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A Review Article: Mixed Solvency Concept in Formulation and Extraction

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ABSTRACT

Enhancement of solubility is one of the difficult tasks which becomes a challenge in the formulation development of a drug with poor aqueous solubility. The poor water solubility of drugs often causes significant problems in producing formulations of sufficiently high bioavailability, preventing effective use of the drugs. The 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 a 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 to reduce the concentration of individual solubilizers (used for solubility enhancement) to minimize the toxic effects of solubilizers. This review article compiles the research projects performed on the mixed solvency concept. The solubility of a large number of drugs has been enhanced by the application of the mixed solvency concept. The mixed solvency concept has been employed for the 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 a mixed-solvency concept. Also, the 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.

INTRODUCTION:

The formulation of solutions presents many technical problems to the industrial pharmacist. A growing number of new therapeutic molecules are limited by low or erratic bioavailability due to poor water solubility. A large percentage of drugs currently in preclinical and clinical development are considered poorly water-soluble. Special techniques are required to solubilize poorly water-soluble drugs. Solubility of drugs can be increased by a variety of contemporary methods such as hydrotropic solubilization, solid dispersions, inclusion complex formation, altering the pH, and using cosolvents but excess amount of these agents may have adverse effects.

The mixed solvency concept was proposed by Dr. R.K. Maheshwari in 2009.

All substances which exist in a liquid state at room temperature are known as solvents.

No solvent is the universal solvent. Whatever the name of a solvent we take, it is a good solvent for some solutes and a bad solvent for other solutes. The mixed solvency concept proposed by Dr. R.K. Maheshwari states that and everything present in this universe has got solubilizing power whether it is gas, liquid, or solid. All substances are known as solubilizers. Each substance (solubilizer) is a good solubilizer for some solutes and a bad solubilizer for other solutes.

The name mixed solvency concept illustrates that a concentrated solution containing small concentrations of different solubilizers may give additive solvent actions or decreased solvent actions or synergistic solvent actions.

A concentrated solution may be made by using a combination of several solubilizers in safe concentrations. If this solution increases the solubility of insoluble drugs sufficiently then this technique may solve the problem of toxicity issue in pharmaceutical formulations.

- Any poor solvent for a particular solute may be made a strong solvent by the use of proper solubilizers.

- The mixed solvency concept may reduce the total concentration of individual solubilizers necessary to produce a modest increase in solubility by employing additives in lower concentrations from the point of view of the safety of solubilizers. This approach shall be applicable to prepare different dosage forms of the poorly soluble drugs.

- The mixed solvency approach can be utilized to perform titrimetric and spectrophotometric analysis of poorly soluble drugs precluding the use of organic solvents.

- The approach shall be useful to develop various novel drug delivery systems using safer mixed solvent systems precluding the use of toxic, pollutant organic solvents.

- Synergistic action in solvent character can be obtained. For example, solubilities of ibuprofen in aqueous solutions of 40 % w/v PEG-400, 40 % w/v PEG-4000, 40 % w/v urea, and 40 % w/v sodium citrate are 0.593% w/v, 0.440% w/v, 0.599 % w/v and 0.531% w/v, respectively. However, an aqueous solution made by mixing 10% w/v each of PEG-400, PEG-4000, urea and sodium citrate (total dissolved substances 40 % w/v) has solubility of 1.329% w/v for ibuprofen. This shows synergistic solvent action due to application of mixed solvency concept.

Dissolution

Dissolution of a solute in a solvent involves hydrogen bonding and weak van der Waals forces between molecules of solute and molecules of solvent. Whatever matter exists in a liquid state at room temperature is known as a solvent. Each liquid (solvent) possesses good solubilizing power for some solutes and bad solubilizing power for other solutes. About 35% of drugs are water-soluble and about 65% of drugs are water-insoluble. This means water is a good solvent for some solutes (e.g. for 35% drugs) and a bad solvent for other solutes (e.g. for 65% drugs). Thus, we can say that water possesses good solubilizing power for some solutes and bad solubilizing power for other solutes. Similarly, each matter (liquid, gas, or solid) is known as a solubilizer in the mixed solvency concept. Molecules of all solids (in liquid state) and gases (in liquid state) also possess good solubilizing power for some solutes and bad solubilizing power for other solutes.

SOLID AS SOLVENT

The molecules of a solid may come in the liquid state in three ways:

A. By melting

B. By dissolution in a solvent

C. By eutectic formation

Once the molecules of a solid come in a liquid state, the molecules of solid can be involved in hydrogen bonding weak van der Waals forces with the molecules of solute.

A. By melting

Molecules of solids may come in the liquid state by melting

Melted urea (a clear colorless liquid at about 132℃, its m.p.) has good solubilizing power for diclofenac sodium (m.p. 283℃). One gram of melted urea (at about 132 ℃) easily dissolves 1 gm of diclofenac sodium. Diclofenac sodium (m.p. 283 ℃) does not melt at 132℃ (temperature of melted urea) rather diclofenac sodium is dissolved by melted urea. (Note-This is just proof that melted solid has solvent action. Do not relate with dosage form etc.)

One gram clear colorless melted phenol at about 44℃ (m.p. of phenol is 44℃) dissolves about 500 mg of nalidixic acid (m.p. 230℃). This means, melted phenol has very good solubilizing power for nalidixic acid.

(Note-This is just proof that melted solid has solvent action. Do not relate with dosage form etc.)

B. By eutectic formation

Table-1 and Table-2 illustrate the fact that eutectic liquid possesses good solubilizing properties for compounds listed in the left column. Eutectic liquid possesses bad solubilizing properties for compounds listed in the right columns. If we check the solubilities of a large number of compounds, some will fall in the left column and others will fall in the right column. Thus, we can say that eutectic liquid is behaving like a solvent. It is thus proved that eutectic liquid is a solvent. Hence, the two solid components (menthol and thymol) of this eutectic liquid have solubilizing power. The molecules of thymol and menthol are available in a liquid state to demonstrate their solubilizing properties as a result of hydrogen bonding and weak van der Waals forces between the molecules of solute and molecules of solids (thymol and menthol).

Table No. 1: Eutectic Mixture (Thymol: Menthol 1: 1) pH 6.5

Compounds having good solubility	**Compounds having bad solubility**
Metronidazole benzoate (more than 200mg/ml)	Satranidazole (less than 5 mg/ml)
Atenolol (>90 mg/ml)	Frusemide (<5 mg/ml)
Ornidazole (>120 mg/ml)	Nimesulide (<5 mg/ml)
Benzocaine (>120 mg/ml)	Aspartame (<5 mg/ml)
Eudragit RSPO (>300 mg/ml)	Carvedilol (<5 mg/ml)
Resorcinol (>190 mg/ml)	Gatifloxacin (<15 mg/ml)
Eudragit RLPO (230 mg/ml)	Piroxicam (<15 mg/ml)
Diltiazem HCl (>150 mg/ml)	Methyl paraben sodium (<5 mg/ml)
BHA (>500 mg/ml)	
Salicylic acid (>70 mg/ml)	

(Note-Not to relate with formulations)

Table No. 2: Eutectic Mixture (Thymol: Menthol 1: 1) pH 6.5

Miscible liquids	**Immiscible liquids**
Ethanol	Glycerin
Propylene glycol	Water
Benzyl alcohol	
Soyabean oil	
PEG-400	
Methanol	

(Note-Not to relate with formulations)

Table-3 shows that one gram of melted menthol (m.p. 44°C) dissolves more than 600mg of ibuprofen. On the other hand, one gram of melted menthol does not dissolve even 5mg of aspartame. It is clear from Table-3 that melted menthol is a good solvent for some solutes (left column) and a bad solvent for other solutes (right column). Molecules of menthol have come in the liquid state by melting.

