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A REVIEW ARTICLE: ECOFRIENDLY AND ECONOMIC ANALYTICAL METHODS USING MIXED SOLVENCY CONCEPT (TITRIMETRY, UV SPECTROPHOTOMETRY, TLC)

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Abstract: The aim of this study is to resolve the problem of solubility of poorly water soluble drugs. Various organic solvents like methanol, chloroform, ethanol, acetonitrile, hexane, toulene, 1,2-dichloroetane, benzene, 1,2-dichloroethene, carbon tetrachloride, 1,1,1-trichloroethane, methyl cyclohexane, chlorobenzene, methylene chloride, nitromethane, ethylene glycol, pyridine, formamide, sulfolane, tetrahydrofuran, 2-methoxy ethanol, tetralin, 1,4- dioxane, 1,2dimethoxy ethane, N,N-dimethylformamide, N,N-dimethyl acetamide, trichloroethylene, N-methylpyrrolidone, methylbutyl ketone, cyclohexane, 2-ethoxyethanol, ethyl acetate, acetic acid, anisole, cumene, heptane, pentane, ethyl formate, propyl acetate, methyl acetate,1-butanol, 2-butanol, butylacetate, ethyl ether, dimethyl sulfoxide, trimethylamine, formic acid, 1-pentanol, isobutyl acetate etc. are used to perform various analytical techniques (HPLC, TLC, HPTLC, UV-spectrophotometry, titrimetry etc). Most of these organic solvents used in analysis have high cost and possess toxic effects. To enhance the solubility of poorly water soluble drugs is very challenging. Poorly water soluble drugs may cause various problems in formulation and characterization. The "Mixed Solvency Concept" gives a path to overcome the problem of solubility of poorly water soluble drugs. This concept states, all the substances whether solids, liquids or gases posseses solubilizing power. This review focuses on the application of mixed solvency concept in various analyses of these poorly water soluble drugs. Such analytical methods are ecofriendly and cost effective. These methods should be adopted by various pharmacopoeias, so that, the use of such costly and harmful organic solvents can be minimized.

Index Terms **- Mixed solvency, Poorly water soluble drugs, Titrimetry, UV Spectrophotometry, TLC, harmful organic solvents, green chemistry**

INTRODUCTION[1]

Many industrial pharmacists face technical problems in formulation of solutions. A growing number of new therapeutic molecules are limited by low bioavailability due to poor water solubility. Advanced methods are required to enhance solubility of poorly soluble drugs. Solubility of drug can be increased by variety of leading methods such as hydrotropic solubilization, inclusion complex methods, altering the pH, solid dispersion and using cosolvents but excess amount of these agents may have adverse effect.

Mixed solvency concept was proposed by Dr. R.K. Maheshwari in 2009. Mixed solvency concept states that each and every substance whether liquid, solid or gas present in universe possesses solubilizing power. All substances present in liquid state at room temperature are known as solvents. No solvent is universal solvent. Whatever the name of solvent we take, it is good solvent for some solutes and bad solvent for others. When the molecules of gas or solid attain a liquid state, they may also be involved in hydrogen bonding and weak van der Waals force with the molecules of solute for the dissolution of solute. Mixed solvency process includes intermolecular interactions with several balancing forces, rather than either a specific complexation event or a process dominated by a medium effect, like co-solvency or salting in, mixed solubilizers have been observed to enhance the aqueous solubility of poorly soluble drugs (like salicylic acid, naproxen, ornidazole etc.)

The mixed solvency concept explains 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 combination of several solubilizers in safe concentrations. If this solution increases the solubility of insoluble drug 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 use of proper solubilizers.
- The mixed solvency approach can be utilized to perform titrimetric and spectrophotometric analysis of poorly soluble drugs precluding the use of organic solvents.
- Synergistic action in solvent character can be obtained.
- For example solubilities of ibuprofen in aqueous solutions of, 40% w/v PEG-4000, 40% w/v urea and 40% w/v sodium citrate are 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% has solubility of 1.329% w/v for ibuprofen. This shows synergistic solvent action due to application of mixed solvency concept.
- 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.
- Mixed solvency concept may reduce the total concentration of individual solubilizers necessary to produce modest increase in solubility by employing additives in lower concentrations from the point of view of safety of solubilizers. This approach shall be applicable to prepare different dosage forms of the poorly soluble drugs.

Table 1, Table 2 and Table 3 list some organic solvents which are harmful and toxic.

Table1: Class-I Organic Solvents

SOLVENTS	CONCERNS
Benzene	Carcinogenic
Carbon tetrachloride	Toxic and environmental hazard
1,2- Dichloroethane	Toxic
1,2- Dichloroethene	Toxic
1,1,1- trichloroethylene	Environmental hazard

Table 2:Class-II Organic Solvents

Acetonitrile	Methyl cyclo hexane	Chlorobenzene
Chloroform	Methylene chloride	Nitro methane
Ethylene glycol	Pyridine	Formamide
Toluene	Hexane	Sulfolane
Methanol	Tetrahydrofuran	2-Methoxy ethanol
Tertalin	1,2-Dichloroethane	1,4- Dioxane
1,2-Dimethoxy ethane	N,N-dimethylformamide	N,N-dimethylacetamide
Trichloroethylene	N- methylformamide	Methylbutylketone

