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Formulation Development of Oral Liquisolid Systems of Poorly Water-Soluble Drug, Hydrochlorothiazide, Using Mixed Solvency Concept and Their Evaluations

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ABSTRACT

The present work is aimed to enhance the drug loading capacity in a liquisolid system, decreasing the required volume of nonvolatile solvent due to enhanced solubility of a drug in nonvolatile solvent using the mixed solvency concept. Hydrochlorothiazide was selected as a model poorly water-soluble drug for exploring the mixed solvency concept to enhance the solubility and hence to enhance the release rate of the drug. The proposed formulation is aimed to enhance the solubility of hydrochlorothiazide by employing the mixed solvency concept and to develop the fast-release capsule of hydrochlorothiazide using the liquisolid technique. The prepared liquisolid dosage form was tested for flow properties, thin layer chromatography, drug excipient interaction studies, drug content determination, disintegration time study, and dissolution studies. The comparative dissolution studies were performed and it was observed that the formulated capsule containing liquisolid formulation released 81.09 % of the drug within 10 minutes, and only 56.25 % drug was released from the marketed tablet formulation within 10 minutes.

1. INTRODUCTION

1.1 Fast release dosage forms [1]

A fast-release dosage system is intended to release the drug at a comparatively faster rate than the conventional release systems making the drug rapidly available for drug absorption at the site promising fast onset of action.

There are several approaches for solubility enhancement that include hydrotropy, complexation, micronization, nanonization, cosolvency, use of surfactant, usage of salt forms, solid dispersion, and recrystallization of supercritical fluids, etc.

The Liquisolid process is a new and effective approach to enhance the solubility of poorly water-soluble drugs. According to this process, water-insoluble drugs can be converted into non-adherent, dry-looking, free-flowing, and acceptably compressible powders by incorporating in suitable non-volatile solvents, and by use of appropriate carrier materials and coating materials. Finally, a liquisolid dosage is formulated that can be capsulated or compressed into tablets.

1.2 Liquisolid systems [2-4]

Liquisolid technique is a novel and advanced method for dissolution and solubility enhancement of poorly water-soluble drugs, practically water-insoluble drugs. This technique was first introduced by Spireas et al. and applied to incorporate water-insoluble drugs into rapid-release solid dosage forms.

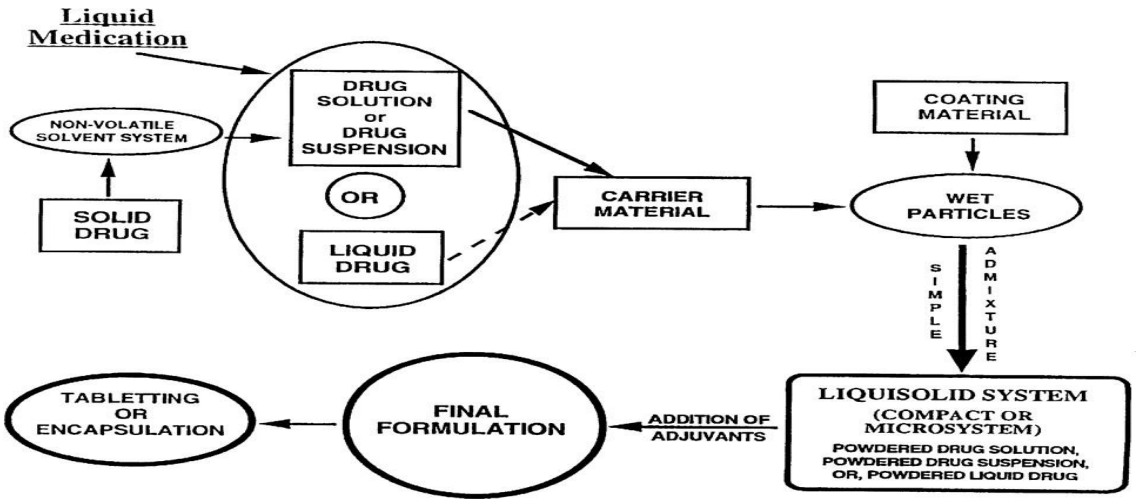

Figure No. 1: Liquisolid systems

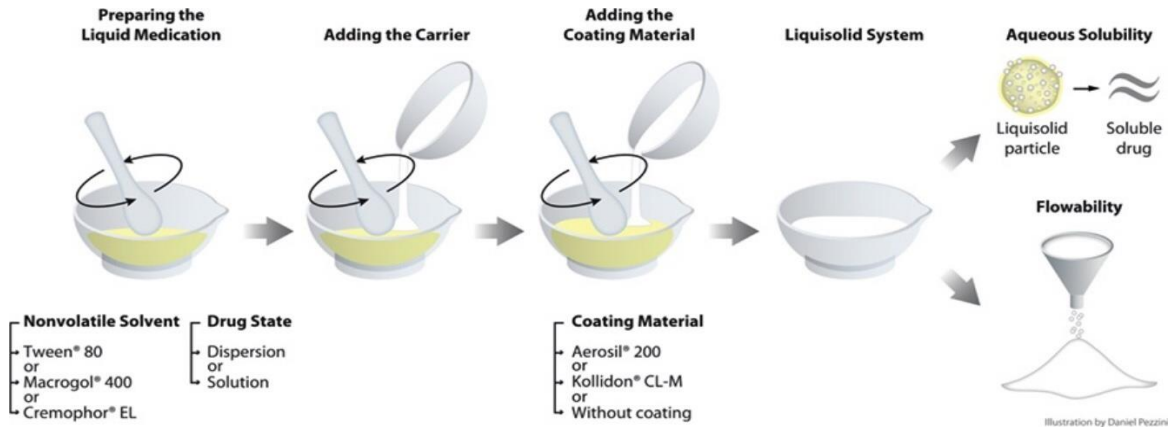

Figure No. 2: Process of formulation

1.3 Mixed solvency concept [5-24]

As per the mixed solvency concept proposed by R. K. Maheshwari, every substance present in the universe has got solubilizing property i.e., all the liquids, gases, and solids possess solubilizing power. As per his statement, each substance is a solubilizer.