Table No. 3: Melted Menthol (Melting Point 44°C)

Compounds having good solubility	Compounds having bad solubility
Ibuprofen (m.p. 78°C) > 600 mg/gm	Aspartame < 5 mg/gm
Salicylic acid (m.p. 159°C) > 200 mg/gm	Piroxicam (m.p. 198°C) < 15 mg/gm
Metronidazole benzoate > 180 mg/gm	Sodium caprylate < 5 mg/gm
Naproxen (m.p. 155°C) > 90 mg/gm	Diclofenac sodium (m.p. 283°C) < 5 mg/gm
Indomethacin (m.p. 158°C) > 90 mg/gm	Satranidazole (m.p. 185°C) < 5 mg/gm
PVP K30 > 180 mg/gm	Gatifloxacin < 15 mg/gm

(Note-Not to relate with formulations)

Table-4 shows that one gram of melted thymol (m.p. 48°C) dissolves more than 250mg of eudragit RLPO and on the other hand one gram of melted thymol does not dissolve even 5mg of sodium caprylate. Thus, melted thymol is a good solvent for some solutes (left column) and a bad solvent for other solutes (right column). Molecules of thymol are in a liquid state and are responsible for hydrogen bonds and weak van der Waals forces with the molecules of solutes for their dissolution.

Table No. 4: Melted Thymol (Melting Point 48°C)

Compounds having good solubility	Compounds having bad solubility
Eudragit RLPO > 250 mg/gm	Sodium caprylate < 5 mg/gm
Piroxicam (m.p. 198°C) > 300 mg/gm	Diclofenac sodium < 5 mg/gm
Salicylic acid > 150 mg/gm	Aspartame < 5 mg/gm
Metronidazole benzoate > 50 mg/gm	
Naproxen (m.p. 155°C) > 100 mg	
Caffeine > 350 mg/gm	
Indomethacin (m.p. 158°C) > 300 mg/gm	
PVP K30 > 300 mg/gm	

(Note-Not to relate with formulations)

C. By dissolution in a solvent

Molecules of a solid may come in a liquid state when the solid is dissolved in a solvent.

1. Solubility of ibuprofen in water = 0.028%. Solubility of ibuprofen in 2M sodium benzoate (28.8% w/v sod. benzoate solution) = 2.390%.

85 times solubility enhancement.

Molecules of sodium benzoate have come in a liquid state. These molecules are responsible for hydrogen bonds and weak van der Waals forces with the molecules of ibuprofen and hence there is high solubility.

2. Solubility of frusemide in ethanol = 1.7% w/v.

Solubility of frusemide in 15%w/v niacinamide solution in ethanol = 5% w/v.

Molecules of niacinamide have come in a liquid state.

3. Solubility of piroxicam in propylene glycol = about 5 mg/ml.

Solubility of piroxicam in a solution containing 10% sodium acetate and 10% sodium caprylate in propylene glycol = about 120mg/ml.

Molecules of sodium acetate and sodium caprylate have come in a liquid state.

SOLUBILIZING PROPERTIES OF GASES

Molecules of gases may come in the liquid state in two ways.

- By liquefaction
- By dissolution in a solvent.

A. BY LIQUEFACTION

In supercritical fluid technology, liquefied carbon dioxide gas (at particular pressure and temperature) is employed to make nanoparticles, to perform purification of compounds, to perform extraction of active constituents from herbal powders, etc. Molecules of carbon dioxide gas have come in the liquid state by liquefaction and are responsible for the

dissolution of solutes due to hydrogen bonding and weak van der Waals forces. To enhance the solubilizing properties of liquefied carbon dioxide for some solutes, other cosolvents like methanol, ethanol, etc are used. Thus, it is proved that liquefied carbon dioxide is a good solvent for some solutes and a bad solvent for other solutes.

B. BY DISSOLUTION

Molecules of gas may come in the liquid state by dissolution in a solvent e.g. concentrated HCl is obtained by dissolution of HCl gas in water. Concentrated HCl contains about 42% w/v of dissolved HCl gas. The solubility of nalidixic acid in concentrated HCl is about 5% w/v (nalidixic acid is a poorly water-soluble drug). The reason for the good solubility of nalidixic acid in concentrated HCl is due to hydrogen bonding and weak van der Waals forces between molecules of HCl gas and nalidixic acid.

Thus, it is proved that gases possess solubilizing properties.

MIXED SOLVENCY CONCEPT

There are two parameters in the mixed solvency concept. The first parameter says that every substance (whether gas, liquid or solid) possesses solubilizing power. The second parameter of the mixed solvency concept states that a concentrated solution of different solubilizers employed in smaller concentrations can also enhance the solubility of a solute significantly.

The second parameter can solve the problem of toxicity of a pharmaceutical formulation. We can avoid the use of a high concentration of a single solubilizer (surfactant or cosolvent or complexing agent or hydrotropic agent etc.) which may be toxic to human beings or animals. We can employ safe smaller concentrations of several solubilizers in one formulation of poorly soluble drug to give formulation in solution form.

The Mixed-solvency concept shall be helpful to formulate various dosage forms of insoluble drugs utilizing safe concentrations of excipients for solubilization. Innumerable safe solvent systems can be made by the mixed-solvency concept.

APPLICATIONS OF MIXED SOLVENCY CONCEPT

1. IN PARENTERAL FORMULATIONS

A. Aqueous and oily injections

Mixed solvency concept, a new technique of solubilization states that all substances whether solids, liquids, or gases possess solubilizing power, and a hence concentrated solution containing various dissolved substances in any liquid can also improve the solubility of poorly soluble drugs. Mixed solvency technique can be employed in the injection formulation of poorly soluble drugs to reduce the concentration of individual solubilizers (used for solubility enhancement) to minimize the toxic effects of solubilizers. For example, in most of the methods of aqueous solubilization, a high concentration of an additive (hydrotropic agent /cosolvents /surfactants/ cyclodextrins, etc.) is required to produce an appreciable increase in solubility of a poorly water-soluble drug. In this case, the solubilizing agent employed to give a desirable solubility for the poorly soluble drug may produce its toxicity. Similarly, the presence of several oil-soluble additives (each in a safe small concentration) in oil, forming a concentrated solution may enhance the oil solubility of a poorly oil-soluble drug efficiently.

Maheshwari R.K. and Shilpkar R. selected rifampicin as a poorly oil-soluble drug (as a model drug). Castor oil was used as model oil and thymol, menthol, camphor, phenol, ethanol, benzyl alcohol, and oleic acid were used as model oil soluble/miscible additives. Oily injection of rifampicin was developed employing the solubilizing properties of these additives. The results of the solubility study revealed the significance of mixed solvency and the stability studies data supports that the developed formulation using this technique gives good chemical stability also. [(1)]

Solanki S.S. et al applied a mixed-solvency approach for the enhancement of aqueous solubility of a poorly water-soluble drug, zaltoprofen (selected as a model drug), by making blends (keeping total concentrations 40% w/v, constant) of selected water-soluble solubilizers urea, sodium benzoate, sodium citrate, nicotinamide, PEG-4000, PEG-6000, propylene glycol, glycerine, PEG-200, PEG-400, and PEG-600. Aqueous solubility of drug in case of selected blends (12 blends) ranged from 9.091 ± 0.011mg/ml–43.055 ± 0.14mg/ml (as compared to the solubility in distilled water 0.072 ± 0.012mg/ml).The enhancement in the solubility of the drug in a mixed solvent containing 10% sodium citrate, 5% sodium benzoate

and 25 % co-solvent (25% co-solvent contains PEG-200, PEG-400, PEG-600, glycerine, and propylene glycol) was more than 600 fold. This proved a synergistic enhancement in the solubility of a poorly water-soluble drug due to the mixed solvency effect. Each solubilized product was characterized by ultraviolet and infrared techniques. Various properties of the solution such as pH, viscosity, specific gravity, and surface tension were studied. The developed formulation was studied for physical and chemical stability. This mixed solvency shall prove a boon for pharmaceutical industries for the development of dosage forms of poorly water-soluble drugs. (2)

