ORIGINAL ARTICLE

Development of Innumerable, Expectedly Safe, and Aqueous Systems to Make Intramuscular Aqueous Injections (Solutions) of Poorly Water-soluble Drugs using Mixed Solvency Concept

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Background: The primary goal of this research is to investigate the concept of mixed solvency in terms of developing a large number of safe solvent systems for aqueous intramuscular injections that include water-soluble additives. As a result, pharmaceutical industries can use these solvent systems to provide intramuscular injections of drugs that are poorly water-soluble. Safe solubilizers' solubilizing properties can be utilised to improve the solubility of poorly water-soluble drugs. **Objective:** The main purpose of this research is to provide pharmaceutical manufacturers with novel approaches for aqueous IM injections. **Materials and Methods:** In the present study, we employed sodium benzoate, sodium acetate, sodium citrate, valine, l-lysine, arginine, ethanol, Tween 80 and benzoic acid as solubilizers and ornidazole, paracetamol, aspirin, salicylic acid, gatifloxacin, naproxen, meloxicam, furosemide, piroxicam, acyclovir, fenofibrate, indomethacin, norfloxacin, and nimesulide. Furosemide was selected as the drug for the formulation of a typical aqueous IM injectable solution. For the drug identification, melting ranges were determined all the drugs using melting point apparatus (Analab Scientific). UV identification was also done for all drugs using UV-visible spectrophotometer (Shimadzu 1700). The pH of blend was estimated using pH meter (Cyber Scan). Drug and excipient interference studies were performed before formulation using UV-visible spectrophotometer. Drug and excipient interference studies also done before the formulation. The composition of formulation is L-lysine (3% w/v), sodium acetate (10% w/v), arginine (10% w/v), and Tween 80 (5% w/v). **Results:** By the solubility studies in different blends, the possibility of some IM injection solution can prepare such as furosemide (20 mg/2 ml), piroxicam (20 mg/2 ml), repaglinide (16 mg/3 ml), indomethacin (25 mg/ml), and acyclovir (20 mg/3 ml) can be produced. Furosemide: Chemical, physical, and freeze thaw studies were performed for the stability study of formulation. The formulation gives satisfactory results during physical and chemical stability studies. The pH of formulation was also performed and it was found similar to the pH of blend (pH-7). **Conclusion:** From this research work, it is clear that mixed solvency concept can be employed to develop a large numbers of expectedly safe aqueous IM injection solution type aqueous solvent systems for poorly water-soluble drugs. Thus, solubilizing power of safe additives can be employed to make marketable aqueous IM injections.

Key words: Furosemide, intramuscular injection, mixed solvency concept, poorly water-soluble drugs, solubility, solvent systems

INTRODUCTION

Parenteral (from the Greek para enterons, meaning "outside the gut") administration refers to the process of introducing nutrients, medications, or other compounds into the body by a pathway other than the alimentary canal. Because the body's natural defences are circumvented when a drug is administered parenterally as compared to orally or rectally, there is a significantly higher risk involved. They

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must be highly pure and absent of any physical, chemical, or biological contaminants as a result. The requirements set forth by the Food and Drug Administration are very strict, and as a result, the pharmaceutical firms that produce these kinds of pharmaceuticals are under a lot of pressure.[1,2] The fascial planes, the connective tissue surrounding the muscles, quickly distributes intramuscularly injected pharmaceutical solutions. Aqueous systems spread nearly immediately after infusion; oily solutions continue to spread for 1–5 min before becoming somewhat set in place. Oily solutions do not spread as widely as the solvent water.

Hydrotropy

In the presence of a significant concentration of an agent, or a hydrotropic agent, hydrotropic solubilization is the rise in the aqueous solubility of a drug that is poorly water-soluble. "A metallic salt of organic acid whose comparatively high concentration in water can improve the aqueous solubility of organic compounds that are merely slightly soluble in water," is how Newberg (1916) defined the term "hydrotropic agent." Salts that increase solubility are referred to as "salting in," whereas salts that reduce solubility are referred to as "salting out." In a particular solvent, additives can increase or decrease a solute's solubility. Salts that improve solubility are referred to as "salting in," and salts that reduce solubility are referred to as "salting out." The way an addition affects the structure of water or interacts with the water molecules in a solvent has a big impact on how it works. The phenomena of "HYDROTROPISM" are caused by salts with large anionic or cationic groups that are particularly soluble in water and are referred to as "Hydrotropic Salts."[3]

Benefits of hydrotropy

- It is a novel, efficient, safe, accurate, precise, and ecofriendly technique for analysing drugs with low water solubility.
- Considering the solvent character is independent of pH, has strong selectivity, and does not require emulsification, this approach is believed to be better to other methods such as micellar solubilization and cosolvency.
- Hydrotropy is a straightforward operation because all that is needed is a water mixture of the drug and hydrotrope.
- This approach does not involve chemically altering hydrophobic drugs, nor does it call for the formation of an emulsion system or the use of organic solvents.

Mixed hydrotropy

Dr. R.K. Maheshwari proposed the mixed hydrotropic solubilization approach in 2008. It is a novel and sophisticated technique for improving the solubility of pharmaceuticals that are poorly water-soluble. Mixed hydrotropic solubilization is the process of increasing the solubility of drugs that are poorly soluble in water by a factor of many using lower ratios of two or more hydrotropic agents. The ratio of a drug's solubility in a hydrotropic solution to its solubility in water, known as the solubility enhancement ratio, can be used to measure the increase in solubility.

Many drugs that are poorly water-soluble have had their aqueous solubility improved by mixed hydrotropic solubilization.[4-11]

Benefits of mixed hydrotropy

- Toxicities in pharmaceutical dosage forms may be caused by high concentrations of a single hydrotropic substance. To overcome the issue of toxicity of hydrotropic agent, mixed hydrotropic solutions comprising two or more hydrotropic agents in acceptable quantities may be used to make a marketable pharmaceutical dosage form.
- The analysis of poorly water-soluble substances (trimetric, spectrophotometric, and TLC analysis) may be done without the utilization of organic solvents in a novel, simple, economical, safe, accurate, precise, and environment friendly manner.
- It inhibits the use of organic solvents, preventing issues with residual toxicity, volatility-related inaccuracy, pollution, expense, and other issues.

Mixed solvency concept

Dr. R.K. Maheshwari proposed the mixed solvency concept in 2009. According to the mixed solvency concept, every substance in the universe, whether liquid, solid, or gas, possesses solubilizing power. Solvents are any substances that exist in a liquid state at room temperature. There is no such thing as a universal solvent. Whatever name we give a solvent, it is a good solvent for some solutes and a bad solvent for others. When gas or solid molecules become liquid, they may involve in hydrogen bonding and weak van der Waals forces with solute molecules to assist in solute dissolution.

The mixed solvency concept states that a concentrated solution comprising small quantities of multiple solubilizers might have additive, reduced, or synergistic solvent activities.

Several solubilizers can be combined in safe amounts to form a concentrated solution. This approach may resolve the toxicity issue in pharmaceutical formulations if it sufficiently increases the solubility of an insoluble substance.

- Using the right solubilizers, any weak solvent for a particular solute can be transformed into a strong solvent.
- Titrimetric and spectrophotometric examination of poorly soluble compounds can be carried out using the mixed solvency technique without the use of organic solvents.
- It is possible to achieve synergistic effect with solvent character.

Mixed solvency concept has been employed to enhance the solubility of several poorly water- soluble drugs.[7,12,13]

MATERIALS AND METHODS

Test tubes, Milli-Q water, Sodium benzoate ($C_3H_50_2MNa$), Sodium citrate (C6H5Na3O7), Sodium acetate($C_2H_3NaO_2$) (purchased from Rankem Pvt. Ltd. Mumbai), Tween 80 ($C_{32}H_{60}O_{10}$), Benzoic acid ($C_7H_6O_2$), Ethanol (CH_3CH_2OH) provided by SGSITS lab, Arginine ($C_6H_{14}N_4O_2$), L-lysine ($C_6H_{14}N_2O_2$) provided by Vishal pharmaceutical pvt. Ltd. APIs (Aspirin [procured as a gift sample from Shree Pharmaceuticals Indore], Naproxen [C14H14O3], Ornidazole [C7H10ClN3O3], Acyclovir [C8H11N5O3], Chlorthalidone [$C_{14}H_{11}C_1N_2O_4S$], Repaglinide [$C_{27}H_{36}N_2O_4$], Salicylic acid [$C_7H_6O_3$] [gift sample from Alkem Lab. Ltd., Mumbai], Gatifloxacin [$C_{19}H_{22}FN_3O_4$] [gift sample from Wockhardt Ltd, Aurangabad] Furosemide, Paracetamol [$C_8H_9NO_2$], [gift sample from IPCA Laboratories Ltd, Ratlam] Indomethacin [$C_{19}H_{16}ClNO_4$], Norfloxacin [$C_{15}H_{13}N_3O_4S$], Ondansetron HCl [$C_{18}H_{20}ClN_3O$], Nimesulide [$C_{13}H_{12}N_2O_5S$] [a gift from Modern Laboratories Pvt. Ltd. Indore], and Piroxicam [Shreya Life Science Pvt. Ltd., Aurangabad]) were used.

MELTING RANGES DETERMINATION

Analoug melting point test apparatus was employed for melting range determination. Results of all drugs melting ranges are shown in Table 1.

UV SPECTROPHOTOMETRIC IDENTIFICATIONS OF DRUGS

Norfloxacin UV identification

100mg of norfloxacin drug was weighed accurately and placed it into a volumetric flask of 100 ml. It was dissolved in appropriate amount of 0.1 M NaOH and made up to 100 ml with 0.1 M NaOH to obtain stock solution of 1000 µg/ml. One milliliter of this solution was pipetted out in 100 ml of volumetric flask and volume was made with 0.1 M NaOH up to mark to obtain solution of 10 µg/ml. The peak of resulting solution was observed at 273 nm (because it shows the maximum peak at 278 nm) [Figure 1].

