



NOVEL APPLICATION OF MIXED SOLVENCY CONCEPT TO DEVELOP AND FORMULATE LIQUISOLID SYSTEM OF A POORLY WATER SOLUBLE DRUG, FUROSEMIDE AND THEIR EVALUATIONS

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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 solubilisers 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 solubilisers 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

Index Terms - Mixed solvency concept, furosemide, liquisolid system, solid solubilisers, solubility

1. INTRODUCTION

LIQUISOLID SYSTEMS¹⁻⁵

The liquisolid approach is a revolutionary and improved approach for improving the dissolution and solubility of pharmaceuticals and medications that are practically water insoluble. Spireas et al. were the first to introduce this technology, which 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. 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.

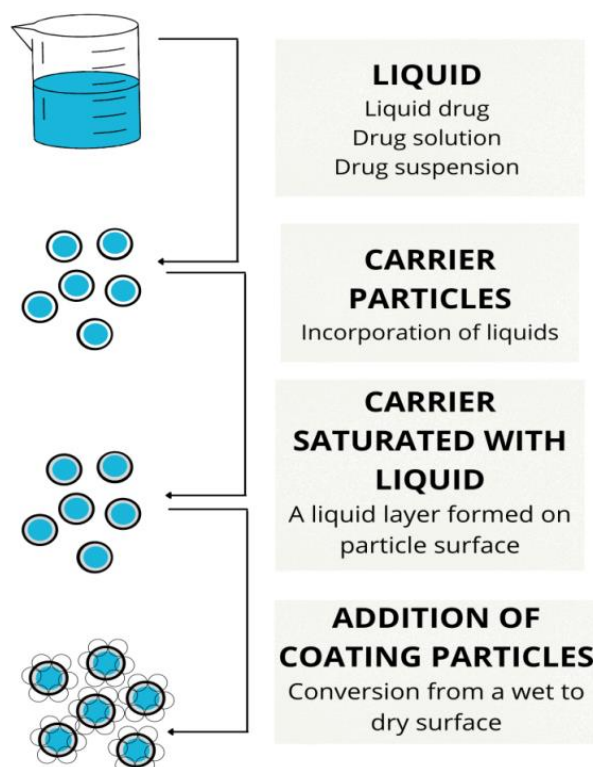


Figure 1: Development of liquisolid system at molecular level

1.1 CORE COMPONENTS OF LIQUISOLID SYSTEM

- **DRUG:** Drugs from all BCS categorization classes.
- **NON-VOLATILE SOLVENT:** This solvent must be low viscosity, inert, hydrophilic, and the boiling point should be high. Propylene glycol, glycerol, fixed oils, polyethylene glycol and glycerin are some examples of liquids.
- **CARRIER:** They are porous materials with a wide surface area that serve as a foundation for medication adsorption in liquid form. Examples include MCC (powder and granular grades), methyl cellulose, amorphous cellulose, and starch.
- **COATING MATERIAL:** These are fine materials with high adsorptive qualities that range in size from 10 nm to 450 nm and are used to completely encase the carrier particle, giving it the appearance of being dry. Examples include aerosil PH 200, silica, syloid, disintegrants, lubricants, and gliders.
- **OTHER EXCIPIENTS:** Prior to encapsulation or compression, binders (sustained release), lubricants, disintegrants, and other additives are employed.

Figure 2 shows core components of liquisolid system

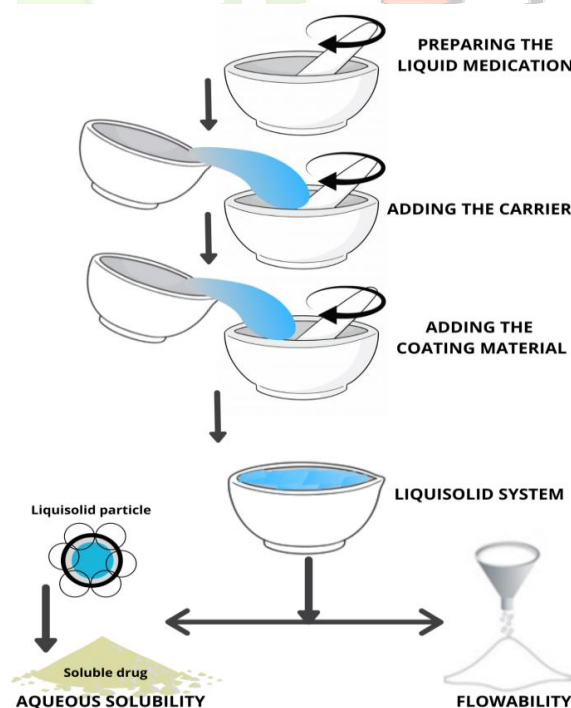


Figure 2: Core components of liquisolid system

1.2 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. Figure 3 depicts the process of formulation of liquisolid systems.

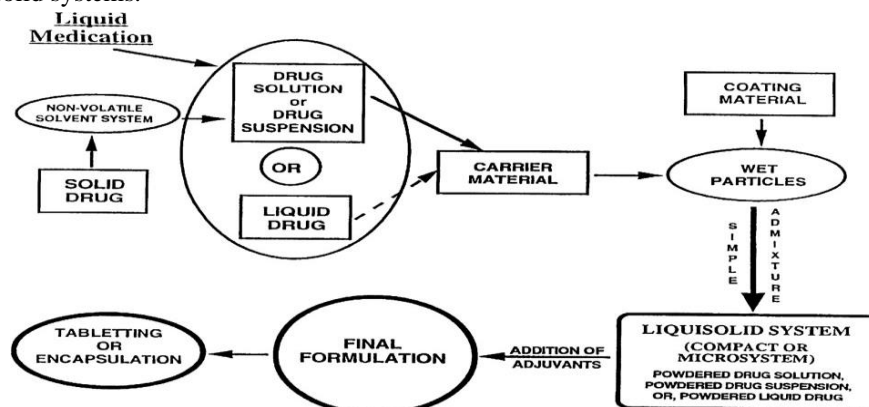


Figure 3: Process of formulation of liquisolid systems

1.3 MECHANISM OF ENHANCED DRUG RELEASE

The three most acceptable methods based on surface area and solubility are:-

- **Increased Surface Area:** Because the drug is distributed widely in solution form, more drug particles come into contact with the media, enhancing the dissolution.
- **Increased Aqueous Solubility:** It's possible that a small amount of non-volatile solvent diffuses from the overall mass and acts as a co-solvent at the particle-dissolution medium interface.
- **Improved Wetting:** The presence of a non-volatile solvent improves the wettability of primary surfactant particles.

1.4 APPLICATIONS OF LIQUISOLID TECHNIQUE

Liquisolid systems are generally employed in formulation and development due to their various applications. Some of the applications of liquisolid systems are illustrated in figure 4.

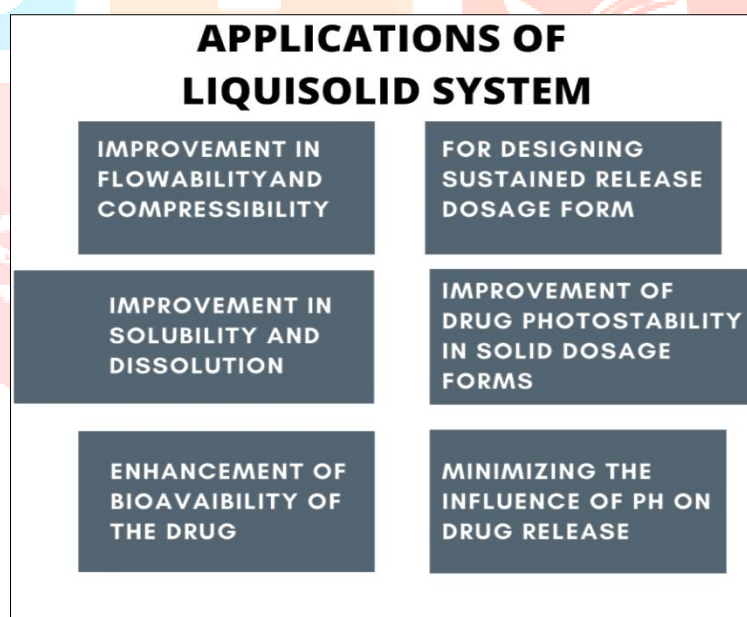


Figure 4: Various applications of liquisolid systems

1.5 ADVANTAGES OF LIQUISOLID SYSTEM

- Number of water-insoluble solid drug can be formulated into liquisolid systems
- Lower production cost than that of soft gelatin capsules
- Production of liquisolid system is similar to that of conventional tablets
- Can be used for formulation of liquid oily drugs
- Helps in enhancing bioavailability of drugs
- Exhibits enhanced in-vitro drug release as compared to commercial counterparts, including soft gelatin capsule preparations
- Increase in drug loading

1.6 DISADVANTAGES OF LIQUISOLID SYSTEM

- Formulation of high dose lipophilic drugs in liquisolid tablet is one of the limitations of this technique
- Requires more efficient excipients and it should provide faster drug release with smaller tablet size
- Higher amounts of carrier and coating materials are required

1.7 LIQUISOLID SYSTEM BY MIXED SOLVENCY APPROACH

Conventional liquisolid system employs a solvent which shows drug solubility to a restricted extent. Drugs with high doses are usually a limitation because, to dissolve them more solvent is required and to adsorb the solvent more adsorbent is used, this results in a final formulation which is not administrable orally. Also, few solvents are available and not all drugs show a significant and desired solubility enhancement.

By utilizing the concept of mixed solvency, a small of solvent can be taken and solid solubilizers can be used to increase the solubility of drug in a small amount of solvent. The small quantity of solvent will not use much of adsorbent and hence orally administrable formulation can be formulated. Also, this can be used for wide range of drugs which hold low aqueous solubility and also for a wide range of dose of drugs.