Table 3:Class-III Organic Solvents

Acetic acid	Cumene	Heptane
Acetone	Ethyl ether	Pentane
Anisole	1-Propanol	2- Propanol
1-Butanol	Isobutanol acetate	Ethyl acetate
2- Butanol	1-Pentanol	Ethyl formate
Ethanol	Methyl acetate	Butyl acetate
Ethyl formate	Propyl acetate	Dimethyl sulfoxide
Formic acid	Isopropyl acetate	Trimethyl amine

Solubilizing power of solids shall minimize the use of harmful organic solvents in future. Class –III organic solvents are relatively safer than class- II and class- I organic solvents. We can potentiate the solvent power of class- III organic solvents by dissolving safe solids in them to replace class- II and class- I organic solvents.

SOLIDS AS SOLVENT

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

I. By melting
II. By dissolution
III. By eutectic formation

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

I. By melting

Molecules of solid may come in 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 1gm 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 500mg of nalidixic acid (m.p. of nalidixic acid is 230℃). 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.)

II. By eutectic formation

Table 4 and Table 5 exemplify the fact that eutectic liquid possesses good solubilizing properties for compounds listed in left column. Eutectic liquid possesses bad solubilizing properties for compounds listed in right columns. If we check solubilities of a large number of compounds, some will fall in left column and other will fall in right column. Thus we can say that eutectic liquid is behaving like solvent. It is thus proved that eutectic liquid can be used as 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 liquid state to express 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 4: 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 5mg/ml)
Atenolol (>90mg/ml)	Furosemide (<5mg/ml)
Ornidazole (>120mg/ml)	Nimesulide (<5mg/ml)
Benzocaine (>120mg/ml)	Aspartame (<5mg/ml)
Eudragit RSPO (>300mg/ml)	Carvedilol (<5mg/ml)
Resorcinol (>190mg/ml)	Gatifloxacin (<15mg/ml)
Eudragit RLPO (230mg/ml)	Piroxicam (<15mg/ml)
Diltiazem HCL (>150mg/ml)	Methyl paraben sodium (<5mg/ml)
BHA (>150mg/ml)	
Salicylic acid (>70mg/ml)	

(Note – do not relate with formulation)

Table 5: Eutectic Mixture (Thymol: Menthol 1:1) pH6.5

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

(Note – do not relate with formulations)

III. By dissolution in a solvent

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

- Solubility of ibuprofen in water = 0.028% solubility of ibuprofen in 2 M sodium benzoate (28.8% w/v sodium benzoate solution) = 2.390%.
  85 - times solubility enhancement. Molecules of sodium benzoate have come in liquid state. These molecules are responsible for hydrogen bonds and weak van der Waals forces with the molecules of ibuprofen hence there is high solubility.
- Solubility of furosemide in ethanol = 1.7% w/v.
  Solubility of furosemide in 15% w/v niacinamide solution in ethanol = 5%. Molecules of niacinamide have come in liquid state.
- 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 120 mg/ml. molecules of sodium acetate and sodium caprylate have come in liquid state.

SOLUBILIZING PROPERTIES OF GASES

Molecules of gases may come in liquid state by two methods:

- By liquefaction.
- By dissolution in a solvent.

1. **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 of herbal powders etc. Molecules of carbon di oxide have come in liquid state by liquefaction and are responsible for dissolution of solutes due to hydrogen bonding and weak van der Waals forces. To enhance the solubilizing properties of liquefied carbon di oxide for some solutes, other co solvents like methanol, ethanol etc. is used. Thus it proved that, liquefied carbon di oxide is good solvent for some solutes and bad solvents for other solutes.

2. **BY DISSOLUTION**

Molecules of a gas may come in liquid state by dissolution in a solvent e.g. concentrated HCl is obtained by dissolution of HCl gas in water. Concentrated HCl is 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 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 also possess solubilizing properties.