Table 1: Melting ranges of drugs

S. No.	Drug	Melting ranges (°C)
1.	Ornidazole	72–75
2.	Paracetamol	157–159
3.	Nimesulide	146–149
4.	Aspirin	136–138
5.	Salicylic acid	161–162
6.	Naproxen	155–156
7.	Gatifloxacin	182–184
8.	Acyclovir	254-256
9.	Ondansetron HCl	228–230
10.	Chlorthalidone	222–223
11.	Furosemide	207–208
12.	Repaglinide	130–132
13.	Indomethacin	162–164
14.	Norfloxacin	220–224

Gatifloxacin UV identification

100 mg of gatifloxacin drug was weighed accurately and placed it into a volumetric flask of 100 ml. It was dissolved with 70 ml of milli-Q water and, then, diluted to a capacity of 100 ml with milli-Q water to get 1000 µg/ml. One milliliter of solution was pipetted from the above solution into another 100 ml volumetric flask; then, volume was made up to 100 ml using milli-Q water. The resulting solution had a concentration of 10 µg/ml. The peak of resulting solution was observed at 287.5 nm [Figure 2].

Paracetamol UV identification

100mg of paracetamol drug was weighed accurately and placed it into a volumetric flask of 100 ml. It was dissolved in 20 ml of methanol and then diluted to 100 ml with milli-Q water to get 1000 µg/ml. One milliliter of solution was pipetted from the above solution into another 100 ml volumetric flask; then, volume was made up to 100 ml using milli-Q water. The resulting solution had a concentration of 10 µg/ml. The peak of resulting solution was observed using a UV-visible

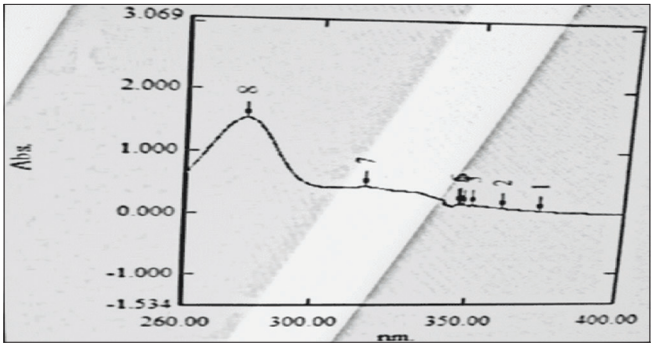

Figure 1: Norfloxacin UV identification

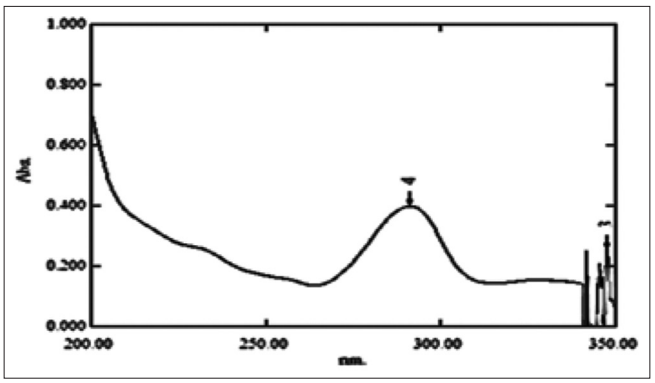

Figure 2: Gatifloxacin UV identification

spectrophotometer set to 243 nm. The obtained graph matched the one in the research paper, as shown in Figure 3.

Acyclovir UV identification[14]

A 100 ml volumetric flask was filled with acyclovir that had been weighed at 100 mg. It was dissolved in the 70 ml of milli-Q water, and then, milli-Q water was used to make a volume of 100 ml, yielding 1000 µg/ml. From the above solution, 1 ml was pipetted out and transferred to another 100 ml volumetric flask. Milli-Q water was used to volume make up to 100 ml. The resultant solution had a 10 µg/ml concentration. The peak of resulting solution was observed at 253 nm [Figure 4].

Ondansetron HCl UV identification[15]

100 mg of ondansetron HCl was weighed and then transferred to a volumetric flask with a volume of 1000 ml. Six hundred milliliters of milli-Q water were added to dissolve the drug with continuous shaking, and then, the volume was made up to 1000 ml with milli-Q water to obtain 100 µg/ml. Ten milliliters of the above solution were pipetted out and transferred to another 100 ml volumetric flask. The volume was made with up to 100 ml with milli-Q water, 10 µg/ml of the solution as a result. The peak of resulting solution was observed at 310 nm using a UV-visible spectrophotometer [Figure 5].

Piroxicam UV identification

100 mg of piroxicam was weighed and then added to a 100 ml volumetric flask. It was dissolved in 70 ml of 0.1M methanolic HCl, and the volume was then increased to 100 ml with the same concentration to produce 1000 µg/ml. In a 100 ml volumetric flask, 1 ml of the above solution was pipetted out. With 0.1M methanolic HCl, the volume was raised to 100 ml. The resultant solution had a 10 µg/ml concentration. After that, a UV-visible spectrophotometer was used to observe the peak at 354 nm [Figure 6].

Ornidazole UV identification

A 100 ml volumetric flask was filled with a properly weighed 100 mg of ornidazole. To obtain 1000 µg/ml, it was dissolved at about 70 ml of milli-Q water, and then, the volume was made up to 100 ml with milli-Q water. One milliliter of the above solution was pipetted out in another 100 ml volumetric flask. Milli-Q water was used to dilute the volume to 100 ml. The solution had a 10 µg/ml concentration. Then, at 319.5 nm, the peak was observed using a UV-visible spectrophotometer [Figure 7].

Aspirin UV identification

Aqueous ethanolic solution preparation

One hundred milliliters of ethanol and 100 ml of water were measured using 100 ml of volumetric flask and, then, transferred both of them into 250 volumetric flask and mixed.

Drug's solution preparation

Aspirin was weighed accurately at 100 mg and, then, added to a volumetric flask holding 100 ml. It was dissolved in 70 ml of the aqueous ethanolic solution-mentioned above;

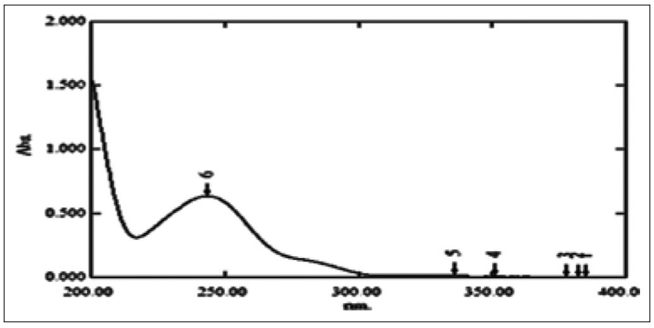

Figure 3: Paracetamol UV identification

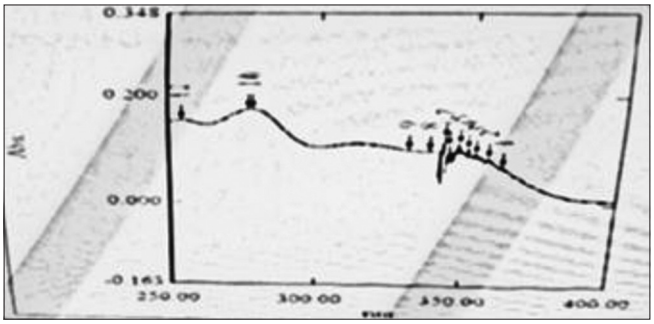

Figure 4: Acyclovir UV identification

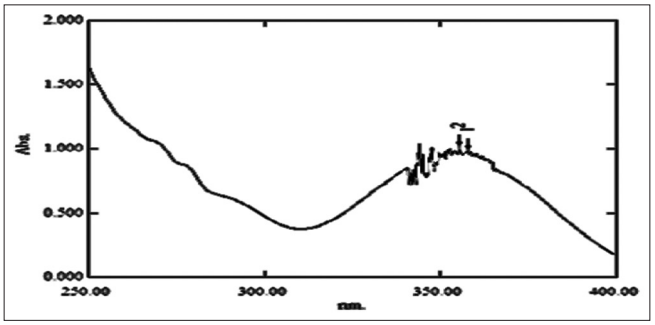

Figure 5: Ondansetron HCl UV identification

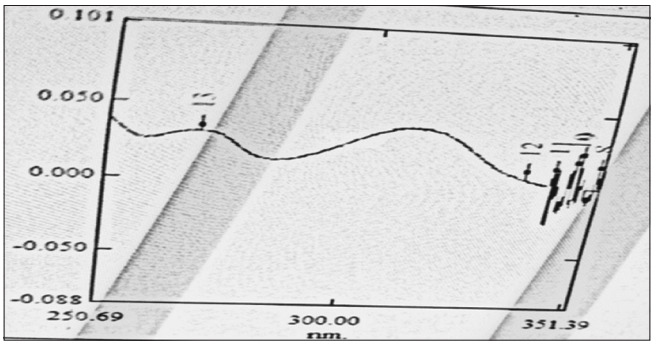

Figure 6: Piroxicam UV identification

then, volume was made up to 100 ml by adding aqueous ethanolic solution to achieve a concentration of 1000 µg/ml. From the abovementioned solution in another 100 ml volumetric flask, 1 ml was pipetted out. The volume was made up to 100 using an aqueous ethanolic solution to achieve 10 µg/ml. The peak was observed at 276 nm using a UV-visible spectrophotometer, as shown in Figure 8.

PREPARATION OF SOLVENT SYSTEM

To make Blend-1, 10 g each of sodium benzoate, sodium citrate, and ethanol (10 ml) were added to a 100 ml volumetric flask along with enough milli-Q water to dissolve the substances. The mixture was then rapidly shaken for 15–20 min when we get clear solution milli-Q water that was used to make up the volume up to 100 ml.

The pH of the blend was measured using pH meter. The pH of this solution was found out to be 5. Compositions of all blends are shown in Table 2.

NOTE: Similarly, other blends (B-2 to B-17) were also prepared. Compositions of all blends are mentioned below in Table 2.

