissolution profile in 0.1 N HCl of final batch in propylene glycol (LSS-PG-03), pure drug and marketed formulation.

Friability testing

Roche friabilator was used for testing. Ten tablets of LSS-PG-03 were taken. The tablets were weighed before testing. They were tumbled for 100 revolutions. After that, the tablets were reweighed. The weight loss was in the accepted range and hence the test was passed. Similarly, the test was performed for tablets of LSS-Gly-02 and tablets of LSS-Gly-03. The results were in accepted range for all three batches [13].

Drug content uniformity

Since the drug present in each tablet is less than 10% of the average weight of tablets, therefore, content uniformity test was conducted.

Ten tablets of LSS-PG-03 were taken. Each 40 mg tablet was transferred in a 1000 ml volumetric flask. The volumetric flask was filled with 700 ml of D.M. water, shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Above solution was filtered. The absorbance was then measured at 333 nm against a blank of D.M. water. Similarly, all remaining 9 tablets of LSS-PG-03 tablets were tested. The content of all of the tablets was between 85 and 115 percent. As a result, tablets of LSS-PG-03 passed the drug content uniformity test [14].

Ten tablets of LSS-Gly-02 were taken. Each 20 mg tablet was transferred in a 1000 ml volumetric flask. The volumetric flask was filled with 700 ml of D.M. water, shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Above solution was filtered. The absorbance was then measured at 333 nm against a blank of D.M. water. Similarly, all remaining 9 tablets of LSS-Gly-02 tablets were tested. The content of all of the tablets was between 85 and 115 percent. As a result, tablets of LSS-Gly-02 passed the drug content uniformity test [15].

Ten tablets of LSS-Gly-03 were taken. Each 20 mg tablet was transferred in a 1000 ml volumetric flask. The volumetric flask was filled with 700 ml of D.M. water, shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Above solution was filtered. The absorbance was then measured at 333 nm against a blank of D.M. water. Similarly, all remaining 9 tablets of LSS-Gly-03 tablets were tested. The content of all of the tablets was between 85 and 115 percent. As a result, tablets of LSS-Gly-03 passed the drug content uniformity test [9].

Hardness

Three tablets each of LSS-PG-03, LSS-Gly-02 and LSS-Gly-03 were taken. Hardness test was performed with the help of Monsanto hardness tester [10].

CONCLUSION

The goal of this research was to look into the possibilities of using small amounts of mixed solid solubilizers to improve drug loading capability in liquisolid formulations, improve flow property and improve drug solubility in non-volatile solvent using the mixed solvency principle, and fast release of a drug which possess poor water solubility. The primary goal of this study is to demonstrate that solids may be utilized as effective solubilizers. These solids can be utilized appropriately for solvent action in the future, giving alternative sources for: solvents that are environmentally acceptable and do not require toxic organic solvents, as well as solvents that are economically advantageous. To investigate the idea of mixed solvency concept and in order to improve solubility and, as a result, the release rate of a drug with low aqueous solubility. As a model drug, furosemide was chosen.

In the present research, liquisolid system of furosemide was prepared in two different solvent systems of propylene glycol and glycerin. Approximate solubility of furosemide in propylene glycol was found to be 25 mg/ml. In accordance with mixed solvency concept, various solid solubilizers in small quantities were mixed in propylene glycol to enhance the solubility of drug. In the blend of 10% sodium caprylate and 10% sodium acetate, the approximate solubility of furosemide was found to be 220 mg/ml. Likewise, approximate solubility of furosemide in glycerin was found to be 3.5 mg/ml. In accordance with mixed solvency concept, various solid solubilizers in small quantities were mixed in glycerin to enhance the solubility of drug. In a blend of 5% sodium caprylate, 5% sodium citrate and 5% sodium acetate, the approximate solubility of furosemide was found to be 120 mg/ml. In another blend of 2.5% sodium caprylate, 2.5% L-arginine, 2.5% sodium acetate, 2.5% Niacinamide and 5% sodium benzoate, the approximate solubility of furosemide was found to be 140 mg/ml. Hence, it proved that the solids have got solubilizing power.

REFERENCES

[1] Agrawal R., Maheshwari R K. *J Drug Deliv Therapeut,* **2018,** 8(6-s):5-8.

[2] Akinlade B., Elkordy A A., Essa E A., et al., *Scientia Pharmaceutica,* **2010,** 78(2): 325-344.

[3] Savkare DA., Malavi RB., Gholap VD., et al., *Int J Pharm Scie Res,* **2017,** 8(7): 68-75.

[4] Lu M., Xing H., Jiang J., et al., *Asian J Pharm Scie,* **2017,** 12(2):115-123.

[5] Kawabata Y., Wada K., Nakatani M., et al., *Int J Pharmaceut,* **2011,** 420(1):1-10.

[6] Maheshwari RK., Shilpkar, R. *Int J Pharm Bioscie,* **2012,** 3(1): 179-189.

[7] Solanki SS., Soni LK., Maheshwari RK. *J Pharmaceut,* **2013.**

[8] Pawar PB., Rawat S., Mahajan YY., et al., *Int J Drug Delivery,* **2013,** 5(2): 152.

[9] Soni LK., Solanki SS., Maheshwari RK. *J Pharm Res Int,* **2014,** 3: 549-568.

[10] Gour V., Garg A., Shukla YA., et al., *Asian J Biomat Res,* **2016,** 2(1): 38-45.

[11] Gayakwad PS., Gavit AJ., Rajput PV., et al., *World J Pharmaceut Resear,* **2014,** 3(4): 1642-1664.

[12] Solanki S S. *Asian J Pharm,* **2017.**

[13] Maheshwari N., Maheshwari RK. *IJSR,* **2018,** 8(12): 1313-1320.

[14] Padiyar A., Maheshwari RK. *J Drug Delivery Therap,* **2017,** 7(7): 44-45.

[15] Khan MA. *Int J Res Develop Pharm Life Scie,* **2013,** 2(5): 580-582.