In the case of gases, the molecules of gas may come in a liquid state in two ways:

i. By liquefaction: In supercritical fluid technology, carbon dioxide is liquified at a particular temperature and pressure. The solvent action of molecules of carbon dioxide is utilized for the preparation of nanoparticles, for extraction of active constituents from herbal powders, for purification of compounds, etc.

ii. By dissolution of gas in a solvent: Concentrated hydrochloric acid is such an example. The molecules of hydrochloric acid gas come in a liquid state after dissolution in water. The solubility of a poorly water-soluble drug, nalidixic acid, in concentrated hydrochloric acid is about 5 % w/v. Hydrogen bonding and weak Van der Waals forces between the molecules of nalidixic acid and the molecules of hydrochloric acid play the role.

In cases of solids, the molecules of solid come in a liquid state in three ways:

i) By melting: Molecules of a solid may come in the liquid state by melting. Example - Melted urea (a clear colorless liquid at about 132 ºC m.p.) has good solubilizing power for diclofenac sodium (m.p. 283 ºC). One gram melted urea at about 132 ºC easily dissolves one gram of diclofenac sodium.

ii) By dissolution in a solvent: Molecules of a solid may come in a liquid state when the solid is dissolved in a solvent.

Example- Solubility of ibuprofen in water is 0.028 %. Solubility of ibuprofen in 2 M sodium benzoate (28.8 % w/v) solution is 2.390 % (84-fold solubility enhancement).

iii) By eutectic formation: Molecules of solid can also come in a liquid state by the formation of eutectic mixtures. Example - When an equal proportion of menthol and thymol are triturated together, a clear, colorless eutectic liquid is obtained. This eutectic liquid is good solvent for metronidazole, atenolol, ornidazole, resorcinol, BHA, salicylic acid, etc.

Table No. 1: Applications of mixed solvency in pharmaceutical formulation development

Sr. No.	Name of drug	Formulation	Name of solubilizers employed	Purpose of mixed solvency	References
1	Furosemide	Fast dissolving oral film.	Sodium caprylate, sodium benzoate, sodium citrate, and niacinamide.	To improve drug loading.	Garima Carpenter
2	Cefixime	Liquisolid system	Sodium acetate, sodium caprylate, and propylene glycol.	To increase the release rate of the drug.	Rinshi Agrawal
3	Hydrochlor-othiazide	Aqueous Injection	Tween80, ethanol, PEG 400, sodium benzoate, PVP K25, PEG 4000	To increase the solubility of the poorly water-soluble drug.	Himanshi Gupta
4	Candesartan cilexetil	Dry powder Injection for	Sodium Caprylate,	To increase the solubility	Neelesh Maheshwari

		reconstitution	Sodium benzoate, Sodium citrate, Sodium acetate, Beta cyclodextrin	of the poorly water-soluble drug.	
5	Torsemide	Solid dispersion (Fast dissolving)	Sodium acetate, Sodium citrate, Sodium caprylate, Beta cyclodextrin.	To improve solubility and ensure fast dissolving formulation	Jaydeep Singh Baghel
6	Nimesulide	Aqueous topical solution and gel	Sodium benzoate, Sodium caprylate, Sodium oleate, Benzyl alcohol, Propylene glycol.	To increase the solubility of the poorly water-soluble drug.	Pawan Mulani
7	Piroxicam	Liquisolid system	Sodium caprylate, Sodium acetate, Sodium benzoate, Niacinamide.	To increase the release rate of the drug.	Shruti Jain

2. PREFORMULATION STUDIES

2.1 Preparation of calibration curves

2.1.1 Preparation of calibration curve of hydrochlorothiazide in D.M. water

About 50 mg of hydrochlorothiazide drug was weighed accurately and transferred to a 50 ml volumetric flask. The drug was dissolved by the addition of 20 ml of 30 % sodium benzoate

solution and volume was made up to 50 ml with demineralized water, to obtain a solution of 1000 mcg/ml. One ml of the above solution was taken and diluted up to 50 ml with D.M. water to obtain the dilution of 20 mcg/ml concentration. Likewise 2.0 ml, 3.0 ml, 4.0 ml, 5.0 ml solutions were taken and diluted up to 50 ml to obtain dilutions of 40, 60, 80 and 100 mcg/ml concentrations, respectively. Absorbances of these solutions (20, 40, 60, 80, 100 mcg /ml) were measured at 317 nm against respective reagent blanks on the Shimadzu-1700 UV spectrophotometer.

Table No. 2: Absorbance data for calibration curve of hydrochlorothiazide in D.M. water (in presence of sodium benzoate) at 317 nm

Sr. No.	Concentration of drug (mcg/ml)	Mean of absorbances ± Standard Deviation (n=3)
1	0	0.000 ± 0.00
2	20	0.235 ± 0.0017
3	40	0.489 ± 0.0023
4	60	0.738 ± 0.0036
5	80	0.942 ± 0.0112
6	100	1.196 ± 0.0056

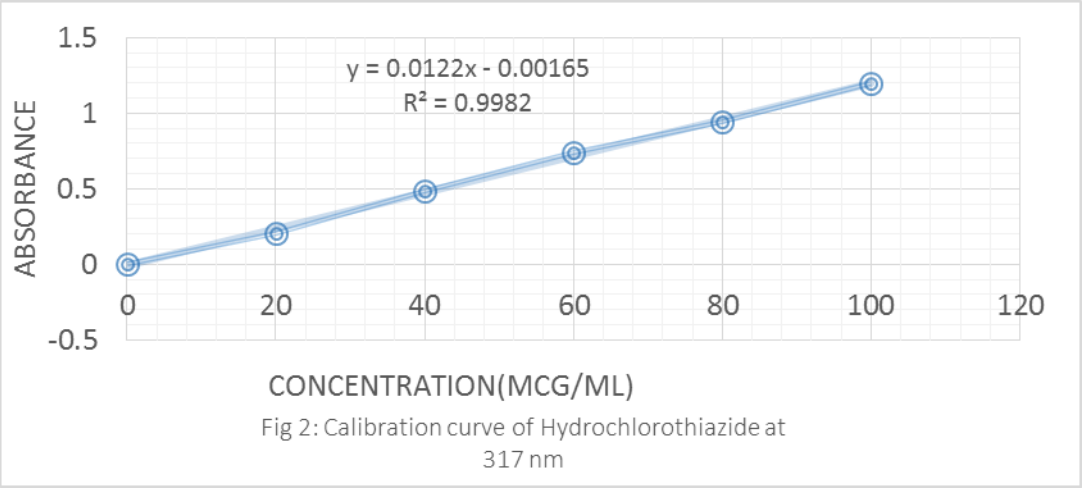

Figure No. 3: Calibration curve of Hydrochlorothiazide in D.M. water at 317 nm

2.1.2 Preparation of calibration curve of hydrochlorothiazide in 0.1 N HCl

The calibration curve was prepared in 0.1N HCl in presence of sodium caprylate. The