Figure 5 depicts a comparative notion for liquisolid formulation by conventional method and mixed solvency approach.

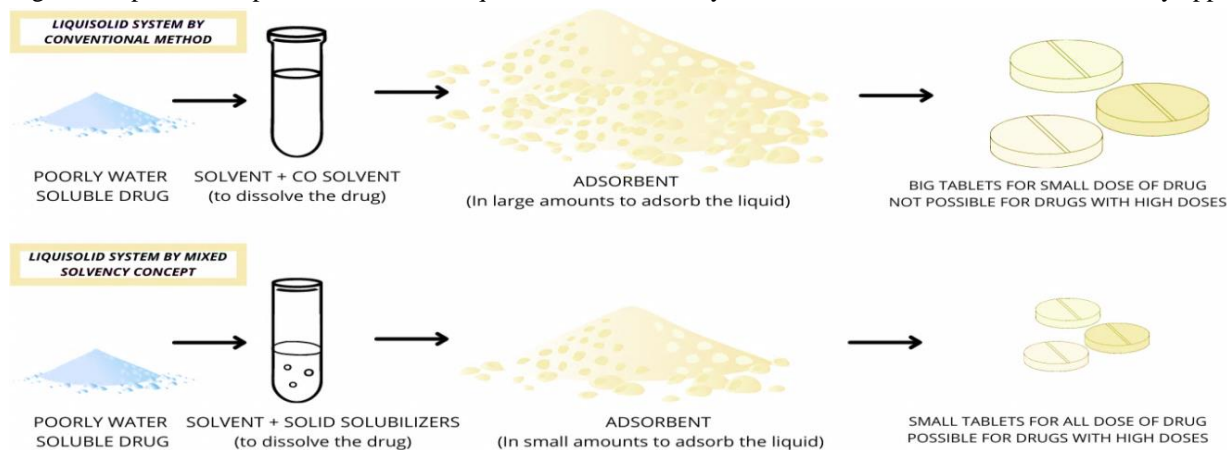


Figure 5: Comparison between formulation of liquisolid system by conventional method and by mixed solvency concept

1.8 EVALUATIONS OF LIQUISOLID DOSAGE FORM

- Differential scanning calorimetry(DSC)
- Powder X-ray diffraction(PXRD)
- Flow property
- Angle of repose
- Infra-red spectroscopy
- Dissolution testing of liquisolid formulations

2. MIXED SOLVENCY CONCEPT IN FORMULATION ⁶⁻⁴²

Enhancement of solubility is one of the difficult tasks which becomes challenge in formulation development of drug with poor aqueous solubility. Poor water solubility of drugs often causes significant problems in producing formulations of sufficiently high bioavailability, preventing effective use of the drugs. Mixed solvency concept proposed by Dr. R.K. Maheshwari in 2009 is a new concept of solubilization states that all substances whether solids, liquids or gases possess solubilizing power and hence concentrated solution containing various dissolved substances in any liquid can also improve the solubility of poorly soluble drugs. This technique can be employed in various formulations of poorly soluble drugs in order to reduce concentration of individual solubilizer (used for solubility enhancement) to minimize the toxic effects of solubilizers. This review article compiles the research projects performed on mixed solvency concept. Solubility of a large number of drugs have been enhanced by application of mixed solvency concept. Mixed solvency concept has been employed for formulation development of a large number of poorly soluble drugs. Oily injections, aqueous injections, syrups (in solution form) and topical solutions have been made using mixed-solvency concept. Also, mixed solvency concept had been widely employed in the formulation development of SEDDS, microspheres, nasal gels, solid dispersions, liquid solid systems, oral films, vaginal films etc.

3. MATERIAL

The drug used in the whole study was a gift sample from Sellwell Pharmaceuticals, Sanwer road, Indore.

4. DRUG CHARACTERIZATION

4.1 UV SPECTROPHOTOMETRIC ANALYSIS OF FUROSEMIDE IN 0.1 M SODIUM HYDROXIDE

About 50 mg of furosemide drug was weighed. It was dissolved in 400 ml 0.1 M sodium hydroxide solution in a volumetric flask of 500 ml capacity. Then the flask was shaken so that the drug dissolves completely. After that, 0.1 M sodium hydroxide solution was used to make up the volume up to 500 ml to obtain the stock solution of 100 µg/ml concentration. 5 ml of stock solution was taken and diluted up to 100 ml with 0.1 M sodium hydroxide solution to obtain dilution of 5 µg/ml concentration. The resulting solution was scanned between 200-400 nm on Shimadzu-1700 UV spectrophotometer against 0.1 M sodium hydroxide solution. The spectrum is depicted in figure 6.

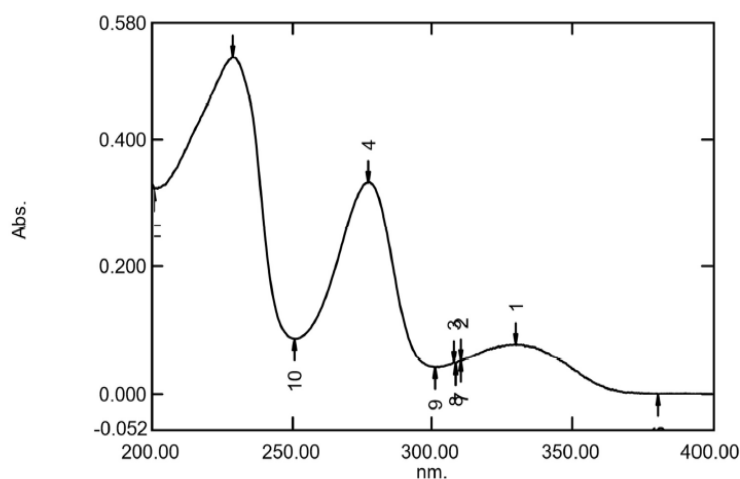


Figure 6: UV spectrum of furosemide in 0.1 M sodium hydroxide

Result and discussion- The drug sample showed peaks at 228nm, 271nm and 333nm in 0.1 M sodium hydroxide solution. The selected peak was 333nm for further estimation to avoid interference of solubiliser. This peak is same as in reported literature.

4.2 MELTING RANGE DETERMINATION OF FUROSEMIDE

Open capillary method was used for determination of the melting range of furosemide. The drug powder sample (furosemide) was filled in a capillary tube with one end closed and connected to a thermometer mounted in a liquid paraffin-filled Thiele's tube. The tube was heated and the drug's melting range was calculated.

Results and discussion- Melting point range of sample of furosemide drug was found to be 205°C to 208°C, which is same as in the reported literature.

4.3 INFERENCE

Melting point, UV spectrophotometry, and DSC investigations were used to characterize the furosemide drug sample that was obtained. All of the observed data matched what had been published in the literature.

As a result, it was deduced that the obtained drug sample was pure furosemide, which was then employed for future research.

5. METHOD

5.1 PREFORMULATION STUDIES

• PREPARATION OF CALIBRATION CURVE OF FUROSEMIDE IN D.M. WATER

About 100 mg of drug was weighed accurately and transferred in a 100 ml volumetric flask. The drug was dissolved by addition of 20 ml 30 % sodium benzoate solution and the volume was made up to 100 ml with D.M. water, so as to obtain solution of 1000 µg/ml. Two ml of the above solution was taken and diluted up to 100 ml by D.M. water to obtain dilution of 20 µg/ml concentration. Likewise, 4.0 ml, 6.0 ml, 8.0 ml, 10.0 ml solutions were taken and diluted up to 100 ml to obtain dilutions of 40, 60, 80 and 100 µg/ml concentrations, respectively. Absorbances of these solutions (20, 40, 60, 80, 100 µg/ml) were measured at 333 nm against respective reagent blanks on Shimadzu-1700 UV spectrophotometer. The absorbance data for the calibration curve of furosemide in D.M. water (in the presence of sodium benzoate) at 333 nm is shown in table 1 and figure 7 shows the furosemide calibration curve in D.M. water (in presence of sodium benzoate).

Table 1: Absorbance data for calibration curve of furosemide in D.M. water (in presence of sodium benzoate) at 333 nm

S.No..	Concentration (µg/ml)	Absorbance (Mean±SD) (n=3)
1	0	0.0±0.0
2	20	0.303±0.005
3	40	0.611±0.001
4	60	0.910±0.001
5	80	1.211±0.005
6	100	1.501±0.005

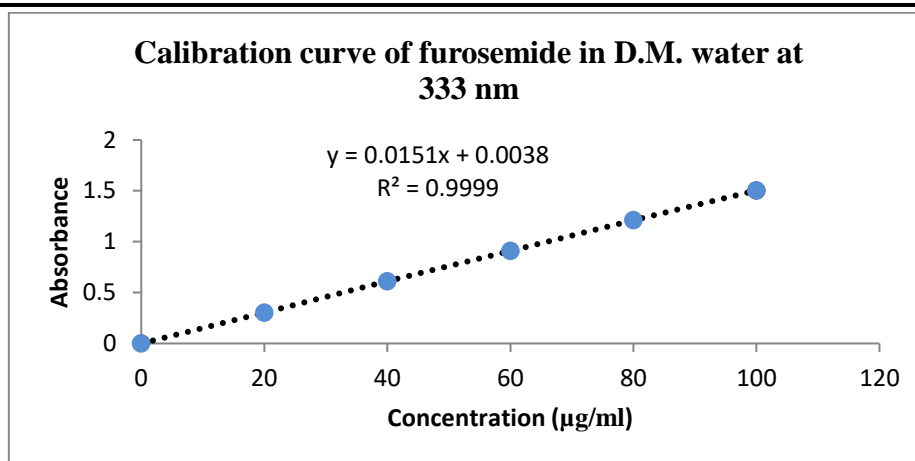


Figure 7: Calibration curve of furosemide at 333 nm in D.M. water

• **PREPARATION OF CALIBRATION CURVE OF FUROSEMIDE IN 0.1 N HCl**

About 100 mg of drug was weighed accurately and transferred in a 100 ml volumetric flask. The drug was dissolved by addition of 20 ml 30 % sodium benzoate solution and the volume was made up to 100 ml with 0.1 N HCl, so as to obtain solution of 1000 µg/ml. Two ml of the above solution was taken and diluted up to 100 ml by 0.1 N HCl to obtain dilution of 20 µg/ml concentration. Likewise, 4.0 ml, 6.0 ml, 8.0 ml, 10.0 ml solutions were taken and diluted up to 100 ml to obtain dilutions of 40, 60, 80 and 100 µg/ml concentrations, respectively. Absorbances of these solutions (20, 40, 60, 80, 100 µg/ml) were measured at 333 nm against 0.1 N HCl on Shimadzu-1700 UV spectrophotometer. The absorbance data for the calibration curve of furosemide in 0.1 N HCl (in the presence of sodium benzoate) at 333 nm is shown in table 2 and figure 8 shows the furosemide calibration curve in 0.1 N HCl (in presence of sodium benzoate).