Pawar P.B. et al developed an aqueous injection using the mixed solvency concept. In the present work poorly water-soluble drug ofloxacin was selected as the model drug. Solubilizing properties of lignocaine hydrochloride, niacinamide, sodium benzoate, sodium citrate, PEG-400, PEG-4000, PVP-40000, ethanol, and propylene glycol were tried for solubility enhancement. For the expected synergistic enhancement effect on the solubility of this poorly water-soluble drug, ofloxacin, various blends of solubilizers were tried to decrease the amounts of solubilizers employed for the desired solubility enhancement. The study further opens the chances of preparing dry powder injection of poorly water-soluble drugs which are not stable in an aqueous solution, ready to use injection. (3)

Solanki S.S. et al enhanced the aqueous solubility of indomethacin drug-using mixed solvency approach. Model solubilizers were employed for increasing the solubility of the poorly water-soluble drug indomethacin. Mixed solvent (40%) blends of selected water-soluble substances urea, sodium benzoate, sodium citrate, nicotinamide, PEG-4000, PEG-600, propylene glycol, glycerine, PEG-200, PEG-400, PEG-600 were studied. Based on solubility studies, different formulations were developed. The prepared formulations were characterized by ultraviolet and infrared techniques. Various properties of solutions such as pH, viscosity, specific gravity, and surface tension were studied. The developed formulation was studied for physical and chemical stability. (4)

Table-5 illustrates various model drugs used and model solubilizers employed in aqueous and oily injections of poorly water-soluble drugs.

Table No. 5: Mixed solvency in aqueous and oily injections of poorly water-soluble drugs

Sr. No.	Model drug used	Model additives employed (Model solubilizer)	Ref. No.
1.	Rifampicin	• Castor Oil • Thymol • Menthol • Camphor • Phenol • Ethanol • Benzyl alcohol • Oleic acid	1
2.	Zaltoprofen	• Propylene glycol • Glycerine • PEG-200 • PEG-400 • PEG-600	2
3.	Ofloxacin	• Lignocaine hydrochloride • Sodium benzoate • Sodium citrate • Niacinamide • PEG-400 • PEG-4000 • PVP 40000 • Ethanol • Propylene glycol	3
4.	Indomethacin	• Urea • Sodium benzoate • Sodium citrate • Nicotinamide • Propylene glycol, • Glycerine, • PEG-200, • PEG-400 • PEG-600 • PEG-4000 • PEG-6000	4
6.	Metronidazole	• Sodium benzoate • PEG-4000	5

		• PEG-400 • PEG-6000 • Niacinamide • PVP K 30	
7.	Gatifloxacin	• Nicotinamide • Sodium benzoate • Sodium citrate • Ethanol • PEG-400 • Propylene glycol	6
8.	Aceclofenac	• Urea • Sodium citrate • Glycerin • PEG-200 • PEG-300 • PEG-400 • PEG-600 • Propylene glycol • Ethanol	7

B. Dry powder injection for reconstitution

Maheshwari N. and Maheshwari R.K. employed the use of the mixed solvency concept by formulating the dry injection of the poorly water-soluble drug and to decrease the concentration of individual solubilizers required to produce a substantial increase in solubility and thereby resulting in expected synergistic enhancement of solubility of the drug in water. In this work, a poorly water-soluble drug, candesartan cilexetil, was selected as a poorly water-soluble drug and its dry injection for reconstitution was formulated. Candesartan cilexetil is an anti-hypertensive drug belonging to the category of angiotensin II type 1 (AT1) receptor antagonist (AII-RA). However, it has low aqueous solubility and undergoes extensive hepatic first-pass metabolism, leading to poor drug bioavailability (15%) and therefore, higher doses are required to achieve the desired therapeutic efficacy. To get expected synergistic enhancement in solubility, various blends of solubilizers were tried thereby reducing the number of individual solubilizers employed to achieve the desired solubility enhancement ratio. The successful completion of the research work was there for the preparation of stable dry injection for reconstitution of candesartan cilexetil. [8]

Padiyar A. and Maheshwari R.K. formulated dry powder injection for reconstitution for poorly water-soluble drug aspirin, where safe concentrations of additives have been employed in the formulation. The blend contained 5% w/v sodium benzoate (a safe buffering agent), 5% w/v PVP K30 (a plasma expander), 2.5% w/v niacinamide (a safe stabilizer), 7.5% w/v PEG-4000 (a safe solubilizer) and 5% w/v lignocaine hydrochloride (a safe local anesthetic).[9]

Table-6 illustrates various model drugs used and model solubilizers employed in dry powder injection for reconstitution of poorly water-soluble drugs.

Table No. 6: Mixed solvency in dry powder injection for reconstitution of poorly water-soluble drugs

Sr. No.	Model drug used	Model additives employed (Model solubilizer)	Ref. No.
1.	Candesartan cilexetil	• Sodium benzoate • Sodium caprylate • Sodium citrate • Sodium acetate • β-Cyclodextrin	8
2.	Asprin	• Sodium benzoate • PVP-K30 • Niacinamide • PEG-4000 • Lignocaine HCl	9

2. IN ENHANCEMENT OF SOLUBILITY OF POORLY WATER SOLUBLE DRUGS

Enhancement of solubility is one of the difficult tasks which becomes a challenge in the formulation development of an orally administered drug with poor aqueous solubility. The poor water solubility of drugs often causes significant problems in producing formulations of sufficiently high bioavailability, preventing effective use of the drugs.

Khan M.A. employed the mixed-solvency concept to increase the solubility of poorly water-soluble drugs in the aqueous solution containing blends of hydrotropic agents, co-solvents, and water-soluble solutes which may give a synergistic enhancement effect on the solubility of such drugs. In the given investigation, a mixed solvency approach has been applied for the enhancement of aqueous solubility of a poorly water-soluble drug, diclofenac sodium (selected as a model drug), by making blends of randomly selected water-soluble substances from among the hydrotropic agents (urea, sodium acetate); water-soluble solutes (PEG-4000, PEG-6000); and co-solvents (PEG-200, PEG-400). The aqueous solubility of diclofenac sodium was observed at room temperature in the randomly selected blends of solubilizers containing different combinations keeping the total concentration of solubilizers 50%w/v constant. Diclofenac sodium has λmax 276 nm and obeys Beers Law in the concentration range of 10-60 µg/ml. The results suggest that the solubility of diclofenac sodium was enhanced significantly using a mixed solvency approach. [10]