sodium caprylate solution (20 %w/v) was prepared in Milli Q water. For calibration curve, 50 mg drug was taken in 50 ml volumetric flask and dissolved in 20 ml of 20 % sodium caprylate solution and the volume was made up to 50 ml with 0.1 N HCl. This stock solution of 1000 mcg/ml was appropriately diluted to prepare solutions of different concentrations (20-100 mcg/ml). The absorbances of these solutions were noted at 317 nm against respective reagent blanks. It was repeated three times.

Table No. 3: Absorbance data for calibration curve of hydrochlorothiazide in 0.1 N HCl at 317 nm

Sr. No.	Concentration (mcg/ml)	Mean of absorbances ± Standard Deviation (n=3)
1	0	0.00 ± 0.000
2	20	0.197 ± 0.0010
3	40	0.396 ± 0.0015
4	60	0.613 ± 0.0021
5	80	0.795 ± 0.0012
6	100	0.992 ±0.0035

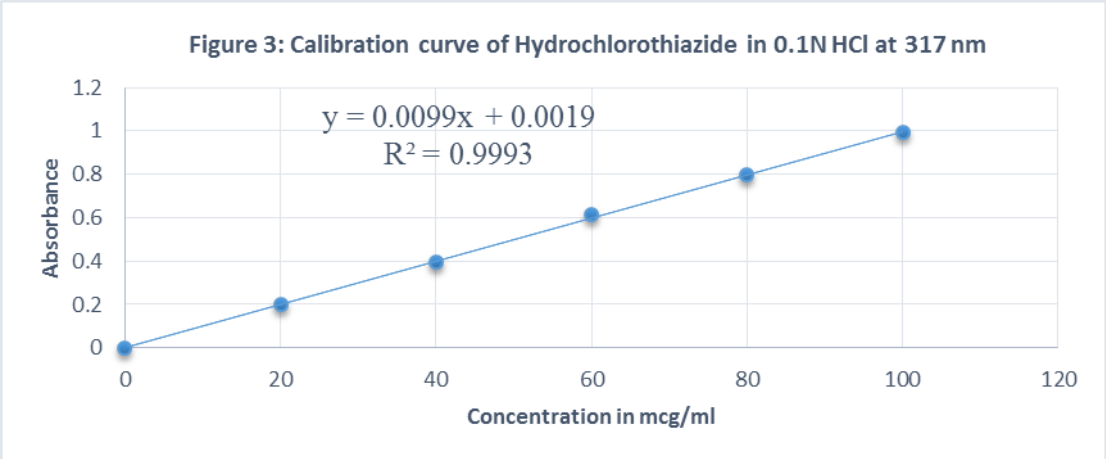

Figure No. 4: Calibration curve of Hydrochlorothiazide in 0.1 N HCl at 317 nm

2.2 DEVELOPMENT OF SOLVENT SYSTEM

Since the determining solubility of hydrochlorothiazide in propylene glycol is less than the desired solubility, the mixed solvency approach was used to create a solvent system in which various solid solubilizers were dissolved as per their respective safe concentrations in the propylene glycol and PEG400 and making them a strong solvent which can be used for the preparation of dosage form. Various solid solubilizers were used individually or in combination for the preparation of blends and drug solubility studies were performed.

2.2.1 Approximate solubility of various solubilizers in propylene glycol

Procedure:

1 ml of propylene glycol was taken in a 10 ml volumetric flask, 10 mg sodium caprylate (SC) was added to it and shaken on vortex for about 20 mins to get it dissolved. As soon as it gets dissolved 10 mg more SC was added to it and again shaken on vortex for about 20 minutes. The same procedure was repeated till a suspension was obtained. It was found that 300 mg sodium caprylate was dissolved in 1 ml of propylene glycol to get a clear solution. After the addition of 10 mg more of SC, a suspension was obtained. Similarly, the solubility of sodium benzoate and PVP K25 was determined in propylene glycol.

Table No. 4: Approximate Solubility of various solubilizers in propylene glycol

Solubilizers (abbreviation)	Approximate solubility in propylene glycol (% w/v)
Sodium caprylate (SC)	30
PVP K25	5
Sodium benzoate (SB)	5

2.2.2 Approximate solubility of various solubilizers in PEG 400

Procedure

1 ml of PEG 400 was taken in10 ml volumetric flask,10 mg sodium caprylate (SC) was added to it and shaken on vortex for about 20 mins to get it dissolved. As soon as it gets dissolved,10 mg more SC was added to it and again shaken on vortex for about 20 mins. The same procedure was repeated till a suspension was obtained. It was found that 100 mg of sodium

caprylate was dissolved in 1 ml of PEG 400 to get a clear solution. After the addition of 10 mg excess of SC (total 110 mg), a suspension was obtained. Similarly, the solubility of sodium benzoate and PVP K25 was determined in PEG 400.

Table No. 5: Approximate solubility of various solubilizers in PEG 400

Solubilizers (abbreviation)	Approximate solubility in PEG 400 (% w/v)
Sodium caprylate (SC)	10
Sodium benzoate (SB)	5
PVP K25	5

2.2.3 Determination of approximate solubility of hydrochlorothiazide in Propylene glycol and PEG 400

Procedure-

1 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 for about 20 min., again 2.5 mg drug was added in batches until a suspension was obtained and solubility was noted. 1ml of PEG 400 was taken in 10 ml volumetric flask, and 2.5 mg drug was added to it, with vigorous shaking on vortex for about 20 mins, again 2.5 mg drug was added in batches until a suspension was obtained and solubility was noted.