Table 2: Absorbance data for calibration curve of furosemide in 0.1 N HCl (in presence of sodium benzoate) at 333 nm.

S.No..	Concentration (µg/ml)	Absorbance (Mean±SD) (n=3)
1	0	0.0±0.0
2	20	0.308±0.001
3	40	0.616±0.001
4	60	0.918±0.001
5	80	1.245±0.002
6	100	1.516±0.004

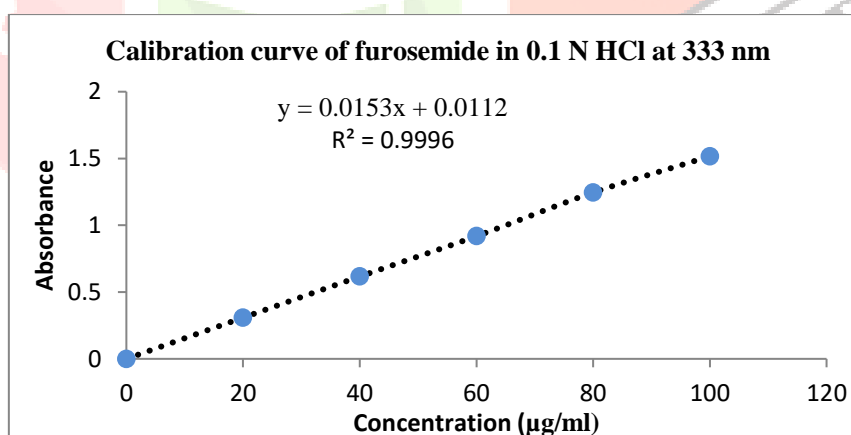


Figure 8: Calibration curve of furosemide at 333 nm in 0.1 N HCl

• **DETERMINATION OF APPROXIMATE SOLUBILITY OF FUROSEMIDE IN PROPYLENE GLYCOL AND GLYCERIN**

One ml of propylene glycol was taken in a 10 ml volumetric flask and 2.5 mg drug was added to it, with vigorous shaking on vortex (Remi cm 101 plus) until it got dissolved or for about 20 minutes. Once a clear solution is obtained, again 2.5 mg drug was added to it with vigorous shaking on vortex (Remi cm 101 plus) until it got dissolved or for about 20 minutes. When clear solution was obtained, again 2.5 mg drug was added. Similarly, the drug was added, shaken and dissolved in batches until a suspension was obtained and solubility was noted.

Two ml of glycerin was taken in a 10 ml volumetric flask and 1 mg drug was added to it, with vigorous shaking on vortex (Remi cm 101 plus) until it got dissolved or for about 20 minutes. Once a clear solution is obtained, again 1 mg drug was added to it with vigorous shaking on vortex (Remi cm 101 plus) until it got dissolved or for about 20 minutes. Similarly, the drug was added, shaken and dissolved in batches until a suspension was obtained and solubility was noted.

In the above study, it was noted that both propylene glycol and glycerin are weak solvents for furosemide.

To illustrate the mixed solvency concept, safe quantities of solid solubiliser were used to increase drug loading in propylene glycol and glycerin respectively.

Table 3 illustrates results of approximate solubility studies of furosemide in propylene glycol and glycerin.

Table 3 : Approximate solubility studies of furosemide in propylene glycol and glycerin

S.No.	Solvent	Approximate solubility (mg/ml)
1	Propylene glycol	25
2	Glycerin	3.5

• DEVELOPMENT OF SOLVENT SYSTEM

Solubility of furosemide in propylene glycol and glycerin was less than the desired solubility. Mixed solvency approach was used to create a solvent system in which various solid solubiliser were dissolved according to their respective safe concentrations in propylene glycol and glycerin, resulting in a strong solvent that could be used to prepare dosage forms. For the creation of blends, several solid solubiliser were utilized individually or in combination, and drug solubility experiments were performed.

APPROXIMATE SOLUBILITY OF VARIOUS SOLUBILISER IN PROPYLENE GLYCOL

Ten mg sodium caprylate was added to 1 ml propylene glycol in a 10 ml volumetric flask and agitated on vortex (Remi cm 101 plus) for around 20 minutes to dissolve it. As soon as it was dissolved, ten mg of sodium caprylate was added again and the mixture was agitated for another 20 minutes. When the clear solution was obtained again 10 mg of sodium caprylate was added. The same method was carried out until a suspension was achieved. To get a transparent solution, 250 mg sodium caprylate was dissolved in 1 ml propylene glycol. A suspension was formed after adding another 10 mg of sodium caprylate. Using the same method, approximate solubility of sodium benzoate, sodium acetate, sodium citrate, niacinamide, caffeine, sodium lauryl sulfate, L-arginine and poloxomer 407 approximate solubility in propylene glycol was also investigated. Table 4 illustrates the approximate solubility of various solubilisers in propylene glycol.

Table 4: Approximate solubility of various solubilisers in propylene glycol

S.No.	Solubiliser	Solubility (mg/ml)	Solubility (%w/v)
1.	Sodium acetate	250	25
2.	Sodium benzoate	50	5
3.	Sodium citrate	100	10
4.	Sodium caprylate	250	25
5.	Niacinamide	200	20
6.	Sodium lauryl sulfate	40	4
7.	L-Arginine	140	14
8.	Poloxomer 407	70	7

APPROXIMATE SOLUBILITY OF SOLUBILISER IN GLYCERIN

Ten mg sodium caprylate was added to 1 ml glycerin in a volumetric flask of 10 ml and agitated on vortex (Remi cm 101 plus) for around 20 minutes to dissolve it. As soon as it was dissolved, ten mg of sodium caprylate was added again and the mixture was agitated for another 20 minutes. When the clear solution was obtained again 10 mg of sodium caprylate was added. The same method was carried out until a suspension was achieved. To get a transparent solution, 300 mg sodium caprylate was dissolved in 1 ml glycerin. A suspension was formed after adding another 10 mg of sodium caprylate. Using the same method, approximate solubility of sodium benzoate, sodium acetate, sodium citrate, niacinamide, sodium lauryl sulfate, L-arginine and poloxomer 407, approximate solubility in glycerin was also investigated.

Table 5 illustrates the approximate solubility of various solubilisers in glycerin.

Table 5: Approximate solubility of various solubilisers in glycerin

S.No.	Solubiliser	Solubility (mg/ml)	Solubility (% w/v)
1.	Sodium acetate	250	25
2.	Sodium benzoate	200	20
3.	Sodium citrate	200	20
4.	Sodium caprylate	300	30
5.	Niacinamide	300	30
6.	Sodium lauryl sulfate	150	15

7.	L-Arginine	80	8
8.	Poloxomer 407	70	7

• **RESULTS OF APPROXIMATE SOLUBILITY STUDIES OF FUROSEMIDE IN VARIOUS BLENDS IN PROPYLENE GLYCOL**

Various blends were prepared with different concentrations of a solubiliser. To 1 ml of the blend, 2.5 mg drug was added. The vial was shaken until the drug was completely dissolved or for about 20 minutes. Again 2.5 mg drug was added and it was shaken until the drug was dissolved or for about 20 minutes. When the clear solution was obtained again 2.5 mg of drug was added. The same procedure was repeated until a suspension was obtained. A similar procedure was followed for all the blends and the solubility of the drug was determined in each blend. The results are depicted in Table 6.

Table 6: Results of approximate solubility of furosemide in various blends of propylene glycol

S.No..	Solvent	Blend	Blend composition		Solubility (mg/ml)
			Solubiliser	Concentration	
1	Propylene glycol	B1 _{PG}	Sodium benzoate Sodium acetate Sodium caprylate Sodium lauryl sulfate	5 % 6 % 5 % 4 %	250
2	Propylene glycol	B2 _{PG}	Sodium benzoate Sodium acetate Sodium caprylate	5 % 5 % 5 %	200
3	Propylene glycol	B3 _{PG}	Sodium benzoate Benzoic acid PVP K 30 PEG 400	5 % 5 % 5 % 5 %	60
4	Propylene glycol	B4 _{PG}	Sodium caprylate Sodium acetate	10 % 10 %	220
5	Propylene glycol	B5 _{PG}	Sodium benzoate Sodium acetate Sodium caprylate Niacinamide Sodium lauryl sulfate	5 % 5 % 5 % 2.5 % 2.5 %	210
6	Propylene glycol	B6 _{PG}	Sodium acetate Sodium caprylate Niacinamide	5 % 5 % 5 %	200
7	Propylene glycol	B7 _{PG}	Sodium benzoate Sodium citrate Sodium caprylate Niacinamide Poloxomer 407	4 % 4 % 5.5 % 2.5 % 4 %	210
8	Propylene glycol	B8 _{PG}	Sodium benzoate Sodium caprylate Poloxomer 407 Niacinamide	2.5 % 2.5 % 2.5 % 2.5 %	130
9	Propylene glycol	B9 _{PG}	Sodium benzoate Sodium caprylate L-Arginine Poloxomer 407	2.5 % 2.5 % 2.5 % 2.5 %	140

10	Propylene glycol	B10 _{PG}	Sodium caprylate Sodium acetate	10 % 10 %	240
11	Propylene glycol	B11 _{PG}	Sodium benzoate Sodium acetate Sodium caprylate Niacinamide Sodium lauryl sulfate	5 % 5 % 5 % 2.5 % 2.5 %	210

IN GLYCERIN

Various blends were prepared with different concentrations of a solubiliser. 2.5 mg drug was added to 1 ml of the blend. The vial was shaken until the drug was completely dissolved or for about 20 minutes. Again 2.5 mg drug was added and it was shaken until the drug was dissolved or for about 20 minutes. When the clear solution was obtained again 2.5 mg of drug was added. The same procedure was repeated until a suspension was obtained. A similar procedure was followed for all the blends and the solubility of the drug was determined in each blend. The results are shown in Table 7.