Kendre P.N. et al aimed to enhance the solubility of quercetin, a poorly water-soluble drug in various mixed solvent blends (keeping total concentration 40% w/v, constant). In this technique, blends of solubilizers (sodium acetate, sodium citrate, urea as a hydrotropic agent, propylene glycol, glycerin, PEG-200, PEG-400, PEG-600 as co-solvents, PEG-4000, PEG-6000 as water-soluble solids, etc.) have been employed to increase the solubility. Significant enhancement insolubility of the drug in mixed solvents was observed in the blend which contains 10% sodium citrate, 5% sodium acetate, and 25% co-solvents (25% S co-solvent contain PG, glycerin, PEG-200, PEG-400, PEG-600, PEG-4000, PEG-6000). After improvement of solubility of quercetin in selected blends, topical dosage form (prepared gel) was made by utilizing carbopol ETD 2020 as a gelling agent. The prepared blends and gel were evaluated for pH, surface tension, specific gravity and viscosity and *in–vitro* diffusion study, skin irritation studies, spreadability, etc. The characterization of pure quercetin, blend, and the gel was performed by differential scanning calorimetry (DSC); X-ray diffraction (XRD), etc. From experimental work, it was found that the prepared formulation is safe, effective, non-irritant, non-toxic, and stable with good spreadability. The results showed that mixed solvency has a valuable and unique strategy to ameliorating the solubility of lipophilic herbal anticancer component, quercetin. [11]

Kumar C.J. and Kumar M.D. used a mixed-solvency approach to enhance the aqueous solubility of a poorly water-soluble drug “theophylline” (selected as a model drug), by

making blends of randomly selected water-soluble substances from among the hydrotropic solutes (e.g., urea, sodium acetate), water-soluble solutes (e.g., PEG-4000 and/or PEG-6000); and cosolvents (e.g., PEG-200, PEG-400). The aqueous solubility of theophylline was observed at room temperature in randomly selected blends of solubilizers that contained varying combinations keeping the total concentration 50% (w/v) constant. Theophylline has λmax 274 nm and obeys Beers law in the concentration range of 10–60 μg/mL. The results suggest that the solubility of the theophylline-containing blends of varying combinations was enhanced significantly using the mixed solvency approach. [12]

Gadade D. et al used mixed solvency approach for solubility enhancement of a poorly water-soluble drug, ofloxacin. Various hydrotropic agents including sodium benzoate, urea, sodium citrate, sodium acetate, niacinamide, lignocaine hydrochloride, PEG-6000, PEG-400 were evaluated understudy for enhancing the solubility of the drug. A further effect of various blends of these hydrotropic agents on the solubility of ofloxacin was studied. Aqueous injection of ofloxacin was prepared and evaluated for its antimicrobial effectiveness and stability. It was found that the mixed solvency approach is useful in the solubility enhancement of ofloxacin without affecting its antimicrobial properties. [13]

Table-7 illustrates various model drugs used and model solubilizers employed in the enhancement of solubility of poorly water-soluble drugs.

Table No. 7: Mixed solvency in solubility enhancement of poorly water-soluble drugs

Sr. No.	Model drug used	Model additives employed (Model solubilizer)	Ref.no
1.	Diclofenac sodium	• Urea • PEG-200 • PEG-400 • PEG-4000 • PEG-6000 • Sodium acetate	10
2.	Quercetin	• Sodium acetate • Sodium citrate • Urea • Propylene glycol • Glycerin • PEG-200 • PEG-400 • PEG-600 • PEG-4000 • PEG-6000	11
3.	Theophylline	• Urea • Sodium acetate • PEG-4000 • PEG-6000 • PEG-200 • PEG-400	12
4.	Ofloxacin	• Sodium benzoate • Urea • Sodium citrate • Sodium acetate • Niacinamide • Lignocaine hydrochloride • PEG-6000 • PEG-400	13
5.	Paracetamol	• Sodium benzoate • Sodium citrate • Niacinamide • Urea	14

3. IN GEL BASED FORMULATION

Kushwaha A. et al aimed to overcome the problem of drug loading by utilization of the novel concept of mixed solvency and minimizing the drug clearance by formulating in situ mucoadhesive gel. Ondansetron hydrochloride was used as a model drug. By this concept, the solubility of this poorly water-soluble drug can be easily increased at nasal cavity pH and a higher drug loading is also expected. As the drug loading of these antiemetic drugs is increased at nasal pH, the amount of drug crossing the olfactory region and blood-brain barrier (BBB = highly lipophilic) will be increased. More amount of drugs will reach the brain's CTZ center and will help in the prevention and treatment of emesis. [15]

Kumar D. worked to develop a mucoadhesive nasal gel of domperidone in an aqueous medium. The mixed solvency concept was used to enhance the aqueous solubility of domperidone. The study was facilitated by collecting fenugreek seeds and subjected them to hydro extraction. The mixed solvency concept was used to improve the aqueous solubility of domperidone. The mucoadhesive agent was extracted from fenugreek seeds by simple hydro extraction. Solubility of domperidone was enhanced by using sodium citrate, urea, glycerine, PVP K 30, PEG-600, propylene glycol, individually and in combinations. Maximum solubility was found in aqueous solution of PVP K 25 (4400.54µg/ml), PVP K 30 (4700.12µg/ml), PVP K 25 + PEG-600 (2202.24µg/ml), PVP K 30 + PEG-600 (2306.92µg/ml), PVP K 30 + PEG-1540 (2288.66µg/ml), PVP K 25 + PEG-400 (2396.22µg/ml), PVP K 25 + PEG-600 (2455.18µg/ml), PVP K 25 + Propylene glycol (2378.24µg/ml), PVP K 30 + PEG-400 (2628.45µg/ml), PVP K 30 + PEG-600 (2698.76µg/ml), PVP K 30 + propylene glycol (2604.22µg/ml). Mucoadhesive properties were provided by using fenugreek seed extract. Mucoadhesive agent extracted from fenugreek seed was observed more viscous than synthetic polymer, i.e., HPMC, Carbopol. Domperidone solubility was enhanced by using various solid and liquid solubilizers individually as well as in combination. In the future, domperidone nasal gel may be used for the treatment of gastroparesis, nausea, vomiting, and replace other conventional dosage forms. [16]

Agrawal A. and Maheshwari R.K. aimed to develop a mucoadhesive *in situ* nasal gel containing domperidone with enhanced drug loading and transnasal permeation properties, which were achieved by improving drug solubility using the concept of mixed solvency. Poloxamer 407 was used as a thermosensitive polymer and carbopol 934P as mucoadhesive

polymer. Initially, the solubility of domperidone was enhanced in aqueous solution by using various solubilizers like sodium citrate (SC), urea (UR), polyvinyl pyrrolidone (PVP), polyethylene glycol 400 (PEG-400), polyethylene glycol 600 (PEG-600) propylene glycol (PG), etc, individually and as a combination of two, three, and four solubilizers, respectively. Maximum solubility of domperidone was achieved at 30% w/w solubilizer concentration, containing mixed blend of PVP K30 (7.5% w/w) + PEG-400 (7.5% w/w) + PEG-600 (7.5% w/w) + propylene glycol (7.5% w/w), enhancing solubility of domperidone by 172.20 times as compared to its solubility in water. *In-situ* gel was prepared by cold technique. Evaluation of the prepared gel was carried out, including properties like phase transition temperature, viscosity, *in-vitro* drug release, drug content, transnasal permeation, and stability studies. *In-vitro* drug release studies of an aqueous solution of the mixed blend were performed and the permeability coefficient was found to be 1.576 × 10-02 cm/hr and flux was found to be 8.64 µg/cm^{2}hr**.** Similarly, *in-vitro* studies for *in-situ* nasal gel were performed and the percent cumulative drug release was 73.05±0.57% in 6 h. Transnasal drug permeation studies result in flux value of 7.04 µg/cm^{2}hr and percent cumulative drug permeated across the membrane as 86.62±0.992%. The results from stability studies revealed that the prepared thermogel showed no significant decrease in drug content and no physicochemical change was observed upon storage in different temperature conditions resulting in a stable formulation. [17]

Table-8 illustrates various model drugs used and model solubilizers employed in the gel-based formulation of poorly water-soluble drugs.