0.5 ml of propylene glycol and 0.5 ml of PEG 400 were taken together in a 10 ml volumetric flask, and 2.5 mg drug was added to it, with vigorous shaking on vortex for about 20 min, again 2.5 mg drug was added in batches until a suspension was obtained and solubility was noted.

In the above study, it was noted that both propylene glycol and PEG 400 are weak solvents for hydrochlorothiazide. To accentuate on mixed solvency concept the use of solid solubilizers in safe concentrations was done to enhance the drug loading in a mixture of 50 % propylene glycol and 50 % PEG 400. The results are shown in Table No. 6.

Table No. 6: Results of approximate solubility studies of hydrochlorothiazide in propylene glycol and PEG 400

Sr. No.	Solvent system	Approximate solubility
1	Propylene glycol	15.0 mg/ml
2	PEG 400	32.5 mg/ml
3	50% PG + 50% PEG 400	35.0 mg/ml

2.2.4 Results of approximate solubility studies of hydrochlorothiazide in various blends

Various blends were prepared with different concentrations of solubilizers and 2.5 mg drug was added to 1 ml of each blend, the vials were shaken for about 20 minutes to dissolve the drug completely, again 2.5 mg drug was added in batches with shaking for 20 minutes until a suspension was obtained. A similar procedure was followed for all the blends and the solubility of the drug was determined. The results are shown in Table No. 7.

Table No. 7: Results of approximate solubility studies of hydrochlorothiazide in various blends

Blend No.	Composition	Approximate Solubility
1.	25% SC + 5% PVP K25 + 1 ml PG	35 mg/ml
2.	25% SC + 1 ml PG	37.5 mg/ml
3.	15% SC + 5% PVP K25 + 5% SB + 1ml PG	32.5 mg/ml
4.	20% SC + 5 % PVP K25 + 5% SB + 5% B-cyclodextrin + 0.5ml PEG 400 + 0.5 ml PG	27.5 mg/ml
5.	20% SC + 0.5ml PEG 400 + 0.5 ml PG	75 mg/ml
6. (Blend A)	5% SC + 2.5% SB + 2% PVP K25 + 0.5ml PG + 0.5ml PEG 400	125 mg/ml
7.	5% SC + 5% SB + 5% PVP K25 + 0.8 ml PG + 0.2 ml PEG 400	55 mg/ml (solidifies)
8. (Blend B)	10% SC + 2.5% SB + 2% PVP K25 + 0.5 ml PEG 400 + 0.5 ml PG	137.5 mg/ml
10.	5% SC + 2% PVP K25 + 2.5%SB + 1ml PG	77.5 mg/ml
11.	30% SC + 5% SB + 5% PVP K25 + 2 drops benzyl alcohol + 1 ml PG	45mg/ml

12.	15% SC + 5% SB + 5% PVP K25 + 10% B cyclodextrin + 1 ml PG	35mg/ml
13.	5%SC + 5% SB + 0.5 ml PEG 400 + 0.5ml PG	60 mg/ml
14.	10% SC + 2.5%SB + 2% PVP K25 + 1ml PG	65 mg/ml
15. (Blend C)	8% SC + 3.5% SB + 2% PVP K25 + 0.5ml PEG400 + 0.5 ml PG	130 mg/ml
16.	8% SC + 3.5% SB + 2% PVP K25 + 1ml PG	80 mg/ml

PVP K25- Polyvinyl pyrrolidone K25, **SB** - Sodium benzoate, **SC** - Sodium caprylate, **PG-** Propylene glycol, **PEG 400**- Polyethylene glycol

2.2.5 Determination of equilibrium solubility of hydrochlorothiazide in selected blends:

Procedure

4 ml of selected blends from approximate solubility studies were filled in clean glass vials and the drug was added in excess amount. The vials were then sealed and kept on a mechanical shaker for 24 hours. After completion of 24 hours, the vials were kept undisturbed for 12 hours to eliminate the chances of supersaturation. The solutions were then filtered through Whatman grade 41 filter and examined under UV spectroscopy after appropriate dilutions with Milli Q. water and equilibrium solubility were calculated.

Table No. 8: Results of equilibrium solubility study of hydrochlorothiazide in selected blends

Blend	Composition of blend	Equilibrium solubility
A	5% SC + 2.5% SB + 2% PVP K25 + 0.5ml PG + 0.5ml PEG 400	142.012 mg/ml
B	10% SC + 2.5% SB + 2% PVP K25 + 0.5ml PEG 400 + 0.5ml PG	158.220 mg/ml
C	8% SC + 3.5% SB + 2% PVP K25 + 0.5ml PEG400 + 0.5 ml PG	146.113 mg/ml

PG- Propylene glycol, **PEG 400**- Polyethylene glycol **SB** - Sodium benzoate, **SC** - Sodium caprylate, **PVP K25-** Polyvinyl pyrrolidone K25

2.3 Equilibrium solubility of hydrochlorothiazide in different mediums

Solubility studies in different aqueous mediums were carried out by adding an excess amount of drug (hydrochlorothiazide) in the 5 ml of respective mediums in clean glass vials and sealed and kept on a mechanical shaker at room temperature for 24 hours and then kept undisturbed for 12 hrs. Then, the solutions were filtered through the Whatman grade 41 filter. The absorbances of the solutions were measured at 317 nm on a double beam UV/Visible spectrophotometer after appropriate dilution with respective medium. The results are reported in Table No. 9.

Table No. 9: Equilibrium solubility of hydrochlorothiazide in different mediums

Sr. No.	Solvent	Solubility (mg/ml)	Description
1	Demineralized Water	0.624	Very slightly soluble
2	0.1 N HCl	0.245	Very slightly soluble

2.4 Drug–solubilizers interference studies in UV spectrophotometric analysis

It was important to study that the solubilizers to be used must not interfere with the absorbance of the drug at 317 nm to make accurate estimations. For this, 100 mg of drug was taken in 100 ml volumetric flask and dissolved in 30 ml ethanol by shaking on vortex for about 5 - 10 mins to get drug dissolved, then the volume was made up to 100 ml with Milli Q water. So, a 1000 mcg/ml stock solution was prepared.