Table 7: Results of approximate solubility of furosemide in various blends of glycerin

S.No..	Solvent	Blend	Blend Composition		Solubility (mg/ml)
			Solubiliser	Concentration	
1	Glycerin	B1 _{Gly}	Sodium benzoate Sodium acetate Sodium caprylate Sodium citrate	2.5 % 2.5 % 2.5 % 2.5 %	100
2	Glycerin	B2 _{Gly}	Sodium caprylate Sodium citrate Sodium lauryl sulfate Poloxomer 407	2.5 % 2.5 % 2.5 % 2.5 %	70
3	Glycerin	B3 _{Gly}	Sodium acetate Sodium citrate	5 % 5 %	60
4	Glycerin	B4 _{Gly}	Sodium caprylate Sodium citrate	5 % 5 %	60
5	Glycerin	B5 _{Gly}	Sodium caprylate L-Arginine Poloxomer 407 Sodium lauryl sulphate	2.5 % 2.5 % 2.5 % 2.5 %	65
6	Glycerin	B6 _{Gly}	Sodium acetate Sodium caprylate Niacinamide Poloxomer 407	2.5 % 2.5 % 2.5 % 2.5 %	60
7	Glycerin	B7 _{Gly}	Sodium caprylate L-Arginine Sodium citrate	5 % 2.5 % 2.5 %	70
8	Glycerin	B8 _{Gly}	Sodium caprylate Poloxomer 407 Sodium benzoate	5 % 2.5 % 2.5 %	60
9	Glycerin	B9 _{Gly}	Sodium caprylate Sodium acetate Sodium citrate	2.5 % 2.5 % 5 %	65

10	Glycerin	B10 _{Gly}	Sodium benzoate Niacinamide Poloxomer 407 Sodium caprylate Sodium citrate Sodium acetate	2.5 % 2.5 % 2.5 % 2.5 % 2.5 % 2.5 %	150
11	Glycerin	B11 _{Gly}	Sodium caprylate Sodium acetate Sodium benzoate Niacinamide	2.5 % 5 % 5 % 2.5 %	110
12	Glycerin	B12 _{Gly}	Sodium caprylate Sodium acetate Sodium citrate	5 % 5 % 5 %	120
13	Glycerin	B13 _{Gly}	Sodium caprylate L-Arginine Sodium acetate Sodium benzoate Niacinamide	2.5 % 2.5 % 2.5 % 5 % 2.5 %	140
14	Glycerin	B14 _{Gly}	Sodium citrate Sodium acetate Sodium benzoate Niacinamide Poloxomer 407 Sodium caprylate	5 % 5 % 2.5 % 2.5 % 2.5 % 5 %	130
15	Glycerin	B15 _{Gly}	Sodium caprylate Sodium citrate Sodium acetate Sodium benzoate	5 % 5 % 5 % 5 %	130
16	Glycerin	B16 _{Gly}	Sodium caprylate Sodium acetate Sodium benzoate	5 % 5 % 10 %	130
17	Glycerin	B17 _{Gly}	Sodium citrate Sodium acetate Sodium benzoate Niacinamide Sodium caprylate	2.5 % 5 % 5 % 2.5 % 5 %	110

• DETERMINATION OF EQUILIBRIUM SOLUBILITY OF FUROSEMIDE IN SELECTED BLENDS

In clean glass vials, 4 ml of the selected blend from approximate solubility trials were filled, and the drug was added in excess. Then, the vials were sealed and placed on a mechanical shaker (Scientech) for 24 hours. They were left undisturbed for 12 hours after the 24 hours was completed. After suitable dilutions with D.M. water and equilibrium solubility calculations, the solutions were filtered through a Whatman grade 41 filter and analyzed on Shimadzu-1700 UV spectrophotometer.

IN PROPYLENE GLYCOL

Table 8 illustrates the equilibrium solubility of furosemide in selected blends of propylene glycol.

Table 8: Equilibrium solubility of furosemide in selected blends of propylene glycol

Blend	Composition	Concentration	Equilibrium solubility
B1 _{PG}	Sodium benzoate Sodium acetate Sodium caprylate Sodium lauryl sulfate	5 % 6 % 5 % 4 %	265.10 mg/ml

B2 _{PG}	5 % Sodium benzoate 5 % Sodium acetate 5 % Sodium caprylate	5 % 5 % 5 %	218.00 mg/ml
B4 _{PG}	10 % Sodium caprylate 10 % Sodium acetate	10 % 10 %	237.00 mg/ml

IN GLYCERIN

Table 9 illustrates the equilibrium solubility of furosemide in selected blends of glycerin.

Table 9: Equilibrium solubility of furosemide in selected blends of glycerin

Blend	Composition	Concentration	Equilibrium solubility
B11 _{Gly}	Sodium benzoate Sodium acetate Sodium caprylate Niacinamide	2.5 % 2.5 % 2.5 % 2.5 %	119.00 mg/ml
B12 _{Gly}	Sodium citrate Sodium acetate Sodium caprylate	5 % 5 % 5 %	133.00 mg/ml
B13 _{Gly}	Sodium caprylate Sodium acetate L-Arginine Niacinamide Sodium benzoate	2.5 % 2.5 % 2.5 % 2.5 % %	161.00mg/ml

• EQUILIBRIUM SOLUBILITY OF FUROSEMIDE IN DIFFERENT MEDIUMS

Solubility experiments in various aqueous media were conducted by putting an excess quantity of furosemide in 5 ml of respective media in clean glass vials, sealing them, and shaking them for 24 hours at room temperature, then leaving them undisturbed for 12 hours. After that, the solutions went through a Whatman grade 41 filter. After suitable dilution with D.M. water, the absorbances of the solutions were measured at 333 nm using a double beam Shimadzu-1700 UV spectrophotometer. Table 10 summarizes the findings.

Table 10: Equilibrium solubility of furosemide in different medium

S.No.	Solvent	Solubility of furosemide (mg/ml)	Solubility (%w/v)
1	D.M. water	0.079	0.0079
2	0.1 N HCl	0.057	0.0057

• DRUG-SOLUBILISER INTERFERENCE STUDIES IN UV SPECTROPHOTOMETRIC ANALYSIS

The absorbance of a standard solution of furosemide in D.M. water and the presence of an excipient was measured to determine if excipients interfere with UV spectrophotometric measurement of furosemide. The accurately weighed 50 mg was dissolved in 450 ml distilled water in a 500 ml volumetric flask and vigorously shaken until a clear solution was produced, and the volume was brought up to 500 ml with D.M. water after complete dissolution (stock solution 100 g/ml). Then 20 ml of the aforementioned solution was collected and diluted to 100 ml with D.M. water, yielding a 20 µg/ml drug solution.

Similarly, excipient solutions were made by dissolving 2000 mg of each solubilizer in 80 ml D.M. water in a 100ml volumetric flask and increasing the volume to 100 ml to create a 2000 µg/ml excipient stock solution.

20 ml of drug stock solution and 10 ml of excipient stock solution were combined in a 100 ml volumetric flask, and the volume was increased to 100 ml with D.M. water. The reagent blank was made by putting 10 ml of excipient stock solution in a 100 ml volumetric flask and filling it with distilled water to make it 100 ml.

The absorbances of these solutions were determined against D.M. water and respective reagent blanks at 333 nm and results are shown below in table 11.

Table 11: Absorbance data for interference study

Drug	Excipients	Drug concentration (µg/ml)	Additives concentration (µg/ml)	λ_{max} (nm)	Absorbance
Furosemide	-	20	2000	333	0.315
Furosemide	Sodium benzoate	20	2000	333	0.309

Furosemide	Sodium acetate	20	2000	333	0.311
Furosemide	Sodium caprylate	20	2000	333	0.313
Furosemide	Sodium citrate	20	2000	333	0.314
Furosemide	Niacinamide	20	2000	333	0.307
Furosemide	L-Arginine	20	2000	333	0.306
Furosemide	Sodium lauryl sulphate	20	2000	333	0.311
Furosemide	Propylene glycol	20	2000	333	0.308
Furosemide	Glycerin	20	2000	333	0.307

Result and discussion

According to the obtained results, it is concluded that no interference was observed in the UV spectrophotometric analysis of the drug due to the presence of excipients or solubiliser on Shimadzu-1700 UV spectrophotometer.

• DRUG EXCIPIENT INTERACTION STUDIES

The physical compatibility of the drug with the excipients was determined by drug-excipient interaction studies. The drug and the excipients were mixed in a 1:1 ratio in separate clean glass vials, which were then tightly sealed and stored for one month at ambient temperature and one month in the refrigerated (2°C - 8°C). After each week, the vials were examined to determine whether there had been any changes in their physical appearance. The investigation's findings are shown in Table 12.