Table No. 8: Mixed solvency in the gel-based formulation of poorly water-soluble drugs

Sr. No.	Model drug used	Model additives employed (Model solubilizers)	Ref.no
1.	Ondansetron Hydrochloride	• PVP K 30 • PEG-400 • Propylene glycol	15
2.	Domperidone	• PVP K 30 • PEG-200 • PEG-600 • Propylene glycol	16
3.	Domperidone	• Sodium citrate • Urea • Polyvinyl pyrrolidone • PEG-400 • PEG-600 • Propylene glycol • Glycerine	17

4. IN LIQUID ORALS

Maheshwari R.K. and Rajagopalan R. explored the mixed solvency concept to formulate the syrups (solutions) of the poorly water-soluble drug, paracetamol (as a model drug). For this, the blends containing solubilizers from the category of hydrotropes, co-solvents, and water-soluble solids were employed. The blends of randomly selected solubilizers were used for solubility studies. Based on the solubility studies, few blends showing the largest solubilities were employed to make the syrup. This may reduce the individual concentration of solubilizers and so reduce their potential of toxicities. The formulated syrups were subjected to accelerated stability studies and they were found quite stable. [18]

Maheshwari R.K. and Rajagopalan R. explored to formulate the syrups (solutions) of the poorly water-soluble drug tinidazole (as a model drug). For this, the blends containing solubilizers from the category of hydrotropes, co-solvents, and water-soluble solids were employed. The blends of randomly selected solubilizers were used for solubility studies.

Based on the solubility studies, few blends showing the largest solubilities were employed to make the syrup. This may reduce the individual concentration of solubilizers and so reduce their potential of toxicities. The formulated syrups were subjected to accelerated stability studies and they were found quite stable. [19]

Soni L.K. et al applied mixed solvency concept for the enhancement of aqueous solubility of the poorly water-soluble drug, indomethacin by making blends of selected water-soluble substances urea, sodium benzoate, sodium citrate, nicotinamide, propylene glycol, glycerine, PEG-200, PEG-300, PEG-400, PEG-600 precluding the use of organic solvents and attempt was made to develop new oral solution (syrup) formulation. Analgesic, anti-inflammatory, and ulcerogenic effects of newly developed oral solution (syrup) formulation (IOS4) of indomethacin using mixed solvency concept were evaluated in laboratory animals. The prepared formulation contains 40% mixed solvents as a vehicle (% combination of UR, SC, PEG-TH, PEG-FH, PEG-SH, GLY, and PG) for the drug. Acetic acid-induced writhings and carrageenan-induced paw edema methods were used to screened analgesic and anti-inflammatory activity of pure drug and formulation. Developed formulation IOS4 exhibited significant (P<0.0001) analgesic and anti-inflammatory effects as observed in the paw edema model. The severity of gastric lesions of standard pure drug and formulation was also insignificant (P< 0.05). [20]

Table-9 illustrates various model drugs used and model solubilizers employed in the liquid oral formulation of poorly water-soluble drugs.

Table No. 9: Mixed solvency in the liquid oral formulation of poorly water-soluble drugs

Sr. No.	Model drug used	Model additives employed (Model solubilizers)	Ref.no
1.	Paracetamol syrup	• Urea • Sodium citrate • Glycerin • Propylene glycol • PEG-300 • PEG-400 • PEG-4000 • PEG-6000	18
2.	Tinidazole syrup	• Sodium benzoate • Urea • Niacinamide • PEG-200 • PEG-400 • PEG-4000 • PEG-6000 • Ethanol	19
3.	Indomethacin syrup	• Propylene glycol • Glycerin • PEG-200 • PEG-400 • PEG-600	20

5. IN FILMS (ORAL AND VAGINAL)

Gahlot N. and Maheshwari R.K. applied a mixed solvency concept to deliver antibacterial therapy in an efficacious way, film dosage form has been proposed for drug delivery in the vagina which can overcome bioavailability issues of poorly water-soluble drugs. The present research work is aimed to explore the application of the mixed solvency concept to increase the solubility of a poorly water-soluble drug, metronidazole. Metronidazole, a slightly soluble

drug in water was tried to be solubilized by employing the combination of solubilizers like niacinamide, sodium benzoate, sodium caprylate, caffeine, and urea to endeavor its fast dissolving film formulations. The procured sample of the drug was characterized by UV, IR, and DSC studies. The formulations were evaluated for various properties of film such as thickness, folding endurance, surface pH, disintegration time, and thin-layer chromatography. Stability studies of vaginal films of metronidazole were performed for ten weeks at room temperature and refrigerated conditions. It was found that 97.54% and 97.58% of the drug was remaining after stability study at respective temperatures in batch F1 and 98.53% and 96.57% in batch F4. It was concluded that the approach of the mixed solvency concept is novel, safe, cost-effective, and user-friendly. It also eliminates the problem of toxicity associated with a high concentration of water-soluble solubilizers. So, it may be employed in dosage form development of drugs with poor solubility to overcome bioavailability issues. [21]

Carpenter G. and Maheshwari R.K. explored the application of the mixed solvency concept to formulate and develop a fast-dissolving oral film of furosemide with improved drug loading. In the present study, a poorly soluble drug, furosemide was tried to be solubilized by employing a combination of physiologically compatible water-soluble additives (solubilizers) to formulate its fast-dissolving formulations. For the development of fast dissolving oral film, firstly, different film-forming polymers were tested for their film properties. The second fast-dissolving layer was also formed and optimized. Solubility studies were conducted to select water-soluble additives for the formulation of a fast-dissolving drug layer. Keeping the total concentration less than 40 % w/v of mixed blends, different aqueous blends were prepared to employ solubilizers from among sodium benzoate, sodium acetate, sodium citrate, urea, niacinamide, glycerin, propylene glycol, polyethylene glycol 200, polyethylene glycol 400, polyethylene glycol 600, and PVP K 30. Maximum solubility of furosemide was found in blends- F5 (10% sodium caprylate +2.5%sodium benzoate+ 2.5% niacinamide) and in blend F7 (10% sodium caprylate +2.5%sodium benzoate +2.5% sodium citrate + 2.5% niacinamide). Prepared films were evaluated for drug content, thickness, folding endurance, tensile strength, and hydration ratio. The present research work aims to explore the application of the mixed solvency concept to formulate and develop a fast-dissolving oral film of furosemide with improved drug loading. In the present study, a poorly soluble drug, furosemide was tried to be solubilized by employing a combination of physiologically compatible water-soluble additives (solubilizers) to formulate its fast-dissolving formulations. For the development of fast dissolving oral film, firstly, different film-forming

polymers were tested for their film properties. The second fast-dissolving layer was also formed and optimized. Solubility studies were conducted to select water-soluble additives for the formulation of a fast-dissolving drug layer. Keeping the total concentration less than 40 % w/v of mixed blends, different aqueous blends were prepared to employ solubilizers from among sodium benzoate, sodium acetate, sodium citrate, urea, niacinamide, glycerin, propylene glycol, PEG-200, PEG-400, PEG-600, and PVP K 30. Maximum solubility of furosemide was found in blends- F5 (10% sodium caprylate +2.5%sodium benzoate+ 2.5% niacinamide) and in blend F7 (10% sodium caprylate +2.5%sodium benzoate +2.5% sodium citrate + 2.5% niacinamide). Prepared films were evaluated for drug content, thickness, folding endurance, tensile strength, and hydration ratio. [22]

Table-10 illustrates various model drugs used and model solubilizers employed in the film formation of poorly water-soluble drugs.