100 mg sodium caprylate or other excipient was taken in another 100 ml volumetric flask and dissolved using 50 ml of Milli Q. water and then the volume was made up to 100 ml with Milli Q. water to get 1000 mcg/ml stock solution.

2 ml of drug solution and 10 ml of sodium caprylate solution were then taken in another 100 ml volumetric flask and volume was made up to 100 ml using Milli Q water. So here, 20 mcg/ml drug solution was prepared and the solution of sodium caprylate was of 100 mcg/ml and absorbance of the drug was noted against reagent blank at 317 nm.

A similar experiment was performed for all the other excipients such as PVP K25, sodium benzoate, propylene glycol, PEG 400, and ethanol. Here it is important to know that the

absorbance of drug solution of concentration 20 mcg/ml was reported to be 0.217 against Milli Q water.

Result: The values of absorbances in presence of solubilizers and the absorbance of drug solution were approximately the same. Therefore, it was concluded that the solubilizers were not interfering in the UV spectrophotometric analysis of the drug at 317 nm.

2.5 Drug excipient interaction studies

The compatibility of the drug with the excipient was assessed by drug-excipient interaction studies. The drug was mixed with excipient in 1:1 ratio in separate clear glass vials which were then properly sealed and kept undisturbed at different temperature conditions; at room temperature, and in the refrigerator for one month. After every week, vials were withdrawn and contents were observed for any change in their physical appearance. No changes were found in the appearance, hence the drug and excipients did not interact with each other.

3. FORMULATION DEVELOPMENT AND EVALUATION

3.1.1 Selection of solvent system

For the formulation of fast release liquisolid system, a non-volatile solvent system was selected. The non-volatile solvent should be inert, must have a high boiling point, should be preferably water-miscible, and should not be highly viscous and it should have a high boiling point. An equal mixture of Propylene Glycol and PEG 400 was selected in ratio 1:1 in the proposed research work.

Since the solubility of the drug was very less in the 1:1 PG: PEG 400 solvent system, different blends were prepared by dissolving solid solubilizers (use of mixed solvency concept) in the proposed solvent system to make it a strong solvent for dissolving the drug.

Further blend A, Blend B, and Blend C were selected for further studies as they showed a maximum drug solubility.

3.1.2 Selection of carrier and coating material

It is a preferably porous material with sufficient properties of absorption. To be used as carriers, materials with a porous surface and tightly matted fibers in their interior, such as microcrystalline and amorphous cellulose powder and granular grades, are most preferred.

MCC (microcrystalline cellulose) grade PH-200 (with particle size 180 micron) was selected as a suitable carrier in the formulation. The amount of carrier used to make liquid vehicle free-flowing plays an important part in determining the weight of the powder, therefore the carrier with maximum flowable liquid retention potential - (phi value) was selected.

The resulting wet mixture obtained after mixing a suitable amount of carrier is converted into dry-looking, nonadherent, free-flowing, and readily compressible powder by the addition of the calculated amount of coating material. Coating material should be fine and have high absorptive particles. Aerosil, in a concentration of 5 %, was selected as a coating material for further studies. The ratio of the carrier: coating material can be in the range from 50:1 ratio to 5:1 ratio.

Procedure

1 ml of Blend A was taken in a mortar and a sufficient amount of carriers were added (little at a time in batches) till free-flowing powder was obtained using trituration with a pestle. For this, an excess amount of carrier was pre-weighed and kept on butter paper. After obtaining free-flowing powder, the remaining carrier was reweighed and the actual amount required was determined. The results are shown in Table No. 10.

Table No. 10: Selection of carrier material

Sr. No.	Carrier material	Blend A	Approximate amount of carrier required to make powder free-flowing
1	Avicel PH200 (MCC)	1 ml	3345 mg
2	Lactose	1 ml	12541 mg
3	$MgCO_3$	1 ml	2527 mg
4	Talc	1 ml	3981 mg

Based on the above results, MCC was selected as carrier material for further formulation development. $MgCO_3$ was not selected as a carrier material as it shows drug re-adsorption properties.

3.1.3 Preparation method of Liquisolid system

The Blend A (3.8 ml), Blend B (3.3 ml), Blend C (3.6 ml) were taken in the cleaned and dried pestle mortar separately and correctly weighed 500 mg drug was dissolved in them by mixing it by trituration, thus obtaining a clear solution. Into the drug solution, a calculated amount of carrier 7750 mg (LS-01), 6720 mg (LS-02), 7205 mg (LS-03) was added and the drug solution was allowed to adsorb. The mixture was triturated and examined for adhesiveness of the powder and the remaining amount of carrier was again added to decrease the adhesiveness. Further, coating material was added to it by continuous mixing it by trituration. Taking 25 mg as the dose of drug hydrochlorothiazide, 20 doses of liquisolid system were prepared using a carrier and coating material in the quantities noted in Table No. 11. A single dose (25 mg drug) consisted of 640.25 mg powder for LS-01, 556.20 mg powder for LS-02, and 614.10 mg powder for LS-03.

Table No. 11: Quantity of carrier and coating material used for dosage form formulation

Batch No.	Carrier material	Amount of carrier used(mg)	Coating material	Amount of coating material used(mg)	Blend	The volume of blend used (ml)	Net wt. (gm)
LS-01	Avicel PH200	7750	Aerosil	600	A	3.8	12.805
LS-02	Avicel PH200	6720	Aerosil	600	B	3.3	11.124

3.2 EVALUATIONS OF PREPARED LIQUISOID SYSTEM

3.2.1 Drug content

For drug content determination, liquisolid formulation powder equal to 12.50 mg drug was taken in a 500 ml volumetric flask. About 350 ml of 0.1N HCl was added to the volumetric flask and the flask was shaken continuously for 30 minutes and the volume was made up to 500 ml with 0.1 N HCl. The absorbance was then noted at 317 nm in UV spectra against 0.1 N HCl as blank.