Table 12: Observation of physical interaction between drug and excipient

S. No.	Drug-excipients mixture	Initial appearance	Storage conditions								
			Refrigerator (2-8°C)				Room temperature				
			Weeks				Weeks				
			1	2	3	4	1	2	3	4	
1	Furosemide	White powder	No	No	No	No	No	No	No	No	No
2	Furosemide + Sodium benzoate	White powder	No	No	No	No	No	No	No	No	No
3	Furosemide+ Sodium acetate	White powder	No	No	No	No	No	No	No	No	No
4	Furosemide+ Sodium caprylate	White powder	No	No	No	No	No	No	No	No	No
5	Furosemide+ Sodium citrate	White powder	No	No	No	No	No	No	No	No	No
6	Furosemide+ Niacinamide	White powder	No	No	No	No	No	No	No	No	No
7	Furosemide+ L-Arginine	White powder	No	No	No	No	No	No	No	No	No
8	Furosemide+ Sodium lauryl sulphate	White powder	No	No	No	No	No	No	No	No	No
9	Furosemide+ Propylene glycol	White suspension	No	No	No	No	No	No	No	No	No
10	Furosemide+ Glycerin	White suspension	No	No	No	No	No	No	No	No	No

No = No change

5.2 FORMULATION AND DEVELOPMENT OF LIQUISOLID SYSTEM OF FUROSEMIDE

A. 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 B1_{PG}, B2_{PG}, and B4_{PG} showed good solubility of the drug. Likewise, in glycerin as a solvent, blends B11_{Gly}, B12_{Gly}, and B13_{Gly} showed good solubility of the drug. So, all six blends were selected for further studies as they showed maximum drug solubility.

B. 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. 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, MgCO₃ and talc. Table 7.1 shows the results of amount of carrier adsorbed by 1 ml propylene glycol.

Table 7.1: Approximate amount of carrier materials used to adsorb propylene glycol

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

➤ 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, 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 utilized 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, MgCO₃ and talc. Table 13 shows the results of amount of carrier adsorbed by 1 ml glycerin.

Table 13: Approximate amount of carrier material used to adsorb glycerin

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

Based on the above results, in the formulation, MCC (microcrystalline cellulose) grade PH 200 was used as a suitable carrier. Because the amount of carrier needed to make the liquid vehicle free-flowing affects the weight of the powder, the carrier with the highest flowable liquid retention potential (phi value) was chosen.

After mixing an appropriate quantity of carrier, the resulting wet mixture is transformed into a dry-looking, non-adherent, free-flowing, and easily compressible powder by adding a determined amount of coating material. Fine particles with a high absorptive capacity should be used in the coating. Aerosil, with a concentration of 5 % of the coating material was used for further research.

C. PREPARATION OF LIQUISOLID SYSTEM

Blend B1_{PG}, B2_{PG} and B4_{PG} of propylene glycol were chosen. Approximate solubility of furosemide in blend B1_{PG} 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.

Approximate solubility of furosemide in blend B2_{PG} 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.

Approximate solubility of furosemide in blend B4_{PG} 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 14 summarizes the quantity of carrier and coater used for a batch of 50 doses for blends in propylene glycol.

**Table 14: Quantity of carrier and coater used for a batch of 50 doses
(blends in propylene glycol)**

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	28.000	Aerosil	1.400	B1 _{PG}	8.00	39.560
2.	LSS-PG-02	Avicel PH 200	35.000	Aerosil	1.750	B2 _{PG}	10.00	48.950
3.	LSS-PG-03	Avicel PH 200	31.815	Aerosil	1.575	B4 _{PG}	9.10	44.640

Blend B11_{Gly}, B12_{Gly}, B13_{Gly} of glycerin were chosen. Approximate solubility of furosemide in blend B11_{Gly} was found out to be 110 mg/ml. For preparing a batch of 50 doses with 20 mg dose strength, 9.00 ml of blend was taken. Observed density of the blend was 1.29 g/ml, so the weight of the blend (9.00 ml), used to prepare the liquisolid system was 11.70 grams. One gram of drug was dissolved in 9.00 ml blend and this solution was transferred in a clean and dried mortar. For adsorption of this solution, twenty nine point seven zero grams of MCC was used. The amount of aerosil used was 1.485 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 43.885 grams. A single dose of 20 mg furosemide consisted of 877 mg powder for liquisolid system of LSS-Gly-01.

Approximate solubility of furosemide in blend B12_{Gly} was found out to be 120 mg/ml. For preparing a batch of 50 doses with 20 mg dose strength, 8.30 ml of blend was taken. Observed density of the blend was 1.29 g/ml, so the weight of the blend (8.30 ml), used to prepare the liquisolid system was 10.79 grams. One gram of drug was dissolved in the blend (8.30 ml) was transferred in a clean and dried mortar. For adsorption of this solution, twenty seven point three nine zero grams of MCC was used. The amount of aerosil used was 1.369 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 is 40.549 grams. A single dose of 20 mg furosemide consisted of 810 mg powder for liquisolid system of LSS-Gly-02.

Approximate solubility of furosemide in blend B13_{Gly} was found out to be 140 mg/ml. For preparing a batch of 50 doses with 20 mg dose strength, 7.10 ml of blend was taken. Density of the blend was 1.29 g/ml, so the weight of the blend (7.10 ml), used to prepare the liquisolid system was 9.23 grams. One gram of drug was dissolved in 7.10 ml blend and this solution was transferred in a clean and dried mortar. For adsorption of this solution, twenty three point four three zero grams of MCC was used. The amount of aerosil used was 1.117 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. The powder weighed 34.777 grams. Now total weight of free flowing powder shall be 695 mg powder for liquisolid system of LSS-Gly-03.

Table 15 summarizes the quantity of carrier and coater used for a batch of 50 doses for blends in glycerin.

**Table 15 : Quantity of carrier and coater used for a batch of 50 doses
(blends in glycerin)**

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-Gly-01	Avicel PH 200	29.700	Aerosil	1.485	B11 _{Gly}	9.00	42.835
2.	LSS-Gly-02	Avicel PH 200	27.390	Aerosil	1.369	B12 _{Gly}	8.30	40.549
3.	LSS-Gly-03	Avicel PH 200	23.430	Aerosil	1.117	B13 _{Gly}	7.10	34.777

D. EVALUATION OF PREPARED LIQUISOLID SYSTEM

➤ DRUG CONTENT

A liquisolid formulation powder of LSS-PG-01 (791 mg) containing 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, and was 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 measured in Shimadzu-1700 UV spectrophotometer at 333 nm against a blank of D.M. water. LSS-PG-02 and LSS-PG-03 were treated in the same way. The percentage of drug contained in LSS-PG-01, LSS-PG-02, and LSS-PG-03 is shown in table 16.

**Table 16 : Percentage of drug present in
LSS-PG-01, LSS-PG-02, and LSS-PG-03**

S.No.	Batch number	Amount of drug obtained (mg/1000ml)	% Drug present
1.	LSS-PG-01	39.60	99.02
2.	LSS-PG-02	39.80	99.52
3.	LSS-PG-03	39.50	98.75

A liquisolid formulation powder of LSS-Gly-01 (877 mg) containing 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, and was shaken constantly for 30 minutes, and the volume was made up to 1000 ml with D.M. water. Filtration was done on the solution. The absorbance was measured in Shimadzu-1700 UV spectrophotometer at 333 nm against a blank of D.M. water. LSS-Gly-02 and LSS-Gly-03 were treated in the same way. The percentage of drug contained in LSS-Gly-01, LSS-Gly-02, and LSS-Gly-03 is shown in Table 17.

**Table 17: Percentage of drug present in
LSS-Gly-01, LSS-Gly-02, and LSS-Gly-03**

S.No.	Batch number	Amount of drug obtained (mg/1000ml)	% Drug present
1.	LSS-Gly-01	19.85	99.25
2.	LSS-Gly-02	19.74	98.70
3.	LSS-Gly-03	19.85	99.25

➤ DISSOLUTION PROFILE

1) In 0.1N HCl

The dissolution profiles of each batch were examined in order to determine which batch was best for scaling up. For dissolution studies, 0.1N HCl was taken as dissolution media and the paddle rotation speed was kept at 50 rpm at 37±0.5°C in 900ml of media. After 2 minute, twenty ml sample was withdrawn from dissolution media for analysis, and equal quantity of 0.1 N HCl was added. Similar procedure was repeated after different time intervals. Table 18 and 19 shows the quantity of liquisolid powder in each batch used for dissolution studies in 0.1 N HCl.

Table 18: Quantity of liquisolid powder in each batch of propylene glycol used for dissolution studies in 0.1 N HCl

S.No.	Batch	Amount of powder (mg)	Amount of drug
1.	LSS-PG-01	799	40 mg
2.	LSS-PG-02	984	40 mg
3.	LSS-PG-03	894	40 mg

Table 19: Quantity of liquisolid powder in each batch of glycerin for dissolution studies in 0.1 N HCl

S.No.	Batch	Amount of powder	Amount of drug
1.	LSS-Gly-01	884	20 mg
2.	LSS-Gly-02	821	20 mg
3.	LSS-Gly-03	700	20 mg

• **DISSOLUTION PROFILE OF PURE DRUG (FUROSEMIDE) IN 0.1 N HCl**

Table 20 illustrates data for dissolution study of pure drug, furosemide, in 0.1 N HCl

Table 20: Data for dissolution study of pure drug, furosemide, in 0.1 N HCl

Time (mins)	(%) Cumulative drug release
02	04.40
05	11.89
10	17.91
15	19.55
30	20.76
45	22.26
60	25.57

• **DISSOLUTION PROFILE OF LSS-PG-01 IN 0.1 N HCl**

Table 21 illustrates data for dissolution study of LSS-PG-01 in 0.1 N HCl

Table 21: Data for dissolution study of LSS-PG-01 in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	25.80
05	53.84
10	85.85
15	98.40
30	98.40
45	98.40
60	98.40

• **DISSOLUTION PROFILE OF LSS-PG-02 IN 0.1 N HCl**

Table 22 illustrates data for the dissolution study of LSS-PG-02 in 0.1 N HCl.