Table No. 10: Mixed solvency in film formation of poorly water-soluble drugs

Sr. No.	Model drug used	Model additives employed (Model solubilizers)	Ref.no
1.	Metronidazole vaginal film	• Niacinamide • Sodium benzoate • Sodium caprylate • Caffeine • Urea	21
2.	Frusemide fast dissolving oral film	• Sodium benzoate • Sodium acetate • Sodium citrate • Urea • Niacinamide • Glycerin • Propylene glycol • Polyethylene glycol 200 • Polyethylene glycol 400 • Polyethylene glycol 600 • PVP K 30	22

6. IN TOPICAL FORMULATION

Mulani P. and Maheshwari R.K. utilized a mixed solvency concept to develop the topical solutions and gels of the poorly water-soluble drug, nimesulide. For poorly water-soluble drug nimesulide, the combination of solubilizers such as sodium benzoate, sodium caprylate, sodium oleate, propylene glycol, and benzyl alcohol as mixed solvent systems were used to decrease the overall concentration of solubilizers required to produce a substantial increase in solubility of the drug and thereby resulting in expected enhanced permeation of nimesulide from its topical formulations. The procured sample of nimesulide was characterized by melting point, IR, UV, and DSC studies. The formulations were evaluated for various properties of the solution such as pH, viscosity, freeze-thaw study, and thin-layer chromatography. Stability studies of topical solutions and gels were performed for three months at room temperature and 2 to 8 ˚C. It was found that 91.5% at room temperature and 91.4% at 2 to 8º C of the drug was remaining after stability study for three months at respective temperatures in batch first and 91.8 %, at room temperature, 91.6% at 2 to 8º C in batch second. The percent drug remaining of the first formulation of gel at room temperature was 92.7% and at 2 to 8º C it was 92.3 % after three months. The mixed solvency concept was successfully employed to improve the solubility and permeation of poorly water-soluble drug, nimesulide.[23]

Singh S. et al applied the mixed solvency concept to develop the topical solution formulations of the poorly water-soluble drug indomethacin (as a model drug). Due to the low solubility of indomethacin in water, a combination of solubilizers as mixed solvent systems was used to decrease the overall concentration of solubilizers required to produce a substantial increase in solubility and thereby resulting in enhanced permeation of indomethacin from its topical formulation. The procured sample of indomethacin was characterized by melting point, infrared, ultraviolet, and differential scanning calorimeter studies. The formulations were evaluated for various properties of a solution such as pH, viscosity, freeze-thaw study, and thin-layer chromatography. Stability studies of topical indomethacin solutions were performed for 2 months at room temperature, 30°C, and 40°C. The results of stability studies of indomethacin topical solution were satisfactory. It was found that 95.07%, 93.88%, and 93.45% of the drug was remaining after stability study at respective temperatures in batch first and 94.89%, 94.44%, and 94.32% in batch second. [24]

Table-11 illustrates various model drugs used and model solubilizers employed in the topical formulation of poorly water-soluble drugs.

Table No. 11: Mixed solvency in the topical formulation of poorly water-soluble drugs

Sr. No.	Model drugs used	Model additives employed	Ref.No
1.	Nimesulide	• Sodium benzoate • Sodium caprylate • Sodium oleate • Propylene glycol • Benzyl alcohol	23
2.	Indomethacin	• Sodium benzoate • Niacinamide • Caffeine • PEG-400 • Distilled water	24

7. IN SOLID DISPERSION

Solid dispersion term refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or crystalline particles. Solid dispersions are defined as the dispersion of one or more active ingredients in an inert carrier or matrix prepared by melting, solvent, or melting solvent method. The physical state of the drug in the solid dispersions is often transformed from crystalline to amorphous form and the dissolution surface increases because of particle size reduction. Because of promises in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field.

Solid dispersion technique has been utilized to increase the dissolution and thereby the rate of absorption and total bioavailability of poorly water-soluble drugs. The common methods of making solid dispersion are solvent evaporation, fusion- solvent evaporation, fusion, and fusion solvent methods. The use of organic solvent is completely precluded if the solid dispersion is prepared using hydrotropy, mixed hydrotropy, and mixed solvency concepts.

The solid solubilizers (water-soluble carriers) are hydrophilic while the drug is insoluble in water. An appropriate amount of solid solubilizers are used to solubilize the drug in water. Later, water (solvent) is removed to obtain dried solid dispersion. In case, solid solubilizers are not used, the drug is insoluble in water, hence, this method is different from the common solvent method which makes mixed solvency techniques of the highest utilization.

Chaklan N. et al employed mixed solvency concept for the preparation of solid dispersion in 1:4 ratio, accurately weighed 1 gm PVP K 30, 1.5 gm of sodium benzoate, and 1.5 gm of PEG-4000 (so that total weight of the mixture was 4 gm) were taken in a 100 ml beaker and were mixed properly. Then, the minimum possible quantity of warm, distilled water sufficient to dissolve the above mixture was added, because the lesser the amount of water lesser will be the time required to evaporate the water and the chemical stability of the drug may not be affected adversely (during removal of water). Dissolution of the water-soluble additives (solubilizers) mixture was facilitated by the agitation of a Teflon coated magnetic rice bead on a high-speed magnetic stirrer. After the complete dissolution of solubilizers, 1 gm of piroxicam was dissolved in the above solution, and the temperature was maintained in the range of 55- 60ºC to facilitate the evaporation of water. As evaporation proceeded, the speed of the rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet). The wet solid dispersion, thus, obtained was spread on several glass Petri plates and these Petri plates were kept in hot air dry oven maintained at 50±2ºC so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve 40, and were finally stored in an air-tight glass bottle. [25]

Mansuk et al used the mixed solvency concept for the preparation of solid dispersion in a 1:4 ratio (drug: solubilizers blend) accurately weighed 1.5 gm. sodium benzoate,1.5 gm. HP-BCD and 1 gm. PVP K 30 were taken in a 100 ml beaker and were mixed properly. Then the minimum possible quantity of warm, distilled water sufficient to dissolve the above mixture was added, because the lesser the amount of water lesser will be the time required to evaporate it and the chemical stability of the drug may not be affected adversely (during removal of water). After the complete dissolution of solubilizers, 1 gm. of piroxicam was dissolved in the above solution, and the temperature was maintained in the range of 55-60ºC to facilitate the evaporation of water. As evaporation proceeded, the speed of the rice bead

automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet). The same procedure was utilized to prepare solid dispersion in the ratio of 1:6, 1:8,1:10 and1:12 using an appropriate quantity of solubilizers. [26]

Bagel J.S. and Maheshwari R.K. explored the application of the mixed solvency concept to formulate and develop a fast-dissolving solid dispersion. In the present study, a poorly soluble drug, torsemide (model drug) was tried to be solubilized by employing a combination of physiologically compatible water-soluble additives (solubilizers) to formulate its fast-dissolving solid dispersion. For poorly water-soluble drug torsemide, a combination of solubilizers such as sodium caprylate, sodium citrate, sodium acetate, and beta-cyclodextrin as mixed solvent systems were used to decrease the overall concentration of solubilizer required to produce a substantial increase in solubility of torsemide. The procured sample of torsemide was characterized by melting point, IR, UV, and DSC studies. Stability studies of solid dispersion of torsemide were performed for two months at room temperature and cool temperature. All the formulations were physically, chemically, and microbiologically stable. [27]

Chouhan M. et al worked using solid dispersion method through poorly soluble drugs lovastatin formulating it as solid dispersions subsequent preparation of fast dissolving tablets with the prepared solid dispersions using different concentrations of super disintegrates and comparing them with that of the marketed product. Lovastatin is an HMG CoA reductase inhibitor used in the treatment of hyperlipidemias and the prevention of ischemic heart disease. It is practically insoluble in water, sparingly soluble in alcohol, and soluble in acetone. In the present investigation, lovastatin and solid dispersion were prepared by physical mixing, fusion, solvent evaporation, and lyophilization methods using PEG-6000 as an inert amphiphilic carrier. The prepared solid dispersions were evaluated for pre compressional parameters such as angle of repose, Carr's index, particle size, and drug content. [28]

8. IN LIQUISOLID SYSTEM

The technique of "Liquisolid compact" is a type of powdered solution technology. It is a novel method to improve the in vivo solubility of poorly water-soluble drugs. The basic concept here is to convert the liquid form of the drug into free-flowing readily compressible

powder. Here the liquid drug, drug solution, suspension, or emulsion is converted into free-flowing powder by simply adsorbing it on an inert carrier with the addition of various excipients such as binder and others required to prepare the tablet, and then the mass is compressed to tablet. Figure 1 illustrates a molecular level diagram of the liquisolid system.