Table No. 12: Drug content in various batches

Batch No.	Amount analyzed (mg/500 ml)	Drug present %
LS-01	12.44	99.52
LS-02	12.22	97.77
LS-03	12.33	98.64

3.2.3 Dissolution profile

The dissolution profile of each batch was studied to select the most suitable batch for scale-up. For dissolution studies, 0.1N HCl was taken as dissolution media, and the basket rotation speed was kept at 100 rpm at 37 ± 0.5˚C in 900 ml of media. After 1 minute, a 20 ml sample was withdrawn from dissolution media for analysis, and an equal quantity of media was added. A similar procedure was repeated after different time intervals. Table No. 13 shows the quantity of liquisolid powder in each batch capsule used for dissolution studies.

Table No. 13: Amount of powder in each capsule used in dissolution studies

Batch	Amount of powder in capsule	Dose of drug
LS-01	643.33 mg	25 mg
LS-02	568.94 mg	25 mg
LS-03	622.56 mg	25 mg

3.2.3.1 LS-01

Table No. 14: Data for dissolution study (BLEND A)

Time (min)	(%) Cumulative drug release
01	1.49
02	3.80
05	56.69
10	86.26
15	94.95
30	98.07
45	99.77
60	99.72

3.2.3.2 LS-02

Table No. 15: Data for dissolution study (BLEND B)

Time (min)	(%) Cumulative drug release
01	0.8
02	4.81
05	64.52
10	75.12
15	78.36
30	88.46
45	90.31
60	92.96

3.2.3.3 LS-03

Table No. 16: Data for dissolution study (BLEND C)

Time (min)	(%) Cumulative drug release
01	0.67
02	2.79
05	48.04
10	74.6
15	75.04
30	79.76
45	82.24
60	82.26

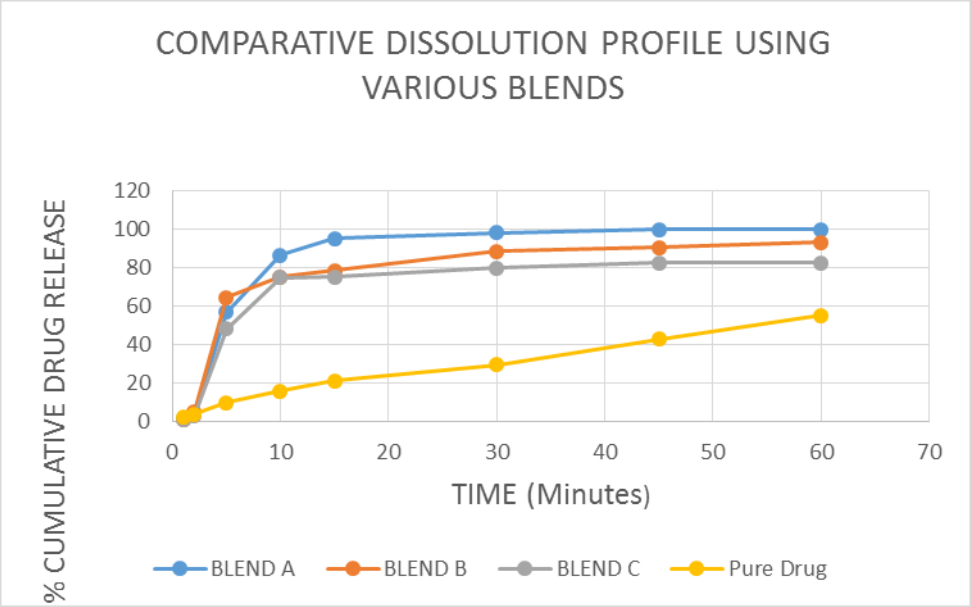

Figure No. 5: Comparative dissolution profile using various blends

3.2.3.4 Dissolution profile of pure drug (hydrochlorothiazide)

Table No. 17: Data for dissolution study of pure drug

Time (min)	(%) Cumulative drug release
01	2.04
02	3.45
05	9.67
10	15.49
15	20.98
30	29.14
45	42.76
60	55.06

From the various dissolution profiles of the different batches, it was shown that almost all the batches released 50 % of the drug within 5 minutes, as compared to the pure drug where only 9.67 % drug was released within 5 minutes. Further, the flow properties of these batches were performed to decide the suitable optimized final batch for further studies.

3.2.4 Flow property

Tapped density is considered to be a fundamental parameter for assessing the behavior of flow and a method for assessing the compressibility of powders. It specifies the compression efficiency and is responsible for influencing the different parameters of the ideal tablet or for measuring the amount of powder to be filled in the capsule filler or hopper. The tapped density of the liquisolid system thus formed was determined by the USP II method using Electrolab Tap Density Tester, having 250 taps per minute.

3.2.4.1 LS-01

Weight of sample = 5.50 gm

Initial Volume of sample (V_0) = 16.20 ml

Volume of sample after 500 tappings (V_1) = 14.0 ml

Volume of sample after 750 tappings (V_2) = 13.50 ml

$$(V_1 - V_2)/ V_1 \% = 3.571 \%$$

Volume of sample after 1250 tappings (V_3) = 13.0 ml

$$(V_2 - V_3)/V_2 \% = 3.703 \%$$

Table No. 18: Data for flow properties of LS-01

Flow properties	Results
Bulk density	0.340 gm/ml
Tapped density	0.423 gm/ml
Compressibility Index	19.753%
Hausners ratio	1.246

3.2.4.2 LS-02

Weight of sample = 4.50 gm

Initial Volume of sample (V_0) = 15.0 ml

Volume of sample after 500 tappings (V_1) = 13.0 ml

Volume of sample after 750 tappings (V_2) =12.5 ml

$$(V_1 - V_2)/V_1 \% = 10.714 \%$$

Volume after 1250 tappings (V_3) = 12.0 ml

$$(V_2 - V_3)/V_2 \% = 4.000 \%$$

Table No. 19: Data for flow properties of LS-02

Flow properties	Results
Bulk density	0.300 gm/ml
Tapped density	0.375 gm/ml
Compressibility Index	20.00 %
Hausners ratio	1.250

3.2.4.3 LS-03

Weight of sample = 3.50 gm

Initial Volume of sample (V_0) = 12.5 ml

Volume of sample after 500 tappings (V_1) = 11.0 ml

Volume of sample after 750 tappings (V_2) = 10.50 ml

$$(V_1 - V_2) /V_1 \% = 4.544 \%$$

Volume after 1250 tappings (V_3) = 10.00 ml

$$(V_2 - V_3)/ V_2 \% = 4.762 \%$$

Table No. 20: Data for flow properties of LS-03

Flow properties	Results
Bulk density	0.280 gm/ml
Tapped density	0.350 gm/ml
Compressibility Index	19.89 %
Hausners ratio	1.250

3.3 Thin layer chromatography studies

To examine the possibility of interaction between drug and solubilizers, thin layer chromatographic studies were performed. A plate of silica gel GF 254 was activated at 110°C for 1 hour and then used.