Table 22: Data for dissolution study of LSS-PG-02 in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	30.80
05	51.88
10	88.74
15	98.67
30	98.67
45	98.67
60	98.67

- DISSOLUTION PROFILE OF LSS-PG-03 IN 0.1 N HCl**

Table 23 illustrates data for the dissolution study of LSS-PG-03 in 0.1 N HCl.

Table 23: Data for dissolution study of LSS-PG-03 in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	32.80
05	57.89
10	89.72
15	97.92
30	97.92
45	97.92
60	97.92

The comparative dissolution profile in 0.1 N HCl of various batches in propylene glycol and the pure drug is illustrated in figure 9.

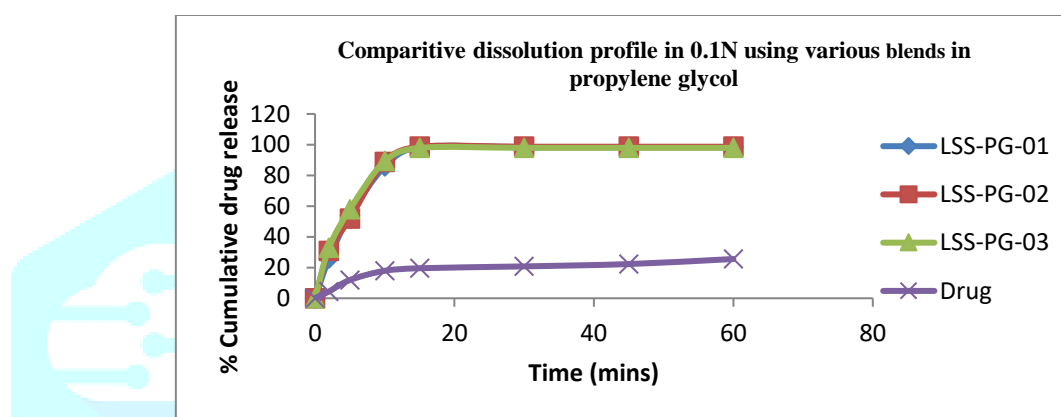


Figure 9 : Comparative dissolution profile in 0.1 N HCl of various batches in propylene glycol and pure drug

Dissolution study of powder of liquisolid system prepared in propylene glycol showed that in 2 minutes approximately 25% of the drug was released, in 5 minutes approximately 50% of the drug was released, in 10 minutes more than 85% of the drug was released and in 15 minutes more that 95% of the drug was released.

- DISSOLUTION PROFILE OF LSS-Gly-01 IN 0.1 N HCl**

Table 24 illustrates data for the dissolution study of LSS-Gly-01 in 0.1 N HCl.

Table 24: Data for dissolution study of LSS-Gly-01 in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	96.29
05	98.27
10	98.27
15	98.27
30	98.27
45	98.27
60	98.27

- DISSOLUTION PROFILE OF LSS-Gly-02 IN 0.1 N HCl**

Table 25 illustrates data for the dissolution study of LSS-Gly-02 in 0.1 N HCl.

Table 25: Data for dissolution study of LSS-Gly-02 in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	96.00
05	99.05
10	99.05
15	99.05
30	99.05
45	99.05
60	99.05

- **DISSOLUTION PROFILE OF LSS-Gly-03 IN 0.1 N HCl**

Table 26 illustrates data for the dissolution study of LSS-Gly-03 in 0.1 N HCl.

Table 26 : Data for dissolution study of LSS-Gly-03 in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	98.10
05	99.20
10	99.20
15	99.20
30	99.20
45	99.20
60	99.20

Figure 10 shows a comparison of dissolution profiles in 0.1 N HCl of various batches in glycerin and pure drug.

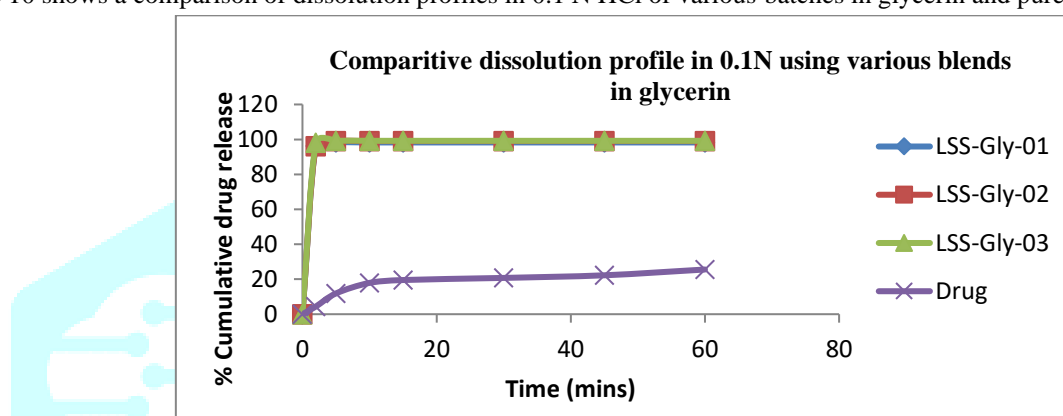


Figure 10 : Comparative dissolution profile in 0.1 N HCl of various batches in glycerin and pure drug

Dissolution study of powder of liquisolid system prepared in glycerin showed that in 2 minutes approximately 95% of the drug was released, in 5 minutes approximately 98% of the drug was released.

2) In D.M. water

The dissolution profile of each batch was studied to select the most suitable batch for scale-up. For dissolution studies D.M. water was taken as dissolution media and the paddle rotation speed was kept at 50 rpm at $37 \pm 0.5^\circ\text{C}$ in 900ml of media. After 2 minutes, twenty ml sample was withdrawn from dissolution media for analysis, and an equal quantity of 0.1 N HCl was added. A similar procedure was repeated after different time intervals. Table 7.7 and 7.8 shows the quantity of liquisolid powder in each batch tablet used for dissolution studies.

- **DISSOLUTION PROFILE OF PURE DRUG (FUROSEMIDE) IN D.M. WATER**

Table 27 illustrates data for the dissolution study of pure drug (furosemide) in D.M. water.

Table 27: Data for dissolution study of pure drug (furosemide) in D.M. water

Time (min)	(%) Cumulative drug release
02	04.00
05	10.15
10	15.19
15	18.56
30	19.77
45	21.96
60	22.11

- **DISSOLUTION PROFILE OF LSS-PG-01 IN D.M. WATER**

Table 28 illustrates data for the dissolution study of LSS-PG-01 in D.M. water.

Table 28: Data for dissolution study of LSS-PG-01 in D.M. water

Time (min)	(%) Cumulative drug release
02	27.80
05	53.84

10	85.72
15	98.40
30	98.40
45	98.40
60	98.40

➤ DISSOLUTION PROFILE OF LSS-PG-02 IN D.M. WATER

Table 29 illustrates data for the dissolution study of LSS-PG-02 in D.M. water.

Table 29: Data for dissolution study of LSS-PG-02 in D.M. water

Time (min)	(%) Cumulative drug release
02	30.80
05	51.88
10	87.12
15	97.50
30	97.50
45	97.50
60	97.50

• DISSOLUTION PROFILE OF LSS-PG-03 IN D.M. WATER

Table 30 illustrates data for the dissolution study of LSS-PG-03 in D.M. water.

Table 30: Data for dissolution study of LSS-PG-03 in D.M. water

Time (min)	(%) Cumulative drug release
02	32.15
05	59.11
10	88.23
15	99.10
30	99.10
45	99.10
60	99.10

Figure 11 shows a comparison of dissolution profiles in D.M. water of various batches in propylene glycol and pure drug.

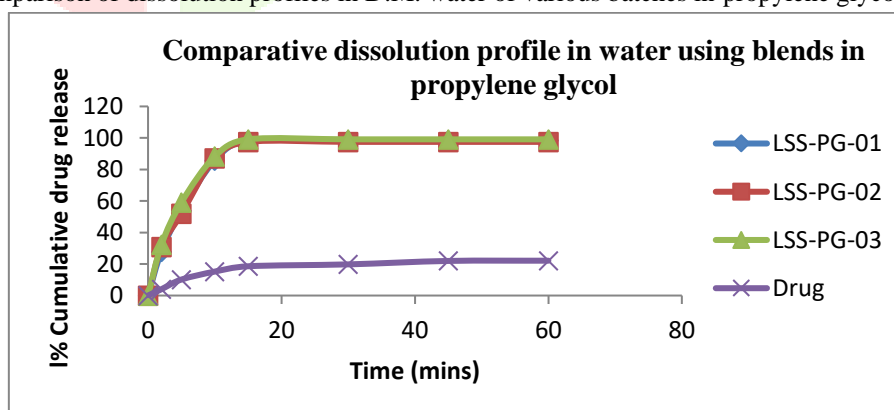


Figure 11: Comparative dissolution profile in D.M. water of various batches in propylene glycol and pure drug

Dissolution study of powder of liquisolid system prepared in propylene glycol showed that in 2 minutes approximately 25% of the drug was released, in 5 minutes approximately 50% of the drug was released, in 10 minutes more than 85% of the drug was released and in 15 minutes more that 95% of the drug was released.

• DISSOLUTION PROFILE OF LSS-Gly-01 IN D.M. WATER

Table 31 illustrates data for the dissolution study of LSS-Gly-01 in D.M. water.