APPLICATIONS OF MIXED SOLVENCY CONCEPT

A. IN TITRIMETRIC ANALYSIS

1. Maheshwari employed mixed solvency concept to analyze salicylic acid in the bulk drug precluding the use of organic solvents (a way to green chemistry). The mean value of percentage drug obtained was are very close to 100, indicating the accuracy of the proposed methods of analysis. Also, these values of the mean percentage drug estimated was very close to the value of mean percentage estimated by a standard method of Indian pharmacopoeia, which confirmed the accuracy of the proposed methods. The proposed analytical methods were further validated by satisfactorily low values of standard deviation, percentage coefficient of variation, and standard error.[2]
2. Maheshwari used mixed -solvency concept for solubility enhancement of poorly water-soluble drug, salicylic acid (as model drug). Various blends containing so called hydrotropes (urea and sodium citrate), cosolvents (glycerin, propylene glycol, PEG-300 and PEG-400) and water - soluble solids (PEG-4000 and PEG-6000) were made to study the influence on solubility of salicylic acid. Most of the blends were found to increase the solubility of salicylic acid synergistically. In the present investigation, the mixed solvency concept has been employed to analyze salicylic acid in the bulk drug sample precluding the use of organic solvents (a way to green chemistry). [3]
3. Jain et al. employed sodium citrate (12% w/v), sodium benzoate(18% w/v), and sodium salicylate (6% w/v), solutions as hydrotropic solubilizing agents to enhance the solubility of aceclofenac drug for its titrimetric analysis. After analysis approximately 100% recovery has been observed. Thus it confirms the accuracy of this technique.[4]
4. Maheshwari developed titrimetric method for the quantitative estimation of furosemide bulk drug and in tablets, with the help of novel application of mixed solvency concept. Furosemide is less soluble in ethanol. To increase the solubility of furosemide, a solution of niacinamide in ethanol (15% w/v) was used. This solvent system was utilized to solubilize the furosemide for its titrimetric analysis. Therefore this solvent system was safer than di methyl formamide, which is a harmful organic solvent used in a pharmacopoeial method. Mixed solvency concept can be utilized to prepare combined concentrated aqueous solutions (in different strengths) of various water soluble additives from the categories of hydrotropes like sodium benzoate, sodium ascorbate, sedum citrate, niacinamide, urea, co-solvents, like glycerin, propylene glycol, ethanol, PEG-200, PEG-300, PEG-400, PEG-500, PEG-600, water soluble solids like PVP, PEG-4000, PEG-6000, PEG-8000, PEG-10000 and cyclodextrins employing them in small safe concentrations to solubilize the poorly water soluble drugs and develop their dosage forms.[5]
5. Jhariya et al. applied mixed solvency approach to overcome the use of hazardous organic solvents like chloroform, benzene, ethanol etc. to enhance the solubility of salicylic acid in aqueous medium, solubilizers such as sodium citrate (5% w/v), glycerin (5% w/v), PEG-400 (5% w/v), urea (5% w/v), PEG-300 (10% w/v) and PEG-4000 (10% w/v) was added. By using this blend solubility of salicylic acid was improved by many folds. Thus this method was proved to be accurate, precise, and reproducible. Therefore the concept is a boon in pharmaceutical field as well as way towards the green chemistry.[6]
6. Maheshwari applied mixed solvency approach for the enhancement of aqueous solubility of a poorly water soluble drug, ibuprofen. It was done by preparing blends and keeping the total concentration constant of randomly selected water soluble substances from among the hydrotropes (urea, sodium benzoates, sodium citrate), water soluble solids (PEG-4000 and PEG-6000) and co-solvents (PEG-300 and PEG-400). Solubility of ibuprofen in distilled water is 0.28% w/v. Three blends (PEG-400, PEG-4000, urea, sodium citrate), (propylene glycol, PEG-400, PEG-4000, sodium citrate), (PEG-300, PEG-400, urea, sodium citrate) they showed good solubility and synergistic effect on solubility of ibuprofen. Therefore, they were utilized to solubilize the poorly water soluble drug, ibuprofen to carry out its titrimetric estimation precluding the use toxic organic solvent. The mean percentage drug estimated by using above three blends was found to be 99.08 %, 100.24 and 98.69% respectively. These values were very close to 100% which indicates the accuracy of the method. [7]

Table 6 illustrates various drugs estimated by using titrimetric method.

Table 6: Application of Mixed Solvency concept in titrimetric analysis

S. No.	Blend solubilizers	Drugs	Organic solvent used in an official method	Solubility enhancement	References
1.	15% Niacinamide solution in ethanol	Furosemide	Dimethyl formamide	More than 3 times	5
2.	5% Glycerin +10% PEG-300 +10% PEG-4000 +5% PEG-400 + 5% Sodium citrate +5% Urea	Salicylic acid	Ethanol	More than 54 times	6
3.	PEG-400 +PEG-300 + Urea + Sodium citrate (10% w/v each)	Ibuprofen	Ethanol	More than 40 times	7

B. IN UV SPECTROPHOTOMETRIC ANALYSIS

- **Solid solubilizers as solvent**

UV spectroscopy is used routinely in analytical chemistry for the quantitative determination of different analytes. Methods discussed for spectrophotometric estimation are ecofriendly and follow the concept of green chemistry.

1. **Estimation of tinidazole tablets by mixed solvency concept:**

Maheshwari et al. prepared two blends by using sodium benzoate, niacinamide and PEG-6000 and tried to solubilize the tinidazole according to mixed solvency concept. More than 3- fold increment in solubility of tinidazole was observed in blend -1 having 8% w/v sodium benzoate, 2% w/v niacinamide, 3% w/v PEG-300, 7% w/v glycerin, 3% w/v propylene glycol and 4% w/v PEG-6000) and blend-2 having 7% w/v sodium benzoate, 3% w/v niacinamide, 8% w/v PEG-300, 4% w/v glycerin, 4% w/v propylene glycol and 4% w/v PEG-6000). These blends were employed to dissolve the drug from powder of its tablet. Calibration curve was plotted with the help of recorded absorbances. The absorbance of standard solutions of 5, 10, 15, 20 and 25 ug/ml was noted at 318nm against reagent blank. The results of the analysis were validated statistically and by recovery studies. The percentage label claims and percentage recoveries estimated were close to 100 with low values of standard deviation, percentage coefficient of variation and standard error for both the formulations. Thus, the method was accurate providing additional advantage of being cost effective and environment friendly.[8]