The solution of hydrochlorothiazide in acetone alone and the aqueous solubilizers blends containing hydrochlorothiazide in LC-01, LC-02, and LC-03 were spotted with the aid of a microdropper on the baseline. Then, the plate was left in the air for sufficient time to dry and transferred to a solvent jar saturated with the solvent system ethyl acetate and 20 % sodium caprylate solution.

After drying the plate for sufficient time, it was observed for visualization of spots under the iodine chamber. The respective Rf values were determined and recorded in Table No. 21.

Table No. 21: R_f values of hydrochlorothiazide present in different solutions

Solvent System	Adsorbent	R_f Value			
		HCTZ/acetone	LC-01	LC-02	LC-03
Ethyl acetate	Silica Gel GF 254	0.44	0.49	0.46	0.51
20 % Sodium caprylate	Silica Gel GF 254	0.43	0.44	0.50	0.48

Inference-

The results of the TLC study revealed that there was no significant difference in R_f values of hydrochlorothiazide solubilized in acetone and hydrochlorothiazide solubilized in solubilizers blend solutions. From the results of the TLC study, it can be concluded that there is no salt formation or complexation of drugs with solubilizer molecules. It can also be concluded that

toxic organic solvents can be safely replaced by safe hydrotropic agents. TLC did by 20 % sodium caprylate solution also proved that the solids possess the solubilizing power.

3.4 Final batch preparation

From the trial batches, LS-01 was selected as the final batch based on the dissolution profile. The batch size was scaled up, to study the effect of various variables such as the amount of carrier, dissolution profile, and disintegration time studies. For final batch studies, 9.5 ml of Blend A was taken in the cleaned and dried pestle mortar, and correctly weighed 1250 mg drug was dissolved in it by mixing it by triturating, yielding a clear solution. Into the solution, a calculated amount of carrier, 19,375 mg avicel PH200 was added and allowed to adsorb the drug solution. The same procedure was repeated as with liquisolid preparation in the trial batches.

Considering 25 mg as the dose of drug hydrochlorothiazide 50 doses of liquisolid system were prepared using 9.5 ml of Blend A and 1250 mg of the drug.

3.4.1 Evaluations

The LS-01 was chosen as the final batch and after preparation of this batch, the formulation was subjected to evaluation for various parameters.

For the evaluation of the formulation, the tests performed were

- Determination of drug content of liquisolid formulation
- Disintegration time of capsules filled with liquisolid formulation
- Comparative dissolution profile
- Flow properties of liquisolid formulation

3.4.1.1 Drug content

To determine the drug content, liquisolid formulation equal to 12.50 mg drug was taken in a 500 ml volumetric flask. About 300 ml of 0.1N HCl was added to the volumetric flask and the flask was continuously shaken for 30 minutes and the volume was made up to 500 ml with 0.1 N HCl. After filtration, the absorbance was then taken at 317 nm in UV spectra. The amount

of drug analyzed was found to be 12.36 mg and the drug content in the scale-up batch was found to be 98.92 %.

3.4.1.2 Disintegration Time studies

Six capsules were individually put into disintegration tubes. In the disintegration beaker, 900 ml 0.1 N HCl was filled and the disintegration test was conducted at 37^{o}C ± 2^{o}C, at 28 - 32 cycles per minute frequency. The disintegration period of capsules filled with batch LS-01 of liquisolid formulation was found to be ranging from 57 seconds and 3 minutes and 10 seconds.

3.4.1.3 Comparative dissolution profile

The dissolution of the prepared batch was conducted against the same pure drug (PD) and tableted marketed formulation (TMF). Liquisolid formulation equal to 25 mg drug was filled in a "00" size capsule. Dissolution studies of the capsule were performed using 0.1 N HCl as dissolution media and the basket rotation speed was kept at 100 rpm at 37 ± 0.5 ˚C in 900 ml of media. After 1 minute, a 20 ml sample was withdrawn from dissolution media for analysis, so 20 ml of 0.1 N HCl was replaced in dissolution media. After 2 minutes, again 20 ml sample was withdrawn, and again dissolution media was replaced by 0.1 N HCl. A similar procedure was repeated after different time intervals.

Table No. 22: Dissolution profile of capsule containing liquisolid (final batch)

Time (min)	(%) Cumulative drug release
01	1.27
02	3.42
05	54.74
10	81.09
15	89.24
30	95.07
45	97.24
60	97.89

Table No. 23: Dissolution profile of marketed 25 mg tablet "AQUAZIDE"

Time (min)	(%) Cumulative drug release
01	1.08
02	2.02
05	27.69
10	58.25
15	76.90
30	89.69
45	95.05
60	95.42

Table No. 24: Comparative dissolution profiles of final batch preparation, pure drug, and marketed formulation

Time (min)	(%) Cumulative drug release		
	Pure Drug	Aquazide tablet (MFT)	Final batch (Capsule)
01	2.04	1.08	1.27
02	3.45	2.02	3.42
05	9.67	27.69	54.74
10	15.49	56.25	81.09
15	20.98	76.90	89.24
30	29.14	89.69	95.07
45	42.76	95.05	97.24
60	55.06	95.42	97.89

From the dissolution profile of the final batch, it was observed that the capsule containing liquisolid formulation released 81.09 % of the drug within 10 minutes, and only 56.25 % drug was released from the marketed tablet formulation within 10 minutes.