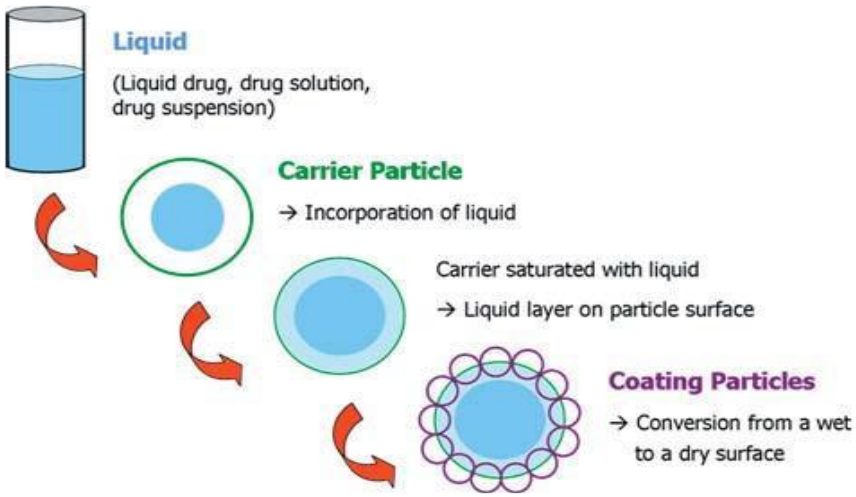

Figure No. 1: Molecular-level diagram

Components

Drug: Drugs of all class of BCS system of classification

Non-volatile solvent: It must be inert, hydrophilic, having low viscosity, and a high boiling point. For example polyethylene glycols (liquids), propylene glycol, glycerol, etc.

Carrier: These are materials with high porosity and a wide surface area that serves as a base to adsorb the liquid form of the drug. For example MCC, methylcellulose, ethylcellulose starch, etc.

Coating material: These are fine materials of size range10nm-450nm. These should be highly adsorptive to cover the carrier particle to make it look dry. For example aerosil 200, silica, syloid, etc.

Disintegrants, **Lubricants, Glidants** There is an absolute necessity of solubility of an amount of drug desired as per the strength of dosage form to be present in the minimum amount of the solvent to be used as a solution. For this purpose, a suitable solvent or solvent system is to be selected.

Application of the mixed solvency concept has been used to enhance the drug loading capacity in liquisolid system and to increase the flow property by reducing the required volume of nonvolatile solvent and enhance the solubility of the drug in a nonvolatile solvent. Cefixime 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.

Agrawal R. and Maheshwari R.K. applied a mixed solvency concept to develop a liquisolid system (powder formulation) of the poorly water-soluble drug, cefixime (as model drug). For poorly water-soluble drug cefixime, a combination of solubilizers such as sodium acetate, sodium caprylate, and propylene glycol as mixed solvent systems were used to decrease the overall concentrations of solubilizers required to produce a substantial increase in solubility and thereby resulting in enhanced drug loading capacity of cefixime. The procured sample of cefixime was characterized by melting point, IR, UV, and DSC studies. Stability studies of the liquisolid system of cefixime were performed for two months at room temperature, 30˚C, and 40˚C. All the formulations were physically, chemically, and microbiologically stable. [29]

Barua D. et al used a mixed solvency concept in preparation of a liquisolid system of the poorly water-soluble drug, Rifabutin. Rifabutin is the broad-spectrum antimicrobial drug, used for the treatment of infection caused by *M. tuberculosis*, *M. avium*, and *M. Leprae* and also used in the treatment of multidrug-resistant TB. Rifabutin is a poorly water-soluble drug (0.19mg/ml) with high permeability. The mixed solvency concept was employed for the improvement of solubility and dissolution rate that improve drug release and oral bioavailability. Different blends were prepared using various solid solubilizers like sodium benzoate, sodium caprylate, and niacinamide in propylene glycol (co-solvent). In this blend K (35%SC+5%NM+5%SB) gives the highest solubility and was selected for further study. A Liquisolid system was prepared using blend K, microcrystalline cellulose as carrier material, and aerosil as coating material. In all the formulations, formulation LSS-01 was selected as the best formulation as it released 98.20% of the drug in 1 hr. The prepared liquisolid system (LSS-01) using the mixed solvency concept was evaluated for drug content, X-RD analysis, dissolution study, and stability study. The drug content in LSS-01 was found to be 100.24± 0.04% & in the physical mixture was found to be 98.9± 0.03%. X-ray diffraction study showed that the crystallinity of the drug is not much reduced. The drug release profile of optimized batch LSS-01 showed enhanced dissolution behavior (98% in 60min.) as compared

to that of the pure drug (46.26±0.011), physical mixture (51.42±0.006), and marketed formulation (48.92±0.009). [30]

Jain S. and Maheshwari R.K. worked to enhance the drug loading capacity in the liquisolid system, using the mixed solvency concept. Piroxicam 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 piroxicam by employing mixed solvency concept and to develop the fast release capsule of piroxicam by using the liquisolid technique. [31]

Table-12 illustrates various model drugs used and model solubilizers employed in the liquisolid formulation of poorly water-soluble drugs.

Table No. 12: Mixed solvency in liquisolid system of poorly water-soluble drugs

S.no	Model drug used	Blend	Solubility (mg/ml)	Ref. no
1.	Cefixime	25% Sodium caprylate + 12.5% Sodium acetate	476.67	29
2.	Rifabutin	35% Sodium caprylate+5% Sodium benzoate + 5% Niacinamide	500	30
3.	Piroxicam	10% Sodium acetate + 10% Sodium caprylate	122.55	31

9. IN MICROSPHERES

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm (1 mm)). Microspheres in drug delivery are used for targeted as well as prolonged drug release in the diseased area. It also protects the unstable or pH-sensitive drugs before and after the administration. There are two types of microspheres; microcapsules and micromatrices, which are described as microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall, and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as micro-particles. Micro-spheres can be manufactured from various natural and synthetic materials. Microspheres play an important role to improve the bioavailability of conventional drugs and minimizing the side effects.

Microspheres have high loading capacity and many polymers are used such as albumin, gelatin, starch, polymethacrylate, polyacrylamide, and poly alkyl cyanoacrylate. Microspheres have a characteristic internal hollow structure and show excellent *in-vitro* floatability. The solvent evaporation technique of microencapsulation is widely applied in pharmaceutical industries to obtain the controlled release of the drug. The obtained polymer microspheres with drug trapped inside can degrade and release the encapsulated drug slowly with a specific release profile. Hollow microspheres are prepared by the emulsion solvent evaporation method. Various polymer/drug ratios are mixed in an organic solvent system, by replacing these organic solvents with mixed solvent the toxicity caused by organic solvent can be reduced.