Table 31: Data for dissolution study of LSS-Gly-01 in D.M. water

Time (min)	(%) Cumulative drug release
02	97.20
05	98.01
10	98.01
15	98.01
30	98.01
45	98.01
60	98.01

- DISSOLUTION PROFILE OF LSS-Gly-02 IN D.M. WATER**

Table 32 illustrates data for the dissolution study of LSS-Gly-02 in D.M. water.

Table 32: Data for dissolution study of LSS-Gly-02 in D.M. water

Time (min)	(%) Cumulative drug release
02	95.18
05	98.20
10	98.20
15	98.20
30	98.20
45	98.20
60	98.20

- DISSOLUTION PROFILE OF LSS-Gly-03 IN D.M. WATER**

Table 33 illustrates data for the dissolution study of LSS-Gly-03 in D.M. water.

Table 33: Data for dissolution study of LSS-Gly-03 in D.M. water

Time (min)	(%) Cumulative drug release
02	97.09
05	99.05
10	99.05
15	99.05
30	99.05
45	99.05
60	99.05

Figure 12 shows a comparison of dissolution profiles in D.M. water of various batches in glycerin and pure drug.

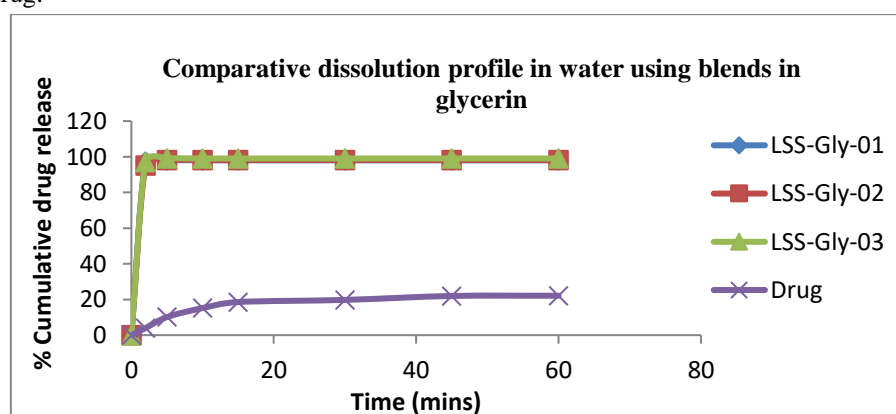


Figure 12: Comparative dissolution profile in D.M. water of various batches in glycerin and pure drug

Dissolution study of powder of liquisolid system prepared in glycerin showed that in 2 minutes approximately 95% of the drug was released, in 5 minutes approximately 98% of the drug was released.

E. FINAL BATCH PREPARATION

From the trial batches, LSS-PG-03, LSS-Gly-02, LSS-Gly-03 were selected for the final batch preparation based on the dissolution profile. All three batches were scaled up.

For preparing a batch of 50 tablets 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 five 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.

For preparing a batch of 50 tablets with 20 mg dose strength, 8.30 ml of blend was taken. Observed density of the blend was 1.29 g/ml, so the weight of the blend (8.30 ml), used to prepare the liquisolid system was 10.79 grams. One gram of drug was dissolved in the blend (8.30 ml) was transferred in a clean and dried mortar. For adsorption of this solution, twenty seven point three nine zero grams of MCC was used. The amount of aerosil used was 1.369 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 is 40.549 grams. A single dose of 20 mg furosemide consisted of 810 mg powder for liquisolid system of LSS-Gly-02.

For preparing a batch of 50 tablets with 20 mg dose strength, 7.10 ml of blend was taken. Density of the blend was 1.29 g/ml, so the weight of the blend (7.10 ml), used to prepare the liquisolid system was 9.23 grams. One gram of drug was dissolved in 7.10 ml blend and this solution was transferred in a clean and dried mortar. For adsorption of this solution, twenty three point four three zero grams of MCC was used. The amount of aerosil used was 1.117 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. The powder weighed 34.777 grams. Now total weight of free flowing powder shall be 695 mg powder for liquisolid system of LSS-Gly-03.

Table 34 shows the amount of carrier and coating material used for the preparation of final batches.

Table 34: Quantity of carrier and coater used for the preparation of final batches

Batch No.	Carrier material	Amount of carrier used (gm)	Coating material	Amount of coating material used (gm)	Blend	The volume of blend used (ml)	Net wt. (gm)
LSS-PG-03	AvicelPH200	31.815	Aerosil	1.575	B4 _{PG}	9.10	44.640
LSS-Gly-02	AvicelPH200	27.390	Aerosil	1.369	B12 _{Gly}	8.30	40.549
LSS-Gly-03	AvicelPH200	23.430	Aerosil	1.117	B13 _{Gly}	7.10	34.777

F. THIN LAYER CHROMATOGRAPHY STUDIES

To examine the possibility of interaction between drug and solubilizer, thin layer chromatographic studies were performed. A plate of silica gel GF 120 was activated at 110°C for 1 hour and then used.

The baseline was spotted with the furosemide solution (1%) in ethanol alone and the aqueous solubiliser blends including furosemide in LSS-PG-03, LSS-Gly-02, and LSS-Gly-03. The plate was then dried in the air for sufficient period of time before being placed in a jar containing 20% sodium acetate solution (mobile phase).

After drying the plate for a suitable time, it was examined for spot visibility in a UV chamber. In Table 35, the corresponding R_f values were calculated and documented.

The results of the TLC study revealed that there was no significant difference in R_f values of furosemide solubilized in ethanol and furosemide solubilized in solubiliser blend solutions. From the results of the TLC study, it can be concluded that there is no reaction of drug with solubilizer molecules. It can also be concluded that toxic organic solvents can be safely replaced by safe hydrotropic solutions. TLC was carried out in a solution of 20 % sodium acetate solution as mobile phase proved that the solids possess the solubilizing power.

Table 35: Results of TLC studies

Solvent System	Adsorbent	R _f Value			
		Pure drug sample	LSS-PG-03	LSS-Gly-02	LSS-Gly-03
20 % Sodium acetate (aqueous)	Silica Gel GF 120	0.82	0.82	0.83	0.82

G. EVALUATIONS

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

None of the tablets from any of the batch went beyond the accepted range of $\pm 5\%$. 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.

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.

The amount of drug analyzed in all the three batches is shown in table 36.

Table 36: Amount of drug analyzed in tablets LSS-PG-03, LSS-Gly-02 and LSS-Gly-03

S.No.	Batch number	Amount of drug analyzed (mg)	Drug content
1	LSS-PG-03	39.81	99.52 %
2	LSS-Gly-02	19.89	99.45 %
3	LSS-Gly-03	19.82	99.10 %

• 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 $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$, at 28-32 cycles per minute frequency. similarly, tablets of lss-gly-02 and lss-gly-03 were tested. the results are shown in table 37.

Table 37: Disintegration time studies for tablets of LSS-PG-03, LSS-Gly-02, LSS-Gly-03

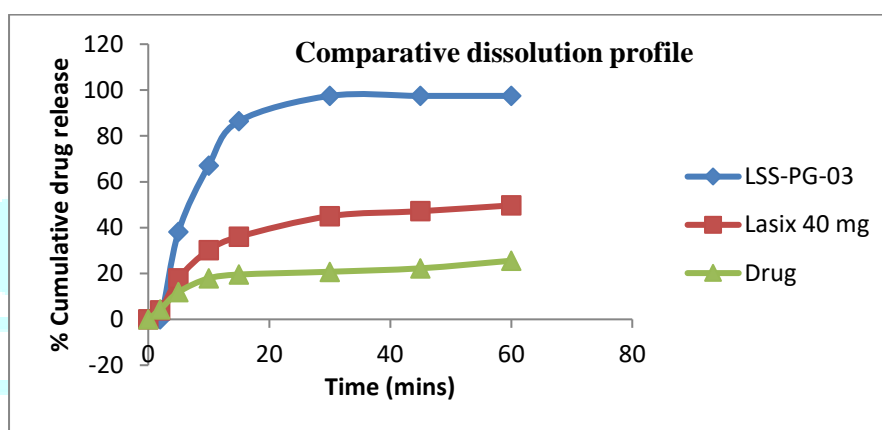
S.No.	Batch number	Disintegration time
1	LSS-PG-03	1 minute and 30 seconds to 3 minutes and 40 seconds
2	LSS-Gly-02	1 minute and 05 seconds to 4 minutes and 10 seconds
3	LSS-Gly-03	57 seconds to 2 minutes and 30 seconds

• 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 $37 \pm 0.5^{\circ}\text{C}$. 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 38 shows the comparative analysis. The comparative dissolution profile in 0.1 N HCl of tablet LSS-PG-03 and pure drug is illustrated in figure 13.

Table 38: Comparative dissolution profile in 0.1 N HCl of final batch in propylene glycol (tablet of LSS-PG-03), pure drug and marketed formulation

S.No.	Time (Mins)	% Cumulative drug release		
		Tablet of LSS-PG-03	Tablet of Lasix 40 mg	Pure drug
1	02	38.22	03.90	04.40
2	05	67.11	17.90	11.89
3	10	86.45	30.20	17.91
4	15	97.45	36.05	19.55
5	30	97.45	45.01	20.76
6	45	97.45	47.17	22.26
7	60	97.45	49.70	25.57

**Figure 13: Comparative dissolution profile in 0.1 N HCl of final batch in propylene glycol (LSS-PG-03), pure drug and marketed formulation**

Dissolution profile of tablet of LSS-Gly-02 and marketed tablet 40 mg was studied and compared. Two tablets of LSS-Gly-02 (20 mg each) were taken and compared with one tablet of Lasix 40 mg. For dissolution, nine hundred ml of 0.1N HCl was taken as dissolution media and the paddle rotation speed was kept at 50 rpm at $37 \pm 0.5^\circ\text{C}$. 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 39 shows the comparative analysis. The comparative dissolution profile in 0.1 N HCl of tablet LSS-Gly-02 and pure drug is illustrated in figure 14.