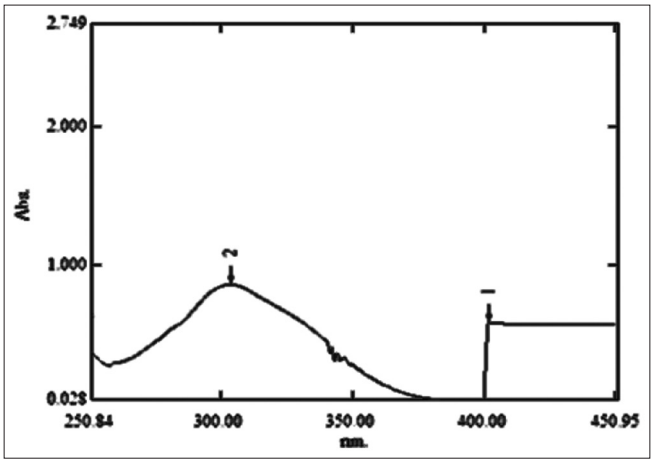

Figure 7: Ornidazole UV identification

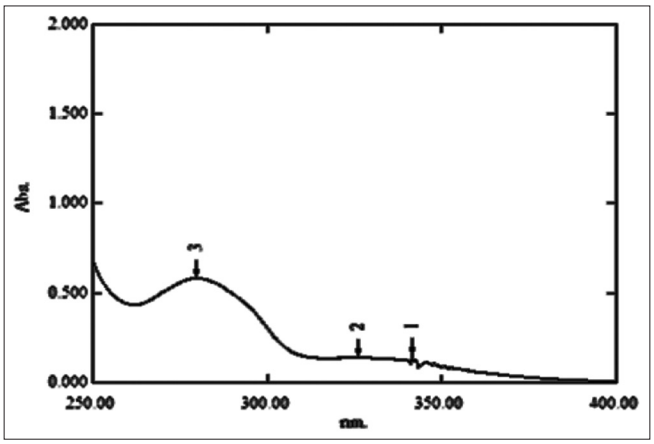

Figure 8: Aspirin UV identification

Solubility studies of poorly water-soluble drug in all blends

First, the butter paper was weighed. 100 mg of drug was accurately weighed. Two milliliter of the blend was taken into a 10 ml volume volumetric flask. The drug was added pinch wise to the blend with vigorously shaking and when a clear solution was obtained that another pinch was added again. Then, shaking was done for 15–20 min. This process is carried out until saturation is achieved. The rest of the drug was weighed. Dissolved drug was calculated. This dissolved drug was converted to % weight/volume ratio.

Similarly, the solubility of other additional drugs were also determined. Results were given in Table 2. The diagrammatic representation of solubility studies was mentioned in Figure-9.

POSSIBILITIES OF AQUEOUS IM INJECTIONS PREPARATION

By the solubility studies, we can prepare the IM aqueous injection of drugs like piroxicam (20 mg/ml) using blend-6, in which the solubility of piroxicam was found out to be 44 mg/2 ml, chlorthalidone (25 mg/2 ml) using blend-7, in which the solubility of chlorthalidone was found out to be 50.9 mg/2 ml, repaglinide (16 mg/2 ml) blend-6, in which the solubility of repaglinide was found out to be 28.1 mg/2 ml, indomethacin (25 mg/ml) using blend-6, in which the solubility of indomethacin was found out to be 53.9 mg/2 ml, acyclovir (20 mg/3 ml) using blend-4, in which the solubility of acyclovir was found out to be 20.4 mg/2 ml, and furosemide (20 mg/2 ml) using blend-5, in which the solubility of furosemide was found out to be 31.8 mg/2 ml.

PREPARATION OF TYPICAL IM INJECTION OF FUROSEMIDE

Preparation of calibration curve

Preparation of furosemide drug's stock solution

50 mg of furosemide drug was weighed and placed into a volumetric flask of 50 ml. To get 1000 µg/ml, 20 ml of blend-5 was used0020to dissolve the drug; then, the volume was increased to 50 ml with milli-Q water (stock solution). Ten milliliters of solution were pipetted from the afore mentioned solution and transferred to another volumetric flask of 100 ml; then, the volume was brought up to 100 ml with milli-Q water to get 100 µg/ml. Appropriate dilutions in the concentration range 20–100 µg/ml were produced from the stock solution using milli-Q water.Using a double beam UV visible spectrophotometer (Shimatzu-1700) at 331 against respective reagent blanks. The absorbances of the resultant drug solutions were determined.

Table 2: Solubility studies of drugs in various blends

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
B-1	Sodium citrate - 10% w/v Sodium benzoate - 10% w/v Ethanol - 10% v/v Milli-Q water - Quantity sufficient Total concentration - 30% pH - 5	Ornidazole 68.05 mg/2 ml (6.8% w/v)	8.03 mg/ml (0.083% w/v)	81.92 folds
		Paracetamol 37.35 mg/2 ml (1.87% w/v)	1.45% w/v[16]	1.29 folds
		Nimesulide 7.35 mg/2 ml (0.37% w/v)	0.01 mg/ml (0.001% w/v)	370 folds
		Aspirin 117.6 mg/2 ml (5.85% w/v)	3g/L[7] (0.3% w/v)	19.50 folds
		Salicylic acid 63.6 mg/2 ml (3.16% w/v)	3g/L (0.3% w/v)	10.56 folds
		Naproxen 16.6 mg/2 ml (0.83% w/v)	0.009% w/v[7]	92.22 folds
		Gatifloxacin 79.4 mg/2 ml (3.97% w/v)	0.631 mg/ml (0.63% w/v)[17]	6.30 folds
		Meloxicam 20.6 mg/2 ml (1.03% w/v)	0.00071% w/v[18]	1450.70 folds
		Acyclovir 14.4 mg/2 ml (0.72% w/v)	1.14 mg/ml[19] (0.114% w/v)	6.32 folds
		Ondansetron HCl 2.6 mg/2 ml (0.13% w/v)	0.0048% w/v[20]	27.08 folds
		Piroxicam 5 mg/2 ml (0.25% w/v)	0.040% w/v[7]	6.25 folds
		Chlorthalidone 6.67 mg/2 ml (0.33% w/v)	0.12% w/v[21]	2.78 folds
		Furosemide 12.8 mg/2 ml (0.64% w/v)	0.064% w/v[7]	10 folds
		Repaglinide 3.2 mg/2 ml (0.16% w/v)	0.0068% w/v[22]	23.53 folds
		Indomethacin 4.6 mg/2 ml (0.23% w/v)	0.036% w/v[7]	6.38 folds
		Norfloxacin 64.4 mg/ml (3.22% w/v)	0.088% w/v[7]	36.59 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
B-2	Sodium citrate - 10% w/v Arginine - 10% w/v Ethanol - 10% v/v Benzoic acid - 2% w/v Milli-Q water - Quantity sufficient Total concentration - 32% pH - 7	Ornidazole 45.8mg/2 ml (2.29% w/v)	8.03mg/ml (0.083% w/v)	27.59 folds
		Paracetamol 65.4 mg/ml (3.27% w/v)	1.45% w/v[16]	2.25 folds
		Nimesulide 23.10 mg/2 ml (1.15% w/v)	0.01 mg/ml (0.1% w/v)	11.55 folds
		Aspirin 141 mg/2 ml (7.05% w/v)	3 g/L[7] (0.3% w/v)	23.50 folds
		Salicylic acid 87.9 mg/2 ml (4.39% w/v)	3g/L (0.3% w/v)	14.65 folds
		Glipizide 43.2 mg/2 ml (2.16% w/v)	37.2 mg/L (0.0037% w/v)	583.78 folds
		Naproxen 9.3 mg/2 ml (4.65% w/v)	0.009% w/v[7]	516.67 folds
		Gatifloxacin 79.4 mg/2 ml (3.97% w/v)	0.631 mg/ml[17] (0.63% w/v)	62.91 folds
		Meloxicam 20.6 mg/2 ml (1.03% w/v)	0.00071% w/v[18]	1450.70 folds
		Acyclovir 14.4 mg/2 ml (0.72% w/v)	1.14 mg/ml[19] (0.114% w/v)	6.32 folds
		Ondansetron HCl 2.6 mg/2 ml (0.13% w/v)	0.0048% w/v[16]	27.08 folds
		Piroxicam 5 mg/2 ml (0.25% w/v)	0.04% w/v[7]	6.25 folds
		Chlorthalidone 6.67 mg/2 ml (0.33% w/v)	0.12% w/v[21]	2.78 folds
		Furosemide 10.8 mg/2 ml (0.54% w/v)	0.064% w/v[7]	8.45 folds
		Repaglinide 3.2 mg/2 ml (0.16% w/v)	0.0068% w/v[22]	23.53 folds
		Indomethacin 5.2 mg/2 ml (0.26% w/v)	0.036% w/v[7]	7.22 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Norfloxacin 32.2 mg/2 ml (1.61% w/v)	0.088% w/v[7]	18.29 folds
B-3	Sodium benzoate - 10% w/v Ethanol - 10% v/v Tween 80-10% v/v Milli-Q water - Quantity Sufficient Total concentration - 30% pH - 6.5	Ornidazole 150 mg/2 ml (7.50% w/v)	0.83 mg/ml (0.083% w/v)	90.36 folds
		Paracetamol 100 mg/2 ml (5.00% w/v)	1.45% w/v[16]	3.45 folds
		Nimesulide 29.1 mg/2 ml (1.45% w/v)	0.01 mg/ml (0.1% w/v)	1,455 folds
		Aspirin 91.1 mg/2 ml (4.56% w/v)	3g/L[7] (0.3% w/v)	15.18 folds
		Salicylic acid 47.3 mg/2 ml (2.37% w/v)	3g/L (0.3% w/v)	7.88 folds
		Naproxen 39.6 mg/2 ml (1.98% w/v)	0.009% w/v	220.00 folds
		Gatifloxacin 48.4 mg/2 ml (2.42% w/v)	0.631 mg/ml[17] (0.63% w/v)	38.41 folds
		Meloxicam 18.1 mg/2 ml (0.91% w/v)	0.00071% w/v[19]	1274.65 folds
		Acyclovir 11.7 mg/2 ml (0.59% w/v)	1.14 mg/ml[19] (0.114% w/v)	5.13 folds
		Ondansetron HCl 2.6 mg/2 ml (0.13% w/v)	0.0048% w/v[17]	27.08 folds
		Piroxicam 3.4 mg/2 ml (0.17% w/v)	0.40% w/v[16]	4.25 folds
		Chlorthalidone 23.4 mg/2 ml (1.17% w/v)	0.12% w/v[21]	9.75 folds
		Furosemide 51.4 mg/2 ml (2.57% w/v)	0.064% w/v[7]	40.16 folds
		Repaglinide 5.2 mg/2 ml (0.26% w/v)	0.0068% w/v	38.24 folds
		Fenofibrate 3.4 mg/2 ml (0.17% w/v)	0.000042% w/v	4,047.62 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Indomethacin 30.0 mg/2 ml (1.5% w/v)	0.036% w/v[7]	41.66 folds
		Norfloxacin 36.8 mg/2 ml (1.84% w/v)	0.088% w/v[7]	20.91 folds
B-4	L-lysin- 10% w/v Arginine - 10% w/v Sodium acetate - 10% w/v Tween 80-5%v/v Milli-Q water - Quantity Sufficient Total concentration - 35% pH - 5	Ornidazole 13.5 mg/2 ml (0.67% w/v)	0.83 mg/ml (0.083% w/v)	8.13 folds
		Paracetamol 86.1 mg/2 ml (4.31% w/v)	1.45% w/v[16]	2.97 folds
		Nimesulide 20 mg/2 ml (1.00% w/v)	0.01 mg/ml[23] (0.1% w/v)	1000.00 folds
		Aspirin 200 mg/2 ml (10.00% w/v)	3 g/L[7] (0.3%)	33.33 folds
		Salicylic acid 100 mg/2 ml (5.00% w/v)	3g/L (0.3%)	16.67 folds
		Naproxen 68.4 mg/2 ml (3.41% w/v)	0.009% w/v	380 folds
		Gatifloxacin 40.5 mg/2 ml (2.03% w/v)	0.631 mg/ml[17] (0.63% w/v)	32.14 folds
		Meloxicam 9 mg/2 ml (0.45% w/v)	0.00071% w/v[18]	633.80 folds
		Acyclovir 20.4 mg/2 ml (1.02% w/v)	1.14 mg/ml[19] (0.114% w/v)	8.94 folds
		Ondansetron HCl 21.2 mg/2 ml (1.06% w/v)	0.0048% w/v[20]	220.83 folds
		Piroxicam 27.4 mg/2 ml (1.37% w/v)	0.040% w/v[7]	34.25 folds
		Chlorthalidone 13.5 mg/2 ml (0.68% w/v)	0.12% w/v[21]	5.63 folds
		Furosemide 100 mg/2 ml (5.00% w/v)	0.064% w/v[7]	78.13 folds
		Repaglinide 6.4 mg/2 ml (0.32% w/v)	0.0068% w/v[22]	47.06 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Fenofibrate 30.4 mg/2 ml (1.52% w/v)	0.000042% w/v	36,190.48 folds
		Indomethacin 21.8 mg/2 ml (1.09% w/v)	0.036% w/v[7]	30.28 folds
		Norfloxacin 38.4 mg/2 ml (1.92% w/v)	0.088% w/v[7]	21.81 folds
B-5	Sodium benzoate - 5% w/v Arginine - 7% w/v L-lysine - 3% w/v Tween 80-10% v/v Milli-Q water - Quantity Sufficient Total concentration - 25% pH - 7	Ornidazole 29.1 mg/2 ml (1.46% w/v)	0.83 mg/ml (0.083% w/v)	17.53 folds
		Paracetamol 29.2 mg/2 ml (1.46% w/v)	1.45% w/v[16]	Similar with water solubility
		Nimesulide 8.2 mg/2 ml (0.41% w/v)	0.01mg/ml (0.001% w/v)	410.00 folds
		Aspirin 85 mg/2 ml (4.25% w/v)	3g/L (0.3%)	14.17 folds
		Salicylic acid 72.1mg/2 ml (3.605% w/v)	3g/L (0.3%)	12.02 folds
		Naproxen 57.5 mg/2 ml (2.88% w/v)	0.009% w/v[7]	319.44 folds
		Gatifloxacin 91.4 mg/2 ml (4.57% w/v)	0.631 mg/ml[17] (0.063% w/v)	72.54 folds
		Acyclovir 13.4 mg/2 ml (0.67% w/v)	1.14 mg/ml[19] (0.114% w/v)	5.88 folds
		Ondansetron HCl 10.2 mg/2 ml (0.51% w/v)	0.0048% w/v[16]	106.25 folds
		Piroxicam 15.6 mg/2 ml (0.78% w/v)	0.040% w/v[7]	19.50 folds
		Chlorthalidone 31.8 mg/2 ml (1.59% w/v)	0.12% w/v[21]	13.50 folds
		Furosemide 31.8 mg/2 ml (1.59% w/v)	0.064% w/v[7]	24.84 folds
		Repaglinide 10.2 mg/2 ml (0.51% w/v)	0.0068% w/v[22]	75.00 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Fenofibrate 8.4 mg/2 ml (0.42% w/v)	0.000042% w/v	10,000.00 folds
		Indomethacin 1.6 mg/2 ml (0.08% w/v)	0.036% w/v[7]	2.22 folds
		Norfloxacin 46.0 mg/2 ml (2.30% w/v)	0.088% w/v[7]	26.14 folds
B-6	Valine - 2.5% w/v Sodium benzoate - 10% w/v Ethanol - 5% w/v Benzyl alcohol - 2.5% v/v Milli-Q water - Quantity Sufficient Total concentration - 20% pH - 7	Ornidazole 45.5 mg/2 ml (2.28% w/v)	0.83 mg/ml (0.083% w/v)	27.40 folds
		Paracetamol 74.1 mg/2 ml (3.71% w/v)	1.45% w/v[16]	2.56 folds
		Nimesulide 3.9 mg/2 ml (0.19% w/v)	0.01 mg/ml (0.001% w/v)	195.00 folds
		Aspirin 100 mg/2 ml (5.00% w/v)	3 g/L[7] (0.3%)	16.67 folds
		Salicylic acid 100 mg/2 ml (5.00% w/v)	3 g/L (0.3%)	16.67 folds
		Naproxen 13.5 mg/2 ml (0.67% w/v)	0.009% w/v[7]	75.00 folds
		Gatifloxacin 37.9 mg/2 ml (1.89% w/v)	0.631 mg/ml[17] (0.063% w/v)	30.08 folds
		Acyclovir 33.9 mg/2 ml (1.69% w/v)	1.14 mg/ml[19] (0.114% w/v)	14.87 folds
		Ondansetron HCl 1.92 mg/2 ml (0.096% w/v)	0.0048% w/v	20.00 folds
		Piroxicam 34.5 mg/2 ml (1.73% w/v)	0.040% w/v[7]	43.13 folds
		Chlorthalidone 4.36 mg/2 ml (0.22% w/v)	0.12% w/v[21]	1.83 folds
		Furosemide 58.9 mg/2 ml (2.95% w/v)	0.064% w/v[7]	46.02 folds
		Repaglinide 28.1 mg/2 ml (1.41% w/v)	0.0068% w/v[22]	206.62 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Fenofibrate 9.0 mg/2 ml (0.45% w/v)	0.000042% w/v	10,714.29 folds
		Indomethacin 53.9 mg/2 ml (2.70% w/v)	0.036% w/v[7]	74.86 folds
		Norfloxacin 66.4 mg/2 ml (3.22% w/v)	0.088% w/v[18]	37.72 folds
B-7	Sodium benzoate - 5% w/v Sodium acetate - 5% w/v Ethanol - 5% v/v Milli-Q water - Quantity sufficient Total concentration - 15% pH - 7.5	Ornidazole 45.5mg/2 ml (2.28% w/v)	0.83 mg/ml (0.083% w/v)	27.41 folds
		Paracetamol 70.1 mg/2 ml (3.51% w/v)	1.45% w/v[16]	2.42 folds
		Nimesulide 6.7 mg/2 ml (0.34% w/v)	0.01 mg/ml (0.001% w/v)	340.00 folds
		Aspirin 98 mg/2 ml (4.90% w/v)	3g/L[7] (0.3% w/v)	16.33 folds
		Salicylic acid 100 mg/2 ml (5.00% w/v)	3g/L (0.3% w/v)	16.67 folds
		Naproxen 17.8 mg/2 ml (0.89% w/v)	0.009% w/v	98.89 folds
		Gatifloxacin 37.9 mg/2 ml (1.89% w/v)	0.631 mg/ml[17] (0.063% w/v)	30.08 folds
		Acyclovir 83.2 mg/2 ml (4.16% w/v)	1.14 mg/ml[19] (0.114% w/v)	36.49 folds
		Ondansetron HCl 7.4 mg/2 ml (0.37% w/v)	0.0048% w/v[17]	77.08 folds
		Piroxicam 50.96 mg/2 ml (2.55% w/v)	0.040% w/v[7]	63.75 folds
		Chlorthalidone 56.5 mg/2 ml (2.83% w/v)	0.12% w/v[21]	23.58 folds
		Furosemide 17.9 mg/2 ml (0.89% w/v)	0.064% w/v[7]	13.98 folds
		Repaglinide 14.44 mg/2 ml (0.72% w/v)	0.0068% w/v[22]	105.88 folds
		Fenofibrate	0.000042% w/v	16,190.48 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		13.5 mg/2 ml (0.68% w/v)		
		Indomethacin 56.5 mg/2 ml (2.83% w/v)	0.036% w/v[7]	7.86 folds
		Norfloxacin 39.4 mg/2 ml (1.97% w/v)	0.088% w/v[7]	22.38 folds
B-8	Sodium benzoate - 5% w/v L-lysine - 5% w/v Ethanol - 5% v/v Milli-Q water - Quantity Sufficient Total concentration - 15% pH - 7	Ornidazole 38.6 mg/2 ml (1.93% w/v)	0.83 mg/ml (0.083% w/v)	23.25 folds
		Paracetamol 44.4 mg/2 ml (2.21% w/v)	1.45% w/v[16]	1.52 folds
		Nimesulide 22 mg/2 ml (1.10% w/v)	0.01 mg/ml (0.001% w/v)	1,100.00 folds
		Aspirin 9.6 mg/2 ml (0.48% w/v)	3g/L[7] (0.3%)	1.60 folds
		Salicylic acid 56.30 mg/2 ml (2.82% w/v)	3g/L (0.3%)	9.38 folds
		Naproxen 22.2 mg/2 ml (1.11% w/v)	0.009% w/v[7]	123.33 folds
		Gatifloxacin 37.9 mg/2 ml (1.89% w/v)	0.631 mg/ml[17] (0.063% w/v)	30.08 folds
		Acyclovir 11.6 mg/2 ml (0.58% w/v)	1.14 mg/ml[19] (0.114% w/v)	5.09 folds
		Ondansetron HCl 5.8 mg/2 ml (0.29% w/v)	0.0048% w/v[20]	60.42 folds
		Piroxicam 2.2 mg/2 ml (0.11% w/v)	0.040% w/v[7]	2.75 folds
		Chlorthalidone 2.6 mg/2 ml (0.13% w/v)	0.12% w/v[21]	Similar to the reported water solubility
		Furosemide 11.2 mg/2 ml (0.56% w/v)	0.064% w/v[7]	8.75 folds
		Repaglinide 3.2 mg/2 ml (0.16% w/v)	0.0068% w/v[22]	23.53 folds
		Fenofibrate	0.000042% w/v	15,476.19 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		13 mg/2 ml (0.65% w/v)		
		Indomethacin 3.8 mg/2 ml (0.19% w/v)	0.036% w/v[7]	5.28 folds
		Norfloxacin 14.1 mg/2 ml (0.71% w/v)	0.088% w/v[7]	8.01 folds
B-9	Sodium benzoate - 5% w/v Sodium citrate - 7% w/v Ethanol - 5% v/v Milli-Q water - Quantity sufficient Total concentration - 17% pH - 7	Ornidazole 13.1 mg/2 ml (0.66% w/v)	0.83 mg/ml (0.083% w/v)	7.89 folds
		Paracetamol 17.2 mg/2 ml (0.86% w/v)	1.45% w/v[16]	Decrease
		Nimesulide 22.0 mg/2 ml (1.10% w/v)	0.01 mg/ml[23] (0.001% w/v)	1,10 folds
		Aspirin 92.3 mg/2 ml (4.62% w/v)	3g/L[7] (0.3%)	15.38 folds
		Salicylic acid 51.8 mg/2 ml (2.59% w/v)	3 g/L (0.3%)	8.63 folds
		Naproxen 7.2 mg/2 ml (0.36% w/v)	0.009% w/v[7]	40.00 folds
		Gatifloxacin 20.9 mg/2 ml (1.05% w/v)	0.631 mg/ml[17] (0.063% w/v)	16.59 folds
		Acyclovir 18.4 mg/2 ml (0.92% w/v)	1.14 mg/ml[19] (0.114% w/v)	8.07 folds
		Ondansetron HCl 3.21 mg/2 ml (0.16% w/v)	0.0048% w/v[16]	33.44 folds
		Piroxicam 7.2 mg/2 ml (0.36% w/v)	0.040% w/v[7]	9.00 folds
		Chlorthalidone 13.3 mg/2 ml (0.67% w/v)	0.12% w/v[21]	5.54 folds
		Furosemide 22.4 mg/2 ml (1.12% w/v)	0.064% w/v[7]	17.50 folds
		Repaglinide 6.8 mg/2 ml (0.34% w/v)	0.0068% w/v[22]	50.00 folds
		Fenofibrate	0.000042% w/v	5,714.29 folds