2. **Estimation of gatifloxacin tablets using mixed solvency concept:**

Bhawasar et al. employed the concept of mixed solvency for solubility enhancement of poorly water-soluble drug gatifloxacin. Solubility of gatifloxacin was increased by using sodium citrate, sodium benzoate, glycerin, and PEG-4000 (10% each w/v). Mixed solvency concept utilized to analyze gatifloxacin in the bulk drug sample without using toxic organic solvents. Standard stock solutions of 20, 40, 80, 100 and, 120 µg/ml made with distilled water and absorbance noted at 333nm to plot the calibration curve. The percentage label claimed were very close to 100 which indicates that the method used for spectrophotometric estimation was accurate and precise.[9]

3. **Estimation of naproxen tablets using mixed solvency concept:**

Upadhyay et al. investigated that several organic solvents like methanol, chloroform, ethanol, acetonitrile, hexane, and toluene used to carry out the spectrophotometric analysis but its higher cost and toxicity prevents their frequent use. The solubility of naproxen was enhanced by more than 79 fold in one blend having 8% w/v sodium benzoate, 3% w/v PEG-300, 7% w/v PEG -3000, 7% w/v glycerin, 3% w/v propylene glycol and 2% w/v niacinamide as compared to distilled water. The above blend was used for spectrophotometric estimation of naproxen at 331nm. The results of the analysis were validated statistically and by recovery studies. The drug follows beer's law in a concentration range of 50-300 µg/ml. The percentage label claims and percentage recoveries estimated were close to 100 with the low value of standard deviation. Thus, the method used for spectrophotometric estimation was accurate, reproducible and precise. [10]

4. **Estimation of gatifloxacin tablets by using mixed solvency concept:**

Upadhyay et al. developed a new method for spectrophotometric analysis of gatifloxacin in solid dosage form by using mixed hydrotropic agents. More than 4-fold increment was obtained in the solubility of gatifloxacin in the blend containing propylene glycol, PEG-400, PEG-4000, and sodium citrate (10% w/v each) as compared to distilled water. The spectrophotometric estimation of gatifloxacin was done at 288nm. The results of the analysis were validated statistically and by recovery studies. The method obeyed Beer's law in a concentration range of 4-20 µg/ml. The percentage label claims and percentage recoveries estimated were close to 100 with low values of standard deviation. The mixed solvency concept used in the present study did not interfere in this analysis. [11]

5. Estimation of diclofenac sodium tablets by using mixed solvency concept:

Khan et al. aimed to overcome the problem with diclofenac sodium tablets for spectrophotometric estimation (at 276nm), a blend of PEG-300, PEG-400, PEG-6000 and 10% urea each was employed considering the additives not to interfere with the analysis. The data obtained from the proposed method was very secure to those obtained from the standard method (as per the IP method). The solubility of diclofenac sodium was improved by 14 folds compared to distilled water and the percentage label claimed and percentage recovery estimated was close to 100% with having negligible standard deviation and standard error. [12]

6. Estimation of cefixime trihydrate tablets by using mixed solvency concept:

Padiyar et al. developed new method which is economic, ecofriendly, accurate and reproducible for quantitative analysis of cefixime trihydrate tablets. It was investigated that aqueous blend having 5% **w/v** each of sodium citrate, glycerine, PEG-300,PEG-400, urea and 10% **w/v** PEG-4000 was used for solubilization of poorly water soluble drug, cefixime trihydrate to conduct the spectrophotometric analysis. According to mixed solvency concept, each substance whether it may gas, liquid or solid possesses solubilizing power. The solubility of cefixime trihydrate increased to more than 120 fold as compared to water solubility. Calibration curve of cefixime trihydrate was plotted by recording absorbances of standard solutions of 5,10,15,20 and 25 µg/ml at 288nm against respective reagent blank. No interference of solubilizers was seen above 245nm. The percentage drug content in two types of marketed tablets was found very close to 100 with low value of standard deviation. Thus, the method was accurate providing additional advantage of being cost effective and environment friendly.[13]

7. Estimation of cefixime tablets by using mixed solvency concept:

Jain et al. developed UV-spectrophotometric method which was validated as per ICH. The investigation was proposed to solubilize Cefixime by use of mixed solvency concept. A mixed solvent system of 10% w/v sodium caprylate,10% w/v sodium citrate and 10% urea was used for the method development. Cefixime shows maximum absorbance in the concentration range of 5-25 µg/ml at 288 nm. Method of analysis has been validated for different parameters like linearity, accuracy, precision, LOD and LOQ. The analytical method was found to be simple, safe (free from toxicity), economic and eco-friendly.[14]

8. Estimation of piroxicam tablets by using mixed solvency concept:

Manzoor et al. developed a novel method to estimate spectrophotometrically, the piroxicam drug, in tablet formulations without the use of organic solvent. In the investigation, an attempt was made to show that solids can also be wisely used for forbidding organic solvents. The main objective of the present study is to demonstrate the solvency of solid. In the present study, a co-melt (resorcinol and dimethyl urea) obtained by melting resorcinol and dimethyl urea in the ratio of 4:1 on weight basis to extract (dissolve) piroxicam from fine powder of tablets. Distilled water was used for dilution purpose to carry out spectrophotometric estimation at 358 nm without utilizing any organic solvent. Proposed spectrophotometric analytical method is novel, rapid, free from toxicity of organic solvent, accurate and reproducible. The recovery studies and statistical data confirmed the accuracy. Resorcinol, di-methyl urea and the tablet excipients did not interfere in the spectrophotometric estimation at 358 nm.[15]

Table- 7 illustrates the use of solids as a solubilizer to prepare different blends.

Table 7: Application of mixed solvency in spectrophotometric analysis (Solid as solubilisers)

S. No.	Drug	Blend composition	References
1	Tinidazole	i - 8% Sodium benzoate + 2% Niacinamide + 3% PEG-300 + 7% Glycerin + 3% Propylene glycol + 4% PEG-6000 ii – 7% Sodium benzoate + 3% Niacinamide + 8% PEG-300 + 4% Glycerin + 4% Propylene glycol + 4% PEG-6000	8
2	Gatifloxacin	10% Sodium citrate + 10% Sodium benzoate + 10% Glycerin + 10% PEG-4000	9
3	Naproxen	8% Sodium benzoate + 3% Niacinamide +3% PEG-300 +7% PEG-6000 + 7% Glycerin +3% Propylene glycol +2% Niacinamide	10
4	Gatifloxacin	10% Propylene glycol + 10% PEG-400 + 10% PEG-4000 + 10% Sodium citrate	11
5	Diclofenac Sodium	12% Urea + 8% PEG-300 + 5% PEG-400 + 5% Sodium citrate	12
6	Cefixime Trihydrate	5% Sodium citrate + 5% Glycerin + 5% PEG-300 + 5% PEG-400 + 5% Urea +10% PEG-4000	13
7	Cefixime Tablets	10% Sodium caprylate + 10% Sodium citrate + 10% Urea	14
8	Piroxicam	Resorcinol + Di-methyl urea	15

- **Eutectic liquids as solvent**

1. Estimation of norfloxacin tablets by using phenol as solvent:

Maheshwari found that solids can also be act as solvent (i.e solids possesses solvent character) to enhance the solubility of poorly soluble drugs. Norflaxacin was analysed with the help of phenol. Soxhelation was performed by using phenol as solvent. The vapours of boiling phenol got condensed in extraction chamber to effect the extraction of active constituents form powder of crude drugs. The aim of this estimation is to demonstrate solvent action of solids. 0.88 mg/ml norfloxacin was dissolved in distil water while 100 mg of norfloxacin dissolves in 1 gram of melted phenol at 50-60 ℃. It was investigated that at 50-60℃ phenol can be used as solvent to extract out the drug from powder of norfloxacin tablets. For dilution purpose distilled water was used. Absorbances of standard solutions containing 5,10,15,20 and 25 µg/ml were noted at 324nm against reagent blanks to obtain calibration curve. The proposed method is new, simple, environment friendly, accurate and reproducible. The proposed method can be successfully employed in the routine analysis of narfloxacin tablets. Melted phenol can also be tried with other water insoluble drugs which are estimated above 300nm because phenol does not interfere above 300nm.[17]

2. Estimation of nalidixic acid by using eutectic liquid of phenol and niacinamide:

Fouzdar et al. employed a eutectic liquid of phenol and niacinamide to enhance the solubility of nalidixic acid. Phenol and niacinamide were triturated in 25:10 ratio basis of weight to prepare a eutectic liquid. Eutectic liquid was used to dissolve nalidixic acid drug from fine powder of tablets. Dilutions of 10, 20, 30 and 40 µg/ml were made with distilled water to carry out spectrophotometric analysis at 330nm without using organic solvent. Point two mg/ml nalidixic acid dissolved in distilled water at room temperature while solubility of nalidixic acid in eutectic liquid was more than 138 mg/ml. The presence of tablet excipients, phenol and niacinamide did not interfere in the spectrophotometric estimation at 330nm because both phenol and niacinamide do not interfere above 300 nm.[18]

3. Estimation of ornidazole tablet by using eutectic liquid of phenol and lignocaine hydrochloride:

Pandey et al. prepared a eutectic liquid by triturating phenol and lignocaine hydrochloride in 4:1 ratio on the basis of weight. Eutectic liquid was utilized to extract ornidazole drug from fine powder to its tablets. Distilled water was used for dilution to carry out spectrophotometric estimation at 319 nm without using organic solvent. The solubility of ornidazole in distilled water was 8.03 mg/ml while in eutectic was more than150 mg/ml. This spectrophotometric analysis method is novel, rapid, free from toxicity of organic solvent, accurate and reproducible. The presence of tablet excipients, phenol and lignocaine hydrochloride did not interfere in spectrophotometric estimation at 319 nm because phenol dose not interfere above 300 nm and lignocaine hydrochloride did not interfere above 310nm.[19]

4. Estimation of tinidazole tablet by using eutectic liquid of phenol and niacinamide:

Jain et al. employed eutectic liquid of phenol and niacinamide to extract out the tinidazole drug from the fine powder of tablets. Eutectic liquid was prepared by triturating phenol and niacinamide in the ratio of 25:10 on the basis of weight. This eutectic was employed to dissolve tinidazole drug from fine powder of tablets. Dilutions of 5, 10, 15, 20 and 25 µg/ml were prepared with the help of distilled water and absorbance noted at 318nm against reagent blank. Both phenol and niacinamide did not interfere above 300nm.[20]

5. Estimation of ornidazole by using phenol as solvent:

Jain et al. employed mixed solvency by using phenol as solvent. The vapours of boiling phenol got condensed in extraction chamber to effect the extraction of active constituents from powder of crude drugs. Solid excipients can nicely be employed as solubilizers in the development of pharmaceutical dosage form in soluble form of poorly soluble drugs. The solvent character of melted phenol (at 50-60℃), spectrophotometric analysis of ornidazole tablets. Solubility of ornidazole in distilled water was found to be 8.03mg/ml while in phenol was more than 700 mg per gram. Melted phenol was employed to extract out the drug from powder of ornidazole tablets. Dilutions were made with the help of distilled water. Absorbances of standard solutions containing 5, 10, 15 20 and 25 µg/ml were noted at 319 nm against reagent blanks to obtain calibration curve. Phenol does not interfere in spectrophotometric estimation above 300nm.[21]

6. Estimation of tinidazole tablets by using eutectic liquid of phenol and metformin hydrochloride:

Shah et al. performed a spectrophotometric analysis with the help of ecofriendly, novel concept of mixed solvency. Eutectic liquid was prepared by triturating phenol and metformin hydrochloride in the ratio of 4:1on the basis of weight. The blend was utilized to dissolve the tinidazole drug from fine powder of its tablets. Distilled water was used to prepare dilutions. Absorbances of standard solutions of 10, 20, 30 and 40 µg/ml were noted at 318 nm against reagent blank. The presence of tablet excipients, phenol and metformin hydrochloride did not interfere in the spectrophotometric estimation at 318 nm because phenol and metformin hydrochloride does not interfere above 300 nm.[22]

7. Estimation of satranidazole tablet by using eutectic mixture of phenol and metformin hydrochloride:

Sharma et al. prepared a eutectic mixture by triturating phenol and metformin hydrochloride in the ratio of 4:1 on the basis of weight. This eutectic mixture was employed to dissolve satranidazole from fine tablet triturate powder. Dilution of standard solution of 10, 20, 30, 40 µg/ml with the help of distilled water and absorbance were noted at 320 nm without using any type of toxic organic solvents. Solubility of satranidazole in distilled water at room temperature was 6.41 mg/ml while the solubility of satranidazole in mixture was more than 150 mg/ml. Both phenol and metformin hydrochloride does not interfere above 300nm.[23]

8. Estimation of metronidazole tablets by using eutectic liquid of phenol and niacinamide:

Maheshwari et al. utilized the eutectic liquid to enhance the solubility of poorly soluble drug metronidazole precluding the use of harmful organic solvents. Eutectic liquid consisting of phenol and niacinamide in 25:10 ratio on weight basis for spectrophotometric estimation of metronidazole tablets. Solubility of metronidazole in distilled water at room temperature was found to be 7.28 mg/ml while more than 80 mg of metronidazole dissolves in 1ml of eutectic liquid. The eutectic liquid was utilized to extract out the drug from tablet powder of metronidazole tablets. Distilled water was used to prepare dilutions.

Absorbance of standard solution of 5, 10, 15, 20 and 25 µg/ml was noted at 320 nm against reagent blank to calculate the amount of drug in the tablet. Both phenol and niacinamide does not interfere above 300nm.[24]

9. Estimation of tinidazole tablets by using eutectic liquid of phenol and lignocaine hydrochloride:

Maheshwari et al. performed the spectrophotometric analysis of tinidazole table by using a novel concept of mixed solvency. Tinidazole has got the poor solubility in distilled water while significantly high solubility in a eutectic liquid of two solid, namely phenol and lignocaine hydrochloride. Eutectic liquid of phenol and lignocaine hydrochloride in the ratio of 4:1 on weight basis was prepared by vigorous trituration. This eutectic liquid was employed to act as a solvent to extract out the drug tinidazole from the fine powder of its tablets for spectrophotometric estimation at 318 nm. Necessary dilutions were done using distilled water. Solubility of tinidazole in distilled water is 5.38 mg/ml at room temperature while in the approximate solubility in eutectic mixture was more than 200 mg/ml. Tablet excipients along with phenol and lignocaine did not interfere at 318nm.[25]

10. Estimation of nalidixic acid by using niacinamide as solvent:

Apte et al. developed the novel spectrophotometric analytical technique for quantitative estimation of nalidixic acid in tablets using melted niacinamide as solvent. Niacinamide possesses large solubilizing power for nalidixic acid and have approximate solubilty more than 80 mg/ml of melted niacinamide (135℃) whereas aqueous solubility of nalidixic acid is 0.21 mg/ml at room temperature. Calibration curve of nalidixic acid was plotted by reporting the absorbances of standard solutions. The absorbances were observed at 330 nm against respective reagent blanks. The percentage label claim was very close to 100 with significant low values of percentage deviation and standard error. Thus, it indicates that the above method used for spectrophotometric estimation is safe, simple, precise and excludes the use of toxic organic solvents.[26]

11. Estimation of piroxicam tablets by using melted niacinamide:

Mohadikar et al. found that, niacinamide possesses large solubilizing power for piroxicam and have approximate solubility 110 mg/ml of melted niacinamide (135℃) while aqueous solubility of piroxicam was found to be 0.40 mg/ml at room temperature. Calibration curve of piroxicam was plotted by recording the absorbances of standard solutions of 5, 10, 15, 20 and 25 µg/ml at 358nm against respective reagent blanks. The percentage label claim was very close to 100 with significant low values of percentage coefficient of variation and standard error. Thus, it indicates that the method used for the spectrophotometric estimation is safe, simple, and precise and excludes the use of toxic organic solvents. Niacinamide does not interfere above 300nm in spectrophotometric analysis.[27]

12. Estimation of furosemide by using phenol as solvent:

Maheshwari performed spectrophotometric estimation of furosemide by the help of an eco-friendly method. Furosemide is estimated spectrophotometrically by an ecofriendly method. For this purpose, melted phenol (50-60℃) was utilized to extract out the drug from powder of furosemide tablets. Absorbances of standard solutions containing 20, 40, 60, 80 and 100 µg/ml were noted at 330 nm against reagent blank to observe the calibration curve. Recovery studies and statistical data proved the reproducibility, accuracy and precision of the proposed method. Phenol and excipients of tablet did not interfere in spectrophotometric estimation of furosemide at 330nm.[28]

13. Estimation of piroxicam tablets by using eutectic liquid of phenol and metformin hydrochloride:

Goyal et al. performed spectrophotometric estimation of piroxicam tablets by using an ecofriendly and novel method. The eutectic liquid was obtained by triturating phenol crystals and metformin hydrochloride in ratio 4:1 on weight basis was employed to dissolve the piroxicam drug from fine powder of tablets. Dilutions were prepared by using distilled water to perform the spectrophotometric estimation at 358 nm. The solubility of piroxicam in distilled water at room temperature was found to be 0.4 mg/ml while the solubility in eutectic liquid was more than 125mg/ml. the method suggested in this spectrophotometric estimation was novel, free from organic solvents, accurate and précised. Phenol, metformin hydrochloride and tablet excipients did not interfere in spectrophotometric estimation at 358nm.[29]

Table-8 shows some solids as eutectic liquid and as solvent.

Table 8: Some solids can be used as solvent to perform the spectrophotometric analysis

S. No.	Drug	Solid as solvent	References
1.	Salicylic acid	Calcium disodium edentate	16
2.	Norfloxacin tablet	Phenol	17
3.	Nalidixic acid	Eutectic liquid of phenol and niacinamide	18
4.	Ornidazole tablet	Eutectic liquid of phenol and lignocaine hydrochloride	19
5.	Tinidazole tablet	Eutectic liquid of phenol and niacinamide	20
6.	Ornidazole	Phenol	21
7.	Tinidazole tablet	Eutectic liquid of phenol and metformin hydrochloride	22
8.	Satranidazole	Eutectic liquid of phenol and metformin hydrochloride	23
9.	Metronidazole	Eutectic liquid of phenol and niacinamide	24
10.	Tinidazole tablet	Eutectic liquid of phenol and lignocaine hydrochloride	25
11.	Nalidixic acid	Niacinamide	26
12.	Piroxicam tablet	Melted niacinamide	27
13.	Furosemide	Phenol	28
14.	Piroxicam tablet	Eutectic liquid of phenol and metformin hydrochloride	29

C. In TLC:

Thin layer chromatography is a chromatography technique used to separate mixture of chemical substances into its individual compounds. Chromatography consists of two phases: one mobile phase and one stationary phase. TLC plate (stationary phase) is prepared by mixing the silica gel with water. A suitable solvent (mobile phase) is moved along with compound mixture through the TLC plate according to the polarity and the degree of adhesion of each component on the stationary phase. Solutions containing hydrotropic and mixed hydrotropic agents can be used as mobile phases in different proportions so as to adjust polarity/non-polarity and obtain results with negligible tailing effects. Hydrotropic solubilization has been used for enhancing the aqueous solubility of large number of poorly water-soluble drugs.

Various solvent systems employed for TLC of selected as per Indian Pharmacopoeia are as follows table 9.

Table 9: Pharmaceutical methods for TLC of selected drug

S.No.	Drug	Regulatory book	TLC Method	Test solution solvent
			Mobile phase	
1.	Ciprofloxacin HCl	IP	A mixture of 40 volumes of dichloromethane, 40 volumes of methanol, 20 volumes of strong ammonia solution and 10 volumes of acetonitrile	Water
2.	Guaphenesin	IP	A mixture of 80 volumes of carbon tetra chloride and 20 volumes of ethanol (95%)	Dichloromethane
3.	Piperazine citrate	IP	A mixture of 80 volumes of acetone and 20 volumes of strong ammonia solution	80 volumes acetone +20 volumes strong ammonia solution
4.	Propranol HCl	IP	A mixture of 90 volumes of toulene and 10 volumes of methanol	Methanol
5.	Pyridoxine HCl	IP	A mixture of 65 volumes of acetone, 13 volumes of dichloromethane, 13 volumes of tetrhydrofuran and 9 volumes of strong ammonia solutions	Water

A large number of organic solvents, viz. butanol, acetic acid, hexane, acetone, chloroform, ether, ethyl acetate, ethanol, toluene, dichloromethane, heptane, benzene, methanol, acetonitrile, carbon tetrachloride and cyclohexane are employed to perform thin-layer chromatography (TLC) of various drugs. Most of these organic solvents are costly and hazardous to health. Some organic solvents have been reported to be carcinogenic. To a certain extent, such solvents are responsible for environmental pollution also. Also, their disposal requires stringent procedures which makes the process both costly and typical. In the present investigation, hydrotropic and mixed hydrotropic solutions were employed as mobile phase to perform TLC of some drugs precluding the use of organic solvents. Propranolol hydrochloride, Guaifenesin, Ciprofloxacin hydrochloride, Pyridoxine hydrochloride, Lidocaine hydrochloride, Thiamine hydrochloride, Metformin hydrochloride, Piperazine citrate and Losartan potassium were selected as model drugs. Sodium benzoate, sodium citrate, sodium acetate, & niacinamide in various combinations were employed as model hydrotropic agents. In the case of the proposed methods, solutions of the above listed hydrotropic agents in distilled water in different concentrations were employed as mobile phases to perform TLC of the selected drugs. The observed R_f values in the case of proposed methods ranged from 0.33 to 0.84. As per mixed solvency concept, solids also possess solubilizing properties. In mixed hydrotropy, the composition of blends containing various hydrotropic agents can be varied in such a way that proper R_f value of drug spot is obtained without tailing effect. The proposed TLC methods are new, simple, cost-effective, environment-friendly, and safe. In future, hydrotropic solutions shall prove a boon in TLC and high performance thin layer chromatography (HPTLC) analysis of a vast number of drugs discouraging the use of organic solvents to a great extent.[30]

Various TLC studies by using mixed solvent systems are shown in table 10.

Table 10:- TLC studies in various mixed solvent systems

S. No.	Drug	Blend	Rf value
1	Propranolol HCl	7.5% Niacinamide + 7.5% Sodium benzoate	0.80
2	Guaiphenesin	5% Sodium benzoate + 5% Sodium acetate	0.64
		5% Sodium benzoate + 5% Niacinamide	0.70
		5% Sodium benzoate + 5% Sodium citrate	0.69
		10% Sodium benzoate	0.82
		5% Sodium acetate + 5% Sodium citrate	0.66
3	Ciprofloxacin HCl	5% Sodium citrate + 5% Niacinamide	0.47
4	Vitamin B6 HCl	5% Sodium acetate + 5% Sodium citrate	0.84
5	Lidocaine HCl	5% Sodium benzoate + 5% Sodium acetate	0.42
		5% Sodium benzoate + 5% Niacinamide	0.42
		5% Sodium benzoate + 5% Sodium citrate	0.45
		10% Sodium benzoate	0.41
		5% Sodium acetate + 5% Niacinamide	0.37
		5% Sodium citrate + 5% Niacinamide	0.37
		5% Sodium acetate + 5% Sodium citrate	0.37
6	Vitamin B1 HCl	5% Sodium benzoate + 5% Niacinamide	0.48
		10% Sodium benzoate	0.33
7	Metformin HCl	5% Sodium benzoate + 5% Sodium citrate	0.66
		5% Sodium acetate + 5% Sodium citrate	0.56
8	Piperazine HCl	5% Sodium benzoate + 5% Sodium acetate	0.67
		5% Sodium benzoate + 5% Niacinamide	0.65
		5% Sodium benzoate + 5% Sodium citrate	0.60
		5% Sodium acetate + 5% Sodium citrate	0.65
9	Losartan Potassium	5% Sodium benzoate + 5% Sodium acetate	0.73
		5% Sodium benzoate + 5% Sodium citrate	0.63
		10% Sodium benzoate	0.80
		5% Sodium acetate + 5% Niacinamide	0.60
		5% Sodium citrate + 5% Niacinamide	0.56

From the table we can say that the R_f values obtained by the employed methods using the mixed solvent system as mobile phases were nearly satisfactory. The proposed methods were mostly devoid of the tailing effect. Time effectiveness was also observed.

SUMMARY AND CONCLUSIONS

The analytical studies like UV spectrophotometry, titrimetry, TLC, HPLC conducted in pharmaceutical industries, government analytical laboratories, forensic science laboratories etc. involve the use of harmful organic solvents like methanol, hexane, xylene, chloroform, dimethylformamide, diethyl amine, dichloromethane, acetone, ethanol, benzene, carbon tetrachloride, ethyl acetate, toluene, propanol, butanol, tetralin, pyridine, ethyl ether, dimethyl sulfoxide, trimethyl amine,1,4-dioxane, cyclohexane, chlorobenzene, nitro methane, tetrahydrofuran, methylene chloride, 1,2-dichloroethane, formic acid, 1,2-dimethoxy ethane, methyl cyclo hexane and heptane. Most of the class I and II organic solvents are very hazardous to human being. Some of them are carcinogenic as well. The disposal of organic solvents is typical and costly. In the above literature we have seen that all the proposed methods of TLC, UV spectrophotometry, titrimetry and HPLC analysis are simple, cost effective, ecofriendly and safe as they involve the use of mixed solvency which successfully replaced harmful organic solvents. These proposed methods gave the accurate and reproducible results. Such analytical methods are worth adoptable in various pharmacopoeias. Also, the analytical laboratories meant for new analytical method development may adopt such ecofriendly methods.

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