Rathod M. and Agrawal S. prepared floating microspheres of furosemide by using the mixed solvency Concept. The mixed solvency concept was used in this formulation because furosemide drug is a poorly water-soluble drug. It enhanced the solubility of furosemide and also explores the possibility of used ethyl acetate: ethanol as a combination of solvents to prepare hollow floating microspheres replaces dichloromethane: ethanol combination. The result of our present study suggests that floating microspheres of furosemide can be successfully designed and developed by a mixed solvency concept which can reduce individual concentrations of solubilizers and thus there is a reduction in their toxicity and it provided environment-friendly methods. All characteristic parameters of microspheres i.e. particle size, encapsulation efficiency, surface morphology, and *In-vitro* drug release were evaluated. [32]

10. IN SEDDS

Self-emulsifying drug delivery systems (SEDDS), have shown lots of reasonable successes in improving the oral bioavailability of poorly soluble drugs. SEDDS are usually composed of a mixture of oil and surfactant or cosurfactant and are capable of forming fine oil-in-water emulsions upon gentle agitation provided by the GIT motion. After oral administration, SEDDS can maintain the poorly soluble drugs dissolved in the fine oil droplets when transiting through the GIT. Poor aqueous solubility is a common concern in the formulation of pharmaceutical dosage forms. There are several established methods for increasing the equilibrium solubility of non-polar drugs in aqueous vehicles. Cosolvency, the addition of water-miscible solvents to an aqueous system, is one of the oldest, most powerful, and most popular of these. Cosolvents are organic liquids that are substantially miscible with water and

find a high degree of utility in the design of many types of liquid formulations. The use of appropriate cosolvent can increase the aqueous solubility of a drug by several orders of magnitude.

Maheshwari R.K. and Chandana C. formulated SEDDS of candesartan cilexetil. Capryol-90 was selected as an oily phase, acrysol was selected as surfactant phase, whereas a mixture of transcutol-P, camphor, vanillin, and lutrol F-68 (TB3Mix) was selected as an alternate solubilizing system to replace cosurfactant/cosolvent phase of traditionally known methods to prepare SEDDS. The formation of clear emulsion on addition with aqueous phase with low polydispersity index indicates the spontaneous formation of SEDDS. The obtained emulsions were visually clear and did not show any sign of precipitation, coagulation, or phase inversion when kept aside for at least 6 h. The droplet size lies in the range of 80-160 nm not only confirms the closeness of observed values with predicted ones but also infers the higher bioavailability of formed formulation due to its nano range globules size. The drug release found near 80% during the first 30 min indicates the formulation with rapid drug release and infers higher bioavailability, which also confirms the potential application of SEDDS. The surfactant concentration of Acrysol (surfactant) involved in the formulation of SEDDS was in the range of 32% to 45%, which is very less than the traditionally used level of surfactant (usually > 60% surfactant) that indicates the potential of alternate solubilizing cosolvent mixture as a principle outcome of mix solvency to the concept in the formulation of SEDDS. Further, the level/concentration of other ingredients involved in the formulation of SEDDS lies under the permitted amount according to different regulatory bodies the concentration of ingredients was very low than the permitted values under texts. [33]

11. EXTRACTION BY MIXED SOLVENCY CONCEPT

Maheshwari R.K. et al proved that solids can also be employed for the extraction of active constituents from powders of roots, leaves, seeds, fruits, the bark of plants, etc. In the present investigation, sesame oil has been extracted from powdered seeds of sesame using solubilizing powers of two solids, thymol and menthol using different methods. Melted thymol (temperature about 50°C), melted menthol (temperature about 45°C) were observed to have very good solubility for sesame oil. Therefore, they were used for the extraction of sesame oil. Ethanol was found to be a bad solvent for sesame oil. Thymol and menthol improved the solubility of sesame oil in ethanol and helped in extraction. Thymol and menthol are easily removed at about 80°C. Organic solvents are removed from extracts by

suitable methods like heating, vacuum distillation, etc. These solids (menthol and thymol) are also removable. Also, they can be recollected using suitable methods for recycling purposes. Similarly, other solids can also be used for extraction and can later be removed and recollected based on their melting points. [34]

Example:-

- Benzoic acid (M.P. 122ºC) can be removed completely at 140ºC in the oven within one hour.
- Butylated hydroxytoluene (M.P. 70ºC) can be removed completely at 110ºC in the oven within one hour.
- Methylparaben (M.P. 128ºC) can be removed completely at 140ºC in the oven.
- within two hours.
- Vanillin (M.P. 84ºC) can be completely removed in the oven at 140ºC within two hours.
- Menthol (M.P. 44°C) can be completely removed at 80°C within an hour.
- Thymol (M.P 48°C) can be completely removed at 80°C within an hour.

Table-13 illustrates data of approximate solubility studies of sesame oil in various solvents.

Table No. 13: Results of approximate solubility studies of sesame oil

S. N.	Solvent	Approximate solubility
1	Melted thymol (at about 50°C)	More than 1 ml sesame oil in 1 gm melted thymol
2	Melted menthol (at about 45°C)	More than 1 ml sesame oil in 1 gm melted menthol
3	50 % w/v Thymol in ethanol	1.4 ml sesame oil in 1 ml of 50 %w/v thymol in ethanol
4	50 % w/v Menthol in ethanol	0.8 ml of sesame oil in 1 ml of 50 % w/v menthol in ethanol
5	25%w/v thymol 25 %w/v menthol in ethanol	0.9 ml of sesame oil in 1 ml of 25%w/v thymol 25%w/v menthol in ethanol
6	Eutectic liquid M:T - 1:1	More than 1 ml of sesame oil in 1 ml of M:T - 1:1

Table-14 illustrates the yield of sesame oil using different solvent systems.

Table No. 14: Results of extraction studies using different techniques

S. No.	Solvent	Yield of sesame oil
1	Melted thymol	37.6 %w/w (with little pulp)
2	50%w/v Thymol in ethanol	22.0%w/w (pulp was nearly absent)
3	Melted menthol	33.3 %w/w (with little pulp)
4	50%w/v Menthol in ethanol	27.0 %w/w (pulp was nearly absent)
5	25%w/v Menthol 25%w/v Thymol in ethanol	36.6 %w/w (with traces of pulp)
6	Eutectic liquid M : T - 1:1	26.6%w/w (pulp was nearly absent)
7	Hexane	32.3 %w/w (with traces of pulp)

CONCLUSION:

More than 60% of NCEs (new chemical entities) developed in the pharmaceutical industry have poor aqueous solubility. These poorly water-soluble drugs having slow drug absorption lead to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs, solubility is the most important rate-limiting parameter to achieve their desired concentration in systemic circulation for the pharmacological response. The problem of solubility is a major challenge for formulation scientists. The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of the drug development process, especially for the oral-drug delivery system. There are numerous approaches available and reported in the literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen based on certain aspects such as properties of the drug under consideration, nature of excipients to be selected, and nature of intended dosage form.

The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility, in turn, increases the bioavailability for BCS class II drugs.

The paper summarizes the utility of the mixed solvency concept in formulation development and extraction. Various poorly water-soluble drugs can be formulated efficiently with enhancement in their bioavailability and absorption. The concept applies to various formulations (aqueous injections, oily injections, dry powder injections for reconstitution, liquid orals, SEDDS, microspheres, nasal gels, solid dispersions, liquid-solid systems, oral films, vaginal films) and can be used through different routes of administration. The mixed solvency concept was nicely employed for the extraction of an active constituent from herbal powders.

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