ORIGINAL ARTICLE

Novel Techniques to Make Innumerable, Expectedly Safe, and Oily Systems to Make Intramuscular Injections (Solutions) of Poorly Oil Soluble Drugs Using Mixed Solvency Concept

Dharmendra Prajapati, Rajesh Kumar Maheshwari

Department of Pharmacy, Shri G.S. Institute of Technology and Science, Indore, Madhya Pradesh, India

Abstract

A large number of blends of oily solutions containing oil soluble safe additives can be developed. The primary goal of the present study is to investigate the idea of mixed solvency concept. Pharmaceutical manufacturers can then use these blends to develop oily solutions for intramuscular injections that contain drugs that are poorly oil soluble. The main objective of this research is to provide oily intramuscular injection manufacturers some creative ideas. Utilizing the solubilizing properties of safe solubilizers, the solubility of poorly oil soluble drugs can be increased. After toxicological studies, it is anticipated that these injection formulations will be safe and such formulations can be marketed by the pharmaceutical manufacturers. According to the mixed solvency concept, every substance on earth has the ability to dissolve a solute in a solvent system. Hence, a concentrated oily solution containing a variety of oil soluble excipients might work well as a solvent for drugs that are poorly oil soluble. Such a concentrated solution might demonstrate the additive or synergistic solubilizing effects of the solubilizers present in solution for a specific solute.

Key words: Amlodipine besylate injection, mixed solvency concept, novel solvent system, oily injection solution

INTRODUCTION

The words "para" and "enteron," which mean to avoid the intestine, are the roots of the word "parenteral" that defined as "those formulations intended for intravenous administration through rather than the skin or another external boundary tissue through the digestive tract, so that the active ingredients can be injected directly into an organ, blood vessel, lesion or tissue. The key in the current health care environment is parenteral nutritional treatment component for hospitalized patient's products. Subcutaneous, intramuscular, intravenous, intradermal, and intra-arterial parenteral routes of administration, among others, also have good qualities for drug absorption and bioavailability. The approach provides many benefits for patients who cannot take the medication orally and need a quick commencement of action, such as comatose patients. Patients who are in hospitals or who are bedridden are entirely dependent on parenteral nutrition such as fluids, electrolytes, or nutrients administered by parenteral route. With less frequent dosage, novel preparations offer patients prolonged, targeted, and regulated medication administration. Parenteral formulations are more expensive and costlier than traditional formulations in spite of their many advantages. To produce and administer parenteral formulations, specific tools, methods, and equipment are required. Parenteral formulations continue to be a leading choice for the treatment of hospitalized patients despite all of these issues. Parenteral products should be appropriately sterile and absent of pyrogens because they are intended to be injected directly into the blood for that purpose.

Injectable solution

An isotonic aqueous solution, which has a pH near to that of blood and bodily tissues, is the easiest and most practical way

Address for correspondence:
Dharmendra Prajapati, Shri G.S. Institute of Technology and Science, 23, Park Road, Indore - 452 003, Madhya Pradesh, India. Phone: +91-8982451830.
E-mail: prajapatidharmendra851@gmail.com

Received: 12-01-2023
Revised: 18-03-2023
Accepted: 30-03-2023

to present an injectable substance. Large-volume parenteral is a type of parenteral solution. Irrigation fluids, low volume parenteral, and small volume parenteral. Aqueous solutions delivered in higher amounts are called infusion fluids larger amount than what is typically provided by intravenous infusion. Preparations are usually used in infusions for fluid replacement, restoring electrolyte balance, and basic nutrition replacement, etc.[1]

Intramuscular injection

Injections into the muscles are a standard procedure in contemporary medicine. Drugs and vaccinations are delivered using them. This is how a number of medications and practically all injectable vaccinations are administered.

Injections into the muscle are utilized when alternative delivery techniques are not advised. These consist of Injections into the muscles area standard procedure in contemporary medicine. Drugs and vaccinations are delivered using them. This is how a number of medications and practically all injectable vaccinations are administered.