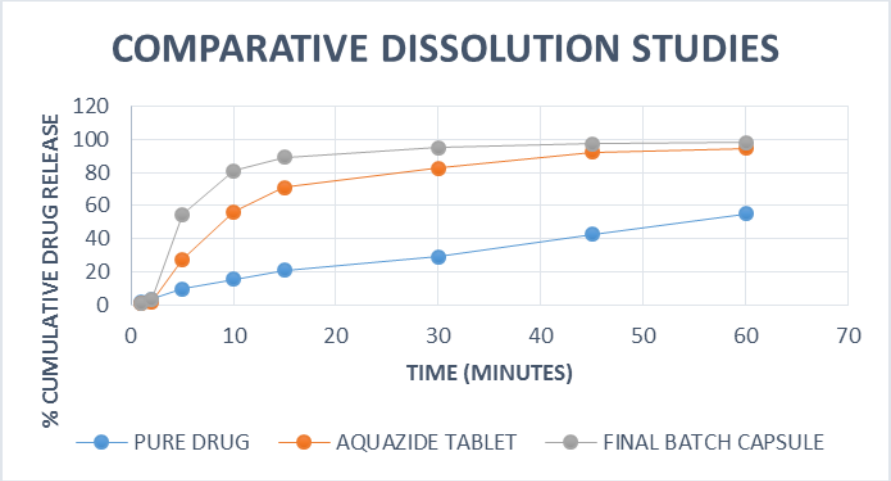

Figure No. 6: Comparative dissolution studies of the final batch, marketed tablet, and pure Drug

3.4.1.4 Flow property

Tapped density is considered a fundamental parameter to judge the flow behavior and an essential tool for process development and solid dosage manufacturing. It is used to determine the amount of powder that can fit in a hopper or capsule filler. The tapped density of the liquisolid system thus developed was calculated by Electrolab Tap density Tester by USP II method, having 250 taps per minute.

Weight of sample = 8.401 gm

Initial volume of sample (V_0) = 20 ml

Volume of sample after 500 tappings (V_1) = 18.9 ml

Volume of sample after 750 tappings (V_2) = 18.7 ml

$$(V_1 - V_2) / V_1\% = 1.05\ \%$$

Volume of sample after 1250 tappings (V_3) = 18.5 ml

$$(V_2 - V_3) / V_2\ \% = 1.06\%$$

Table No. 25: Data for flow properties of the final batch

Flow properties	Results
Bulk density	0.396 gm/ml
Tapped density	0.458 gm/ml
Compressibility Index	11.840 %
Hausner's ratio	1.144

SUMMARY AND CONCLUSION:

The current research study aimed to explore the possibilities of using small amounts of mixed solid solubilizers to increase drug loading capability in the liquisolid formulation, improve the flow property due to a decrease in the required volume of non-volatile solvent, improve drug solubility in non-volatile solvent through the use of the mixed solvency principle and fast release of a poorly water-soluble drug through its formulation as liquisolid system. The main purpose of this research is to show that solids can be used to work efficiently as solubilizing agents. In the future, these solids can be used properly for solvent action, providing alternative sources for solvents offering eco-friendly methods excluding the use of harmful organic solvents or economically beneficial solvents. To explore the concept of the mixed solvency principle to enhance solubility and thus to increase the release rate of the poorly water-soluble drug, hydrochlorothiazide was chosen as a model drug.

In this research work, a 1:1 mixture of Propylene Glycol and PEG 400 was a bad solvent for the hydrochlorothiazide drug. The solid solubilizers such as sodium benzoate, PVP K25, and sodium caprylate made Propylene Glycol: PEG 400 in ratio 1:1 a strong solvent to dissolve approximately 150 mg of drug in 1 ml of a blend (solid solubilizers were dissolved in the Propylene Glycol: PEG 400 to prepare blend). This research work shows that solids have solubilizing power. This concept of mixed solvency improves the bioavailability of the drug and decreases the release time, 80 % of the drug was released within 10 minutes from the prepared liquisolid formulation. Conventional dosage forms 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 the bioavailability of a drug.

Hydrochlorothiazide is considered a prototype member of thiazide class diuretics. It decreases electrolyte reabsorption from the renal tubules. This leads to increased excretion of water and

electrolytes, including sodium, potassium, and magnesium. It is used in the treatment of many diseases such as edema, diabetes insipidus, hypertension, and hypoparathyroidism.

For identification and characterization of the drug, UV spectrophotometric analysis, melting point range determination and differential scanning calorimetry of the drug sample were carried out. The observed values were as per the reported values in the literature.

Preformulation studies were performed which included solubility studies in various blends, preparation of calibration curves in water, and 0.1 N HCl with aid of sodium benzoate and sodium caprylate. Solubilities of hydrochlorothiazide drug samples were reported in Propylene Glycol: PEG 400 and different blends. 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 317 nm.

The fast-release liquisolid system of hydrochlorothiazide was developed using a 1:1 ratio of Propylene Glycol: PEG 400 as a non-volatile solvent. It was made as a strong solvent with the help of various solid solubilizers in small concentrations. Microcrystalline cellulose (avicel PH200) was used as a carrier material. The developed liquisolid powder exhibited about 80 % drug release within 10 mins. The optimized batches showed better dissolution behavior as compared to pure drug and tableted market formulation and the further optimized batch was evaluated for the flow properties, drug content, disintegration time, and drug release studies.

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

The principle of mixed solvency was successfully employed in formulating the fast release liquisolid formulation of poorly water-soluble drug hydrochlorothiazide. In this study, there was no involvement of organic solvents to prepare formulation. Higher costs and toxicity due to residual solvents are the major disadvantages of organic solvents. The present study demonstrates the application of the principle of mixed solvency to solve the problems of the above-mentioned organic solvent-related disadvantages and also to increase the solubility of the drug with increased drug release. Due to poor solubility of drug hydrochlorothiazide in non-volatile solvents, the formulation of the required dose of the drug was not possible as liquisolid system, which was solved using mixed solvency concept and a formulation were

prepared which showed 80 % drug release within 10 mins. Pharmaceutical companies may be benefited from this concept, not only to manufacture fast-release liquisolid system formulations but also to develop other pharmaceutical formulations.

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