Table 39: Comparative dissolution profile in 0.1 N HCl of final batch in glycerin (tablets of LSS-Gly-02), pure drug and marketed formulation

S.No..	Time (Mins)	% Cumulative drug release		
		Tablets of LSS-Gly-02	Tablet of LASIX 40 mg	Pure drug
1	02	50.10	03.90	04.40
2	05	82.15	17.90	11.89
3	10	94.11	30.20	17.91
4	15	94.11	36.05	19.55
5	30	94.11	45.01	20.76
6	45	94.11	47.17	22.26
7	60	94.11	49.70	25.57

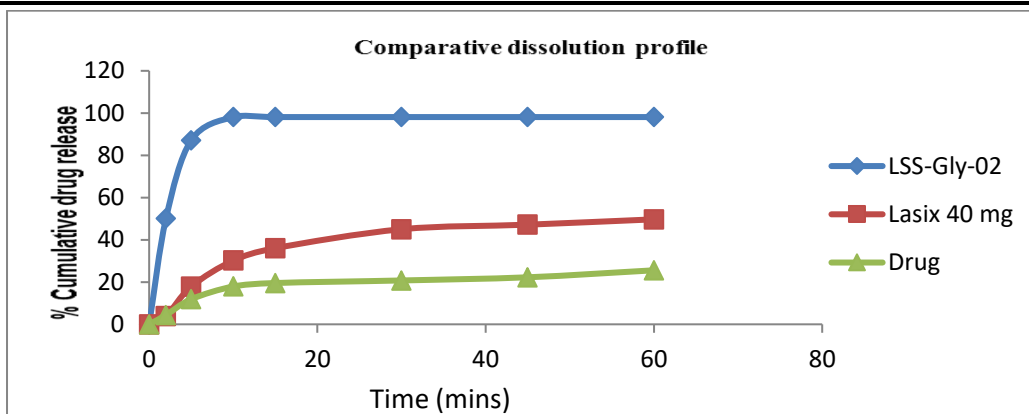


Figure 14: Comparative dissolution profile in 0.1 N HCl of final batch in glycerin (tablets of LSS-Gly-02), pure drug and marketed formulation

Dissolution profile of tablet LSS-Gly-03 tablet and marketed tablet 40 mg was studied and compared. Two tablets of LSS-Gly-03 (20 mg each) were 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 40 shows the comparative analysis. The comparative dissolution profile in 0.1 N HCl of LSS-Gly-03 and pure drug is illustrated in figure 15.

Table 40: Comparative dissolution profile in 0.1 N HCl of final batch in propylene glycol (LSS-Gly-03), pure drug and marketed formulation

S.No.	Time (Mins)	% Cumulative drug release		
		Tablets of LSS-Gly-03	Tablet of LASIX 40 mg	Pure drug
1	02	82.15	3.9	4.4
2	05	93.11	17.9	11.89
3	10	98.96	30.20	17.91
4	15	98.96	36.05	19.55
5	30	98.96	45.01	20.76
6	45	98.96	47.17	22.26
7	60	98.96	49.70	25.57

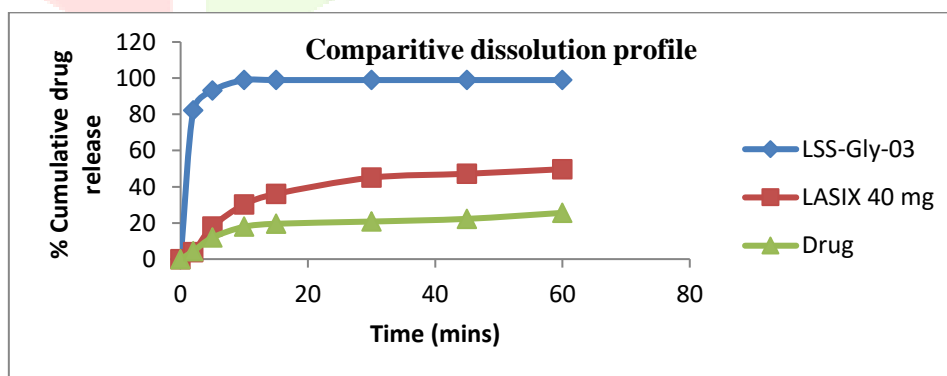


Figure 15: Comparative dissolution profile in 0.1 N HCl of final batch in glycerin (tablets of LSS-Gly-03), pure drug and marketed formulation

Dissolution study of tablets of liquisolid system prepared in propylene glycol (tablets of LSS-PG-03) showed that in 2 minutes approximately 25% of the drug was released, in 5 minutes approximately 50% of the drug was released, in 10 minutes more than 85% of the drug was released and in 15 minutes more that 95% of the drug was released. Dissolution study of tablets of liquisolid system prepared in glycerin (tablets of LSS-Gly-02 and tablets of LSS-Gly-03) showed that in 2 minutes approximately 50% of the drug was released, in 5 minutes approximately 85% of the drug was released and in 10 minutes more that 95% of the drug was released. As compared to marketed tablet which released approximately 3% of the drug in 2 minutes, approximately 15% of the drug in 5 minutes, 30% of the drug in 15minutes and 50% of drug in one hour. The optimized batches demonstrated better dissolution behavior.

- **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.

- **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.

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.

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.

- **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. The results of hardness test are recorded in table 41.

Table 41: Results of hardness test

S.No..	Tablet batch	Hardness (kg/cm ²)	
		Hardness of 3 tablets from each batch (kg/cm ²)	Average hardness of 3 tablets (kg/cm ²)
1.	LSS-PG-03	3	3
		3	
		3	
2.	LSS-Gly-02	3	3
		3	
		3	
3.	LSS-Gly-03	2	2
		2	
		2	

6. SUMMARY AND 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 utilised as effective solubilizers. These solids can be utilised 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 solubilisers 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 solubilisers 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.

This concept of mixed solvency is expected to improve the bioavailability of drug and there will be decrease in the release time. Conventional dosage form such as capsules and tablets can be prepared from this liquisolid system by selecting suitable excipients. Liquisolid formulation prepared from the mixed solvency concept is a promising tool for the enhancement of bioavailability of drug.

Furosemide is a benzoic-sulphonamide-furan. It is a diuretic with fast onset and short duration that is used for edema and chronic renal insufficiency. Furosemide is a loop diuretic (water pill) that prevents your body from absorbing too much salt. This allows the salt to instead be passed in your urine. Furosemide is used to treat fluid retention (edema) in people with congestive heart failure, liver disease, or a kidney disorder such as nephrotic syndrome. Furosemide is also used to treat high blood pressure (hypertension).

The characterization and identification of furosemide was done by UV spectrophotometric analysis, determination of melting range and differential scanning calorimetry of the drug sample were carried out. The observed values were in accordance with the reported values in the literatures.

In preformulation studies solubility studies in various blends was performed. Also, preparation of calibration curves in water and 0.1 N HCl with aid of sodium benzoate was done. Solubility of furosemide drug sample was reported in propylene glycol and glycerin and also in different blends prepared in these two solvent systems. Interaction studies of drug-excipients have shown no interaction and incompatibility between drugs and excipients. UV spectrophotometric study of drugs and solubilizers indicated no drug solubilizer interference at 333 nm.

Propylene glycol and glycerin were used as non-volatile solvents in the development of furosemide rapid release liquisolid systems. Various solid solubilizers at modest concentrations were used to improve drug solubility in these solvent systems. The carrier material was microcrystalline cellulose (Avicel PH 200). Dissolution study of powder of liquisolid system prepared in propylene glycol showed that in 2 minutes approximately 25% of the drug was released, in 5 minutes approximately 50% of the drug was released, in 10 minutes more than 85% of the drug was released and in 15 minutes more than 95% of the drug was released. Dissolution study of powder of liquisolid system prepared in glycerin showed that in 2 minutes approximately 95% of the drug was released, in 5 minutes approximately 98% of the drug was released.

Thin layer chromatography was also performed which concluded that there is no reaction of drug with solubilizer molecules. It was also concluded that toxic organic solvents can be safely replaced by safe hydrotropic solutions. TLC was carried out in a solution of 20 % sodium acetate solution as mobile phase proved that the solids possess the solubilizing power.

One of three trial batches of propylene glycol and two of three trial batches of glycerin were selected for compression into tablets. The tablets formulated were compared with marketed tablet Lasix 40 mg. Dissolution study of tablets of liquisolid system prepared in propylene glycol showed that in 2 minutes approximately 25% of the drug was released, in 5 minutes approximately 50% of the drug was released, in 10 minutes more than 85% of the drug was released and in 15 minutes more than 95% of the drug was released. Dissolution study of tablets of liquisolid system prepared in glycerin showed that in 2 minutes approximately 50% of the drug was released, in 5 minutes approximately 85% of the drug was released and in 10 minutes more than 95% of the drug was released. As compared to marketed tablet which released approximately 3% of the drug in 2 minutes, approximately 15% of the drug in 5 minutes, 30% of the drug in 15 minutes and 50% of drug in one hour. The optimized batches demonstrated better dissolution behavior. The drug content, disintegration time, weight variation, friability, hardness, content uniformity studies and drug release studies were all assessed.

Based on the above findings, it may be concluded that the solubility and release of a poorly water-soluble drug can be enhanced using various solid solubilizers by the application of mixed solvency concept.

The mixed solvency concept was successfully used to create a fast-acting liquisolid version of the water-insoluble medication furosemide. The current work shows how to use the mixed solvency enhance drug solubility while increasing drug release. The formulation of the needed dosage of drug as a liquisolid system was not achievable due to the poor solubility of drug furosemide in non-volatile solvents, which was overcome utilising the mixed solvency idea and a formulation was created that exhibited good drug release. This approach may assist pharmaceutical firms not only in the manufacturing of quick release liquisolid system formulations, but also in the development of other pharmaceutical formulations using mixed solvency concept.

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