Injections into the muscle are utilized when alternative delivery techniques are not advised. Subcutaneous injections take longer to absorb than intramuscular injections. This is due to the fact that muscle tissue receives more blood than the tissue immediately beneath your skin. In addition, muscle tissue has a higher capacity for drug storage than subcutaneous tissue.[2]

Several oil-soluble additives, each in a small concentration, combined with oil to form a concentrated solution may effectively improve a drug's oil solubility. Rifampicin was employed as the model poorly oil soluble drug in this investigation. Thymol, menthol, camphor, phenol, ethanol, benzyl alcohol, and oleic acid were used as model oil soluble/miscible additives, and castor oil was used as the model oil. Solubilizing properties of these excipients were used to develop the solution type intramuscular oily injection of rifampicin. The significance of mixed solvency was highlighted by the solubility study's findings, and data from the stability study confirms that the formulation created using this method also provides good stability.[3]

Mixed solvency concept

The concept of mixed solvency has two parameters. Every substance, whether gas, liquid, or solid, has the ability to dissolve other substances, according to the first parameter. According to the second parameter of the mixed solvency concept, a concentrated solution of various solubilizers used in lower concentrations can also significantly increase a solute's solubility. The concept of mixed solvency has two parameters. Every substance, whether gas, liquid, or solid, has the ability to dissolve other substances, according to the first parameter. According to the second parameter of the mixed solvency concept, a concentrated solution of various solubilizers used in lower concentrations can also significantly increase a solute's solubility. To formulate different dosage forms of insoluble drugs using safe concentrations of excipients for solubilization, the mixed-solvency concept will be useful. The mixed-solvency concept has been employed to enhance the solubility of several drugs.[4-40]

MATERIALS

Amlodipine besylate was obtained as gift sample from MCW Healthcare Private Limited, Indore. Aspirin, Naproxen, Ornidazole, Nimesulide, Glipizide, Glimepiride, Atenolol, Acyclovir, Chlorthalidone were gift samples from Alkem Lab. Ltd. Mumbai. Gatifloxacin was gift sample from Wockhardt Ltd. Aurangabad. Furosemide was gift sample from IPCA Laboratories Ltd. Ratlam. Indomethacin, Norfloxacin, Paracetamol and Ondansetron were gift sample from Modern Laboratories Pvt. Ltd. Indore. Piroxicam was provided by Shreya Life Science Pvt. Ltd. Aurangabad. Ibuprofen was gift sample from Wilcure Remedies, Indore. Diazepam was provided by Ranbaxy laboratories, Dewas. And Hydrochlorothiazide was provided by Schon Pharmaceuticals Ltd. Indore and excipients such as Alcohol, Benzyl alcohol, Benzyl benzoate, Methyl pyrrolidone, Poloxamer 407, Propyl paraben, Benzoic acid, Methyl paraben, and Glyceryl mono stearate was provided by SGSITS institute Indore. The solubilizers were selected in different concentrations [given in Table 1] within their safe limits as given in IIG 2020.

Table 1: Solubilizer's selection (As per inactive ingredient guide 2020 solubilizers

S. No.	Solubilizers	Concentration (%)
1	Alcohol	10
2	Benzyl alcohol	10
3	Benzyl benzoate	10
4	Methyl pyrrolidone	10
5	Poloxamer407	10
6	Propylparaben	10
7	Threonine	10
8	Valine	10
9	Histidine	10
10	Methionine	10
11	Phospholipid	10
12	Benzoic acid	5
13	MethylParaben	5
14.	Glyceryl mono stearate	5

Table 2: Composition of blend-1

S. No.	Solubilizer	For 100 mL	For 50 mL
1.	Propylparaben	10 g	5 g
2.	Benzyl alcohol	10 mL	5 mL
3.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 3: Composition of blend -2

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Methylparaben	5 g	2.5 g
2.	Vanillin	2.5 g	1.25 g
3.	Benzyl benzoate	5 mL	1.25 mL
4.	Ethanol	5 mL	2.5 mL
5.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 4: Composition of blend -3

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Methylparaben	5 g	2.5 g
2.	Propylparaben	10 g	5 g
3.	Ethyloleate	Upto 100 mL	Upto 50 mL

Table 5: Composition of blend-4

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Methylparaben	5 g	2.5 g
2.	Benzoic acid	5 g	2.5 g
3.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 6: Composition of blend-5

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Methylparaben	5