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Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		4.8 mg/2 ml (0.24% w/v)		
		Indomethacin 56.5 mg/2 ml (2.83% w/v)	0.036% w/v	78.47 folds
		Norfloxacin -	0.088% w/v[7]	Insoluble
B-10	Sodium benzoate - 5% w/v Sodium acetate - 7% w/v Ethanol - 5% v/v Milli-Q water - Quantity sufficient Total concentration - 17% pH - 7	Ornidazole 24.9 mg/2 ml (1.25% w/v)	0.83 mg/ml (0.083% w/v)	15.00 folds
		Paracetamol 33.0 mg/2 ml (1.65% w/v)	1.45% w/v[16]	1.14 folds
		Nimesulide 4.9 mg/2 ml (0.25 folds)	0.01 mg/ml (0.001% w/v)	245.00 folds
		Aspirin 60 mg/2 ml (3.00% w/v)	3 g/L[24] (0.3% w/v)	10.00 folds
		Salicylic acid 50.7 mg/2 ml (2.54% w/v)	3 g/L (0.3%)	8.45 folds
		Naproxen 10.9 mg/2 ml (0.55% w/v)	0.009% w/v[7]	60.55 folds
		Gatifloxacin 25.6 mg/2 ml (1.28% w/v)	0.631 mg/ml[17] (0.063% w/v)	20.32 folds
		Acyclovir 22.6 mg/2 ml (1.13% w/v)	1.14 mg/ml[19] (0.114% w/v)	9.91 folds
		Ondansetron HCl 4 mg/2 ml (0.20% w/v)	0.0048% w/v[17]	41.67 folds
		Piroxicam 3 mg/2 ml (0.15% w/v)	0.040% w/v[7]	3.75 folds
		Chlorthalidone 15.2 mg/2 ml (0.76% w/v)	0.12% w/v[21]	6.33 folds
		Furosemide 24.0 mg/2 ml (1.20% w/v)	0.064% w/v[7]	18.75 folds
		Repaglinide 11.0 mg/2 ml (0.55% w/v)	0.0068% w/v	80.88 folds
		Fenofibrate 7 mg/2 ml (0.35% w/v)	0.000042% w/v	8,333.33 folds

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Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Indomethacin 7.5 mg/2 ml (0.38% w/v)	0.036% w/v[7]	10.56 folds
		Norfloxacin 8.3 mg/2 ml (0.41% w/v)	0.088% w/v[7]	4.71 folds
B-11	Sodium benzoate - 5% w/v Sodium acetate - 5% w/v Tween 80-5% v/v Milli-Q water - Quantity sufficient Total concentration - 15% pH - 7	Ornidazole 54.6 mg/2 ml (2.73% w/v)	0.83 mg/ml (0.083% w/v)	32.89 folds
		Paracetamol 33.0 mg/2 ml (1.65% w/v)	1.45% w/v[16]	1.14 folds
		Nimesulide 10.1 mg/2 ml (0.51% w/v)	0.01 mg/ml[23] (0.001% w/v)	505.00 folds
		Aspirin 65.7 mg/2 ml (3.29% w/v)	3 g/L[24] (0.3% w/v)	10.95 folds
		Salicylic acid 36.2 mg/2 ml (1.81% w/v)	3 g/L (0.3% w/v)	6.03 folds
		Naproxen 16.7 mg/2 ml (0.84% w/v)	0.009% w/v[7]	92.78 folds
		Gatifloxacin 24.3 mg/2 ml (1.21% w/v)	0.631 mg/ml[17] (0.063% w/v)	19.29 folds
		Acyclovir 12.6 mg/2 ml (0.63% w/v)	1.14 mg/ml[19] (0.114% w/v)	5.53 folds
		Ondansetron HCl 4 mg/2 ml (0.20% w/v)	0.0048% w/v[20]	41.67 folds
		Piroxicam 10.8 mg/2 ml (0.51% w/v)	0.040% w/v[7]	12.75 folds
		Chlorthalidone 9.0 mg/2 ml (0.45% w/v)	0.12% w/v[21]	3.75 folds
		Furosemide 12.6 mg/2 ml (0.63% w/v)	0.064% w/v[7]	9.84 folds
		Repaglinide 14.0 mg/2 ml (0.70% w/v)	0.0068% w/v[22]	102.94 folds
		Fenofibrate 6.4 mg/2 ml (0.32% w/v)	0.000042% w/v	7,619.05 folds
		Indomethacin	0.088% w/v[7]	6.08 folds

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Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		3.6 mg/2 ml (0.18% w/v)	0.036% w/v[7]	5.00 folds
		Norfloxacin 10.7 mg/2 ml (0.54% w/v)		
B-12	Sodium benzoate - 5% w/v Sodium acetate - 7% w/v Tween 80-2% v/v Arginine - 1% w/v Benzoic acid - 1% w/v Milli-Q water - Quantity sufficient Total concentration - 16% pH - 7	Ornidazole 81.3 mg/2 ml (4.06% w/v)	0.83 mg/ml (0.083% w/v)	48.97 folds
		Paracetamol 14.5 mg/2 ml (0.72% w/v)	1.45% w/v[16]	Decrease
		Nimesulide 6.3 mg/2 ml (0.31% w/v)	0.01 mg/ml[23] (0.001% w/v)	310.00 folds
		Aspirin 14.5 mg/2 ml (0.73% w/v)	3 g/L[7] (0.3% w/v)	2.42 folds
		Salicylic acid 6.5 mg/2 ml (0.33% w/v)	3 g/L (0.3% w/v)	Equal to reported water solubility
		Naproxen 14.7mg/2 ml (0.74% w/v)	0.009% w/v[7]	82.22 folds
		Gatifloxacin 3.0 mg/2 ml (0.15% w/v)	0.631 mg/ml[17] (0.063% w/v)	2.38 folds
		Acyclovir 10.4 mg/2 ml (0.52% w/v)	1.14 mg/ml[19] (0.114% w/v)	4.56 folds
		Ondansetron HCl 1.8 mg/2 ml (0.09% w/v)	0.0048% w/v[16]	18.75 folds
		Piroxicam 1.6 mg/2 ml (0.08% w/v)	0.040% w/v[7]	2.00 folds
		Chlorthalidone 3.0 mg/2 ml (0.15% w/v)	0.12% w/v[21]	1.25 folds
		Furosemide 20.8 mg/2 ml (1.04% w/v)	0.064% w/v[7]	16.25 folds
		Repaglinide 9.6 mg/2 ml (0.48% w/v)	0.0068% w/v[22]	70.59 folds
		Fenofibrate 11.4 mg/2 ml (0.57% w/v)	0.000042% w/v	13,571.42 folds

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Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Indomethacin 5.2 mg/2 ml (0.26% w/v)	0.036% w/v[7]	7.22 folds
		Norfloxacin 21.0 mg/2 ml (1.05% w/v)	0.088% w/v[7]	11.93 folds
B-13	Sodium benzoate - 10% w/v Sodium acetate - 10% w/v Valine - 5% w/v Ethanol - 10% v/v Milli-Q water - Quantity sufficient Total concentration - 35% pH - 5	Ornidazole 4.4 mg/2 ml (0.22% w/v)	0.83 mg/ml (0.083% w/v)	2.65 folds
		Paracetamol 27.3 mg/2 ml (1.37% w/v)	1.45% w/v[16]	-
		Nimesulide 2.3 mg/2 ml (0.12% w/v)	0.01 mg/ml[23] (0.001% w/v)	115.00 folds
		Aspirin 13.6 mg/2 ml (0.68% w/v)	3 g/L[24] (0.3% w/v)	2.27 folds
		Salicylic acid 11.4 mg/2 ml (0.57% w/v)	3 g/L (0.3% w/v)	1.90 folds
		Naproxen 5.8 mg/2 ml (0.29% w/v)	0.009% w/v[7]	32.22 folds
		Gatifloxacin 8.3 mg/2 ml (0.42% w/v)	0.631 mg/ml[17] (0.063% w/v)	6.59 folds
		Acyclovir 25.4 mg/2 ml (1.27% w/v)	1.14 mg/ml[19] (0.114% w/v)	11.14 folds
		Ondansetron HCl 3.0 mg/2 ml (0.15% w/v)	0.0048% w/v[17]	31.25 folds
		Piroxicam 9.6 mg/2 ml (0.48% w/v)	0.040% w/v[7]	12.00 folds
		Chlorthalidone 14.4 mg/2 ml (0.72% w/v)	0.12% w/v[21]	6.00 folds
		Furosemide 22.2 mg/2 ml (1.11% w/v)	0.064% w/v[7]	17.34 folds
		Repaglinide 16.8 mg/2 ml (0.84% w/v)	0.0068% w/v[22]	123.53 folds
		Fenofibrate 9.4 mg/2 ml (0.47% w/v)	0.000042% w/v	11,190.48 folds

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Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		Indomethacin 3.0 mg/2 ml (0.15% w/v)	0.036% w/v[7]	4.17 folds
		Norfloxacin 12.2 mg/2 ml (0.61% w/v)	0.088% w/v[7]	6.93 folds
B-14	Sodium citrate - 10% w/v Tween 80-2% v/v Ethanol - 10% v/v Milli-Q water - Quantity sufficient Total concentration - 22% pH - 7	Ornidazole 3.1 mg/2 ml (0.15% w/v)	0.83 mg/ml (0.083% w/v)	1.88 folds
		Paracetamol 47.3 mg/2 ml (2.37% w/v)	1.45% w/v[16]	1.63 folds
		Nimesulide 6.3 mg/2 ml (0.32% w/v)	0.01 mg/ml (0.001% w/v)	315.00 folds
		Aspirin 29.5 mg/2 ml (1.48% w/v)	0.3% w/v[7]	4.93 folds
		Salicylic acid 49.0 mg/2 ml (2.45% w/v)	3 g/L (0.3% w/v)	8.17 folds
		Naproxen 24.1 mg/2 ml (1.21% w/v)	0.009% w/v[7]	133.89 folds
		Gatifloxacin 7.3 mg/2 ml (0.365% w/v)	0.631 mg/ml[17] (0.063% w/v)	5.79 folds
		Acyclovir 16.0 mg/2 ml (0.80% w/v)	1.14 mg/ml[19] (0.114% w/v)	7.02 folds
		Ondansetron HCl 4.1 mg/2 ml (0.21% w/v)	0.0048% w/v[20]	42.71 folds
		Piroxicam 3.2 mg/2 ml (0.16% w/v)	0.040% w/v	4.00 folds
		Chlorthalidone 6.4 mg/2 ml (0.32% w/v)	0.12% w/v[21]	2.67 folds
		Furosemide 14.4 mg/2 ml (0.72% w/v)	0.064% w/v[16]	11.25 folds
		Repaglinide 9.6 mg/2 ml (0.48% w/v)	0.0068% w/v[22]	70.59 folds
		Fenofibrate -	0.000042% w/v	Insoluble
		Indomethacin	0.036% w/v[7]	6.39 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		4.6 mg/2 ml (0.23% w/v)		
		Norfloxacin 13.9 mg/2 ml (0.69% w/v)	0.088% w/v[7]	7.89 folds
B-15	Sodium citrate - 10% w/v Sodium benzoate - 10% w/v Ethanol - 10% v/v Valine - 10% w/v Milli-Q water - Quantity sufficient Total concentration - 40% pH - 7	Ornidazole 28.6 mg/2 ml (1.43% w/v)	0.83 mg/ml (0.083% w/v)	17.23 folds
		Paracetamol 7.8 mg/2 ml (0.39% w/v)	1.45% w/v[16]	Decrease in solubility
		Nimesulide 4.2 mg/2 ml (0.21% w/v)	0.01 mg/ml (0.001% w/v)	210 folds
		Aspirin 15.4 mg/2 ml (0.77% w/v)	3 g/L[7] (0.3% w/v)	2.57 folds
		Salicylic acid 18.4 mg/2 ml (0.92% w/v)	3 g/L (0.3% w/v)	3.07 folds
		Naproxen 23.8 mg/2 ml (1.19% w/v)	0.009% w/v[7]	132.22 folds
		Gatifloxacin 38.4 mg/2 ml (1.92% w/v)	0.631 mg/ml[17] (0.063% w/v)	30.48 folds
		Acyclovir 26.2 mg/2 ml (1.31% w/v)	1.14 mg/ml[19] (0.114% w/v)	11.49 folds
		Ondansetron HCl 4.4 mg/2 ml (0.22% w/v)	0.0048% w/v[16]	45.83 folds
		Piroxicam 3.2 mg/2 ml (0.16% w/v)	0.040% w/v[7]	4.00 folds
		Chlorthalidone 6.4 mg/2 ml (0.32% w/v)	0.12% w/v[21]	2.66 folds
		Furosemide 14.4 mg/2 ml (0.72% w/v)	0.064% w/v[7]	11.25 folds
		Repaglinide 9.6 mg/2 ml (0.48% w/v)	0.0068% w/v[22]	70.59 folds
		Fenofibrate -	0.000042% w/v	Insoluble
		Indomethacin	0.036% w/v[7]	7.78 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		5.6 mg/2 ml (0.28% w/v)		
		Norfloxacin 11.6 mg/2 ml (0.58% w/v)	0.088% w/v[7]	6.59 folds
B-16	Sodium citrate - 10% w/v Tween 80-2% v/v Ethanol - 10% v/v Sodium benzoate - 10% w/v Milli-Q water - Quantity sufficient Total concentration - 32% pH - 7.5	Ornidazole 8.1 mg/2 ml (0.41% w/v)	0.83 mg/ml (0.083% w/v)	4.88 folds
		Paracetamol 12.5 mg/2 ml (0.63% w/v)	1.45% w/v	Decrease the solubility
		Nimesulide 1.5 mg/2 ml (0.075% w/v)	0.01 mg/ml[23] (0.001% w/v)	75 folds
		Aspirin 7.6 mg/2 ml (0.38% w/v)	0.3% w/v[7]	1.27 folds
		Salicylic acid 12.0 mg/2 ml (0.6% w/v)	3 g/L (0.3% w/v)	2.00 folds
		Naproxen 11.2 mg/2 ml (0.56% w/v)	0.009% w/v[7]	62.22 folds
		Gatifloxacin 4.8 mg/2 ml (0.24% w/v)	0.631 mg/ml[17] (0.063% w/v)	3.81 folds
		Acyclovir 20.0 mg/2 ml (1.00% w/v)	1.14 mg/ml[19] (0.114% w/v)	8.78 folds
		Ondansetron HCl 1.55 mg/2 ml (0.08% w/v)	0.0048% w/v[17]	16.15 folds
		Piroxicam 16.8 mg/2 ml (0.84% w/v)	0.040% w/v[7]	21.00 folds
		Chlorthalidone 0.5 mg/2 ml (0.025% w/v)	0.12% w/v[20]	Decrease the solubility
		Furosemide 7.4 mg/2 ml (0.37% w/v)	0.064% w/v[7]	5.78 folds
		Repaglinide 7.1 mg/2 ml (0.36% w/v)	0.0068% w/v[22]	52.94 folds
		Fenofibrate 5.6 mg/2 ml (0.28% w/v)	0.000042% w/v	6,666.66 folds
		Indomethacin	0.036% w/v[7]	5.83 folds

(Contd...)

Table 2: *(Continued)*

Blend name	Blend composition with total concentration and pH	Approximate solubility of drug in blend	Reported water solubility	Folds solubility enhancement
		4.3 mg/2 ml (0.22% w/v)		
		Norfloxacin 36.8 mg/2 ml (1.84% w/v)	0.088% w/v[7]	20.91 folds
B-17	Sodium citrate - 10% w/v Sodium acetate - 10% v/v Ethanol - 10% v/v Milli-Q water - Quantity sufficient Total concentration - 30% pH - 7	Ornidazole 5.0 mg/2 ml (0.25% w/v)	0.83 mg/ml (0.083% w/v)	3.01 folds
		Paracetamol 22.0 mg/2 ml (1.10% w/v)	1.45% w/v[16]	0.76 folds
		Nimesulide 6.3 mg/2 ml (0.32% w/v)	0.01 mg/ml[23] (0.001% w/v)	320.00 folds
		Aspirin 57.8 mg/2 ml (0.89% w/v)	3 g/L[7] (0.3% w/v)	9.63 folds
		Salicylic acid 62.0 mg/2 ml (3.1% w/v)	3 g/L (0.3% w/v)	10.33 folds
		Naproxen 20.4 mg/2 ml (1.02% w/v)	0.009% w/v[7]	113.33 folds
		Gatifloxacin 26.4 mg/2 ml (1.32% w/v)	0.631 mg/ml[17] (0.063% w/v)	20.95 folds
		Acyclovir 7.2 mg/2 ml (0.36% w/v)	1.14 mg/ml[19] (0.114% w/v)	3.20 folds
		Ondansetron 4.1 mg/2 ml (0.21% w/v)	0.0048% w/v[20]	43.75 folds
		Piroxicam 3.0 mg/2 ml (0.15% w/v)	0.040% w/v[7]	3.75 folds
		Chlorthalidone 4.0 mg/2 ml (0.20% w/v)	0.12% w/v[21]	1.67 folds
		Furosemide 1 mg/2 ml (0.05% w/v)	0.064% w/v[7]	Decrease the solubility
		Repaglinide 9.6 mg/2 ml (0.48% w/v)	0.0068% w/v[22]	70.59 folds
		Fenofibrate	0.000042% w/v	Insoluble
		Indomethacin 3.2 mg/2 ml (0.16% w/v)	0.036% w/v[7]	4.44 folds
		Norfloxacin 7.6 mg/2 ml (0.38% w/v)	0.088% w/v[7]	4.32 folds

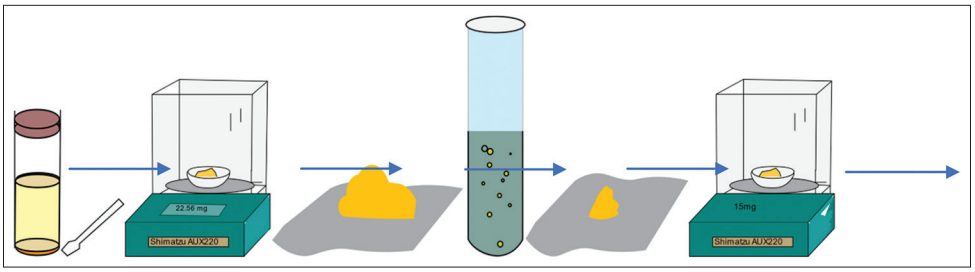

Figure 9: Diagrammatic representation of solubility studies

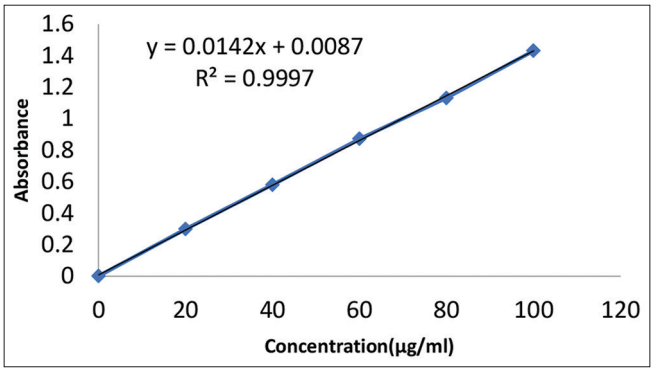

Figure 10: Calibration of furosemide drug

Preparation of blank aliquots

To prepare reagent blank with regard to 1000 µg/ml, 20 ml of blend 5 were taken in 50 ml of volumetric flask, and the volume was then raised up to 50 ml with milli-Q water. To attain a concentration of 100 µg/ml, 10 ml of the above-mentioned solution was pipetted into another volumetric flask having a capacity of 100 ml. With the use of milli-Q water, appropriate dilutions of the stock solution were done to have desired reagent blanks. Calibration curve was plotted between the concentration and absorbance. The calibration curve was mentioned in Figure 10.

Study of interference of excipients in UV-visible spectrophotometric estimation of furosemide

Drug's stock solution preparation

The furosemide, 100 mg, was weighed accurately and then put to a volumetric flask, 100 ml. To dissolve it, approximately 70 ml of milli-Q water were added to the volumetric flask and vortexed for 15–20 min. To get 1000 µg/ml, the volume was then raised to 100 ml with water. To produce 100 µg/ml, 10 ml of the stock solution was pipetted into another 100 ml volumetric flask, and the entire 100 ml was filled with milli-Q water.

Twenty milliliters of 100 µg/ml solution were pipetted out and transferred to 50 ml volumetric flask, the volume was made up to 50 ml with milli-Q water to achieve 20 µg/ml. Absorbance was measured at 331 nm with respect to milli-Q water.

Excipient solutions preparation

To dissolve the solubilizer, 100 mg of it was weighed, transferred to a 100 ml volumetric flask, and 70 ml of milli-Q water was then added. Then, milli-Q water was used to make up the volume up to 100 ml to get 1000 µg/ml. In another 100 volumetric flask, 10 ml of the abovementioned solution was pipetted out in another volumetric flask; then, volume was made up to 100 ml, each solubilizer's solution was made in a similar manner.

In a separate 100 ml volumetric flask, 20 ml of a solubilizer solution containing 100 µg/ml was added along with 20 ml of the drug stock solution (100 µg/ml). Then, milli-Q water was used to make up a volume of up to 100 ml. At 331 nm, absorbance was noted against milli-Q water. Results mentioned in Table 3.

Drug exicipient interaction studies

The goal of this study was to see if the drug furosemide changed physically when they interacted with different excipients. The drugs and excipients were combined and screened in a 1:1 ratio before being put in glass vials with 10 ml capacities and sealed with an aluminium seal for 1 month at various temperatures (room temperature and refrigerator). Each week, vials were withdrawn and the contents were checked for physical changes. Results are shown in Table 4.

Method of preparation of aqueous im injection of furosemide

The intramuscular injection was manufactured in accordance with the information in the preceding Table 4. As per Table 5, the approximate solubility of furosemide was found to be 31.8 mg/2 ml in blend-5. Thus, it was decided to make aqueous IM injection of furosemide of strength 20 mg/2 ml using blend-5. To make a batch of 50 ml (aqueous IM injection), First, blend-5 was made. L-lysin (5 g), sodium acetate (5 g), arginine (5 g), Tween 80 (2.5 ml), and furosemide (0.5 g) were transferred in a 50 ml volumetric flask. About 30 ml of milli-Q water was added and flask was shaken to get a clear solution then volume was made up to 50 ml with milli-Q water. In a separate 50 ml volumetric flask, 5 g furosemide drug was transferred and about 40 ml blend-5 was added. The flask was shaken to dissolve the drug. Then, volume was made up to the mark with blend 5. pH of this injection was

Table 3: Interference of excipients in UV-visible spectrophotometric estimation of drugs

Drug	Solubilizer	Concentration of drug (μg/ml)	Concentration of solubilizer (μg/ml)	λ max	Absorbance
Furosemide	-	20	-	331	0.298
Furosemide	L-Lysine	20	20	331	0.293
Furosemide	Arginine	20	20	331	0.295
Furosemide	Tween 80	20	20	331	0.286
Furosemide	Sodium acetate	20	20	331	0.300

Table 4: Drug excipient interaction studies

S. No.	Drug + Solubilizer (1:1)	Initial	Observation (physical changes)									
			Room temperature (30–35°C)					Freeze conditions (2–8°C)				
			Time (Week)					Time (Week)				
			1	2	3	4	5	1	2	3	4	5
1.	Furosemide+L-lysine	WP	×	×	×	×	×	×	×	×	×	×
2.	Furosemide+Arginine	WP	×	×	×	×	×	×	×	×	×	×
3.	Furosemide+Sodium acetate	WP	×	×	×	×	×	×	×	×	×	×
4.	Furosemide+Tween 80	YWS	×	×	×	×	×	×	×	×	×	×

WP: White powder, YWS: Yellowish-white semisolid, ×: No change

Table 5: Formula for aqueous IM injection of furosemide using blend-5

S. No.	Solubilizers	Formula for 20 mg/2 ml	Formula for 50 ml Batch
1.	L-Lysine	200mg	5 g
2.	Sodium acetate	200 mg	5 g
3.	Arginine	200 mg	5 g
4.	Tween 80	0.1 ml	2.5 ml
5.	Furosemide	20 mg	0.5 g

Table 6: Chemical stability studies of furosemide aqueous IM injection

S. No.	Number of weeks	Absorbance at room temperature (331 nm)
1.	Initial	0.282
2.	1st	0.283
3.	2nd	0.280
4.	3rd	0.283
5.	4th	0.284
6.	5th	0.281
7.	6th	0.284

determined using pH meter (Cyber scan) and was found to be 7.04. After that, 20 vials were prepared. Each vial containing 2 ml of furosemide IM injection solution. Then, two vials were kept for freeze thaw studies. In addition, nine vials were sterilised in a (Sciencetech) autoclave for 30 min at 121°C and 15 lb of pressure. Nine vials were kept at room temperature for chemical stability studies.

Table 7: Physical stability studies of aqueous IM injection of furosemide

S. No.	No. of weeks	Precipitation	Colour development
1.	Initial	Nil	Nil
2.	1st	Nil	Nil
3.	2nd	Nil	Nil
4.	3rd	Nil	Nil
5.	4th	Nil	Nil
6.	5th	Nil	Nil
7.	6th	Nil	Nil

Stability studies of prepared furosemide aqueous IM injection

Chemical stability study using UV-visible spectrophotometer

A single vial, which contains 20 mg/2 ml of aqueous IM injection of furosemide, was taken every week. The content of vials was transferred to 1000 ml volumetric flask contains about 600 ml milli-Q water. Vials and closures were properly rinsed with milli-Q water and rinsing solution was added in 1000 ml volumetric flask. Then, volume was made up to the mark with milli-Q water. After that, the absorbance of the solution was noted at 331 nm against a reagent blank. The results are shown in Table 6.

Physical stability studies

Prepared aqueous IM injection vials were observed at room temperature for precipitation and colour development. Results are shown in Table 7.

Table 8: Freeze thaw studies of aqueous IM injection

S. No.	Number of days	Precipitation		Colour development	
		Room temperature (30–35°C)	Freeze condition (2–8°C)	Room temperature (30–35°C)	Freeze condition (2–8°C)
1.	1st	-	Nil		Nil
2.	2nd	Nil	-	Nil	
3.	3rd	-	Nil		Nil
4.	4th	Nil	-	Nil	
5.	5th	-	Nil		Nil
6.	6th	Nil	-	Nil	
7.	7th	-	Nil		Nil
8.	8th	Nil	-	Nil	
9.	9th	-	Nil		Nil
10.	10th	Nil	-	Nil	
11.	11th	-	Nil		Nil
12.	12th	Nil	-	Nil	
13.	13th	-	Nil		Nil
14.	14th	Nil	-	Nil	

Freeze thaw study

Two vials of aqueous IM injections were kept at room temperature and freeze condition on alternate days. Then, the contents of vials were checked for any precipitation and colour development. Results of freeze thaw studies are shown in Table 8.

pH of formulation

-pH of the final formulation was determined using pH meter (cyber scan). The resultant pH of the formulation was 7.04 pH.

RESULTS

Results of UV identification of drugs

Peaks of all drugs were observed. Drugs norfloxacin shows the maximum peak at (273 nm), gatifloxacin shows the maximum peak at (287.5 nm), paracetamol shows the maximum peak at (243 nm), acyclovir shows the maximum peak at (253 nm), ondansetron HCl shows the maximum peak at (310 nm), piroxicam shows the maximum peak at (354 nm), ornidazole shows the maximum peak at (319.5 nm) and aspirin shows the maximum peak at (276 nm).

DISCUSSION

In the present study, we prepared numerous safe solvent systems for aqueous IM injection for poorly water-soluble drugs. According to solubility studies [Table 2], maximum solubility of ornidazole was 7.50% w/v found out in blend-3, but the reported water solubility of ornidazole is 0.083% w/v. Paracetamol had a maximum solubility of 5.00% w/v in blend-3, but the reported water solubility of paracetamol is 1.45% w/v. Nimesulide had a maximum solubility of 1.45% w/v in blend-3, but the reported water solubility of nimesulide is 0.001% w/v. Aspirin had a maximum solubility of 7.05% in blend-2, but the reported water solubility of aspirin is 0.3% w/v. Salicylic acid had a maximum solubility of 16.67% w/v in blend-4, blend-6, and blend-7, but the reported water solubility of salicylic acid is 0.3% w/v. Naproxen had a maximum solubility of 4.65% w/v in blend 1 and blend-2, but the reported water solubility of naproxen is 0.009% w/v. Acyclovir had a maximum solubility of 4.16% w/v in blend-7, but the reported water solubility of acyclovir is 0.114% w/v. Ondansetron HCl had a maximum solubility of 1.06% w/v in blend-4, but the reported water solubility of ondansetron HCl is 0.0048% w/v. Piroxicam had a maximum solubility of 1.73% w/v in blend-6, but the reported water solubility of piroxicam is 0.040% w/v. Chlorthalidone had a maximum solubility of 2.83% w/v in blend-7, but the reported water solubility of chlorthalidone is 0.12% w/v. Furosemide had a maximum solubility of 5.00% w/v in blend-4, but the reported water solubility of furosemide is 0.064% w/v. Repaglinide had a maximum solubility of 1.14% w/v in blend-6, but the reported water solubility of repaglinide is 0.0068% w/v. Fenofibrate had a maximum solubility of 1.52% w/v in blend-4, but the reported water solubility of fenofibrate is 0.000042% w/v. Indomethacin had a maximum solubility of 2.83% w/v in blend-9, but the reported water solubility of indomethacin is 0.036% w/v. Norfloxacin had a maximum solubility of 3.22% w/v in blend-6, but the reported water solubility of norfloxacin is 0.088% w/v.

CONCLUSION

From this research work, it is clear that mixed solvency concept can be employed to develop a large numbers of expectedly safe aqueous IM injection solution type aqueous solvent systems for poorly water-soluble drugs. Thus, solubilizing power of safe additives can be employed to make marketable aqueous IM injections.

Using those studies, we can conclude that various IM injections of drugs such as furosemide (20 mg/2 ml), piroxicam (20 mg/2 ml), repaglinide (16 mg/3 ml), indomethacin (25 mg/ml), and acyclovir (20 mg/3 ml) can be prepared. Moreover, among all, furosemide was chosen as the drug of choice for the preparation of the typical aqueous IM injection solution. Since it shows the desirable physical and chemical stability as well as freeze thaw studies.

The resultant pH of the formulation was also found to be 7.04. This means that there was no acidity or basicity role in solubility enhancement. Due to the lower viscosity of the IM injection solution, it would be less painful and cause less irritation than the marketed formulation. We did not incorporate additional preservatives in our formulation, because sodium acetate works as a preservative itself, but in this study, we used sodium acetate as a solubilizer.

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REFERENCES

1. Available from: https://www.pharmoutsourcing.com/featured-articles/331618-parenteral-preparations-challenges-in-formulations [Last accessed on 2022 Aug 04].
2. Dums RJ, Alkers MJ, Turco SJ. Parenteral drug administration: Routes, precautions, problems, complications and drug delivery systems. In: Kenneth EA, Herbert AL, Lachman, L, editors. Parenteral Dosage Forms: Parenteral Medications. 2nd ed. New York: Marcel Dekker Inc.; 2005. p. 19-20.
3. Thakur Y, Maheshwari RK. A rview article-ecofriendly and economic analytical methods using hydrotropic solubilization (Titrimetric, UV spectrophotometry, TLC, HPLC). World J Pharm Sci 2020;10:478-507.
4. Thakur Y, Nagwanshi K, Ludhiani S, Maheshwari Rk. A Review Article-ecofriendly and Economic Applications of Mixed Hydrotropic Solubilization in the Pharmaceutical Fields of Analysis and Formulations; 2021.
5. Padiyar A, Maheshwari RK. Novel pharmaceutical dosage form. J Drug Deliv Ther 2018;8:1-2.
6. Patil SS, Patil AS, Patil AV, Patil HK, Salunke PA, Wagh RS. Novel mixed hydroptropic solubilization technique for analytical method development and validation of acyclovir in bulk and tablet formulation by spectrophotometry. Asian J Pharm Anal 2019;9:25-9.
7. Padiyar A, Maheshwari RK. Novel dry injection for reconstitution of aspirin using solid solubilisers. J Drug Deliv Ther 2017;7:44-5.
8. Yadav N, Shukla T, Upmanyu N, Pandey S, Khan M. Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate. J Drug Deliv Ther 2018;8:481-8.
9. Padiyar A, Agrawal OP, Rajpoot K, Tekade RK. Hydrotropy, mixed hydrotropy, and mixed solvency as trending concept for solubilization of lipophilic drugs. In: The future of Pharmaceutical Product Development and Research. Cambridge: Academic Press; 2020. p. 145-78.
10. Soni KS, Sharma K. An ecofriendly spectrophotometric analysis pf poorly-water soluble drug (Nimesulide) using the mixed hydrotropic concept. Asian J Pharm Health Sci 2019;9:1281-4.
11. Remi SL, Varkey J. An ecofriendly novel spectrophotometric estimation and validation of paliperidone in bulk drugs and their dosage forms by mixed hydrotropic solubilisation method. Asian J Pharm Health Sci 2018;8:1996-2001.
12. Padria A, Maheshwari RK, Thakur Y, Ludhiani S. Formulation and development of model dry powder injection for reconstitution of poorly water poorly-soluble drug, diazepam by using mixed solvency concept and their evaluations. Int J Pharm Res Appl 2021;6:1286-96.
13. Mulani P, Maheshwari RK. Formulation development of aqueous topical solutions and gels of poorly water soluble drug nimesulide using novel application mixed solvency concept and their evaluation. Int J Sci Res 2019;8:1521-9.
14. Lasure L, Ansari A, Kalshetti M. Uv spectrophotometric analysis and validation of acyclovir in solid dosage form. Int J Curr Pharm Res 2020;12:100-3.
15. Redasani V, Patel P, Marathe D, Chaudhari S, Shirkhedkar A, Surana S. A review on derivative Uv-spectrophotometry analysis of drugs in pharmaceutical formulations and biological samples review. J Chil Chem Soc 2018;63:4126-34.
16. Padiyar A, Maheshwari RK. Novel Dry Injection for Reconstitution of Aspirin Using Solid Solubilisers. J Drug Deliv Ther 2017;7:44-45
17. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/Gatifloxacin#section=solubility [Last accessed on 2022 Aug 31].
18. National Center for Biotechnology Information.

PubChem Compound Summary for CID 54677470, M.R.A., 2022 Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/54677470 [Last accessed on 2022 Aug 31].
19. National Center for Biotechnology Information (2022). PubChem Compound Summary for CID. United States: National Center for Biotechnology Information; 2022. p. 135398513. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/135398513
20. National Center for Biotechnology Information. PubChem Compound Summary for CID. United States: National Center for Biotechnology Information; 2022. p. 68647. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/68647 [Last accessed on 2022 Aug 31].
21. National Center for Biotechnology Information. PubChem Compound Summary for CID. United States: National Center for Biotechnology Information; 2022. p. 2732. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/2732 [Last accessed on 2022 Aug 31].
22. National Center for Biotechnology Information. PubChem Compound Summary for CID. United States: National Center for Biotechnology Information; 2022. p. 65981. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/65981 [Last accessed on 2022 Aug 31].
23. Purcaru SO, Ionescu M, Raneti C, Anuta V, Mircioiu I, Belu I. Study of nimesulide release from solid pharmaceutical formulations in tween 80 solutions. Curr Health Sci J 2010;36:42-9.
24. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/aspirin#section=solubility [Last accessed on 2022 Aug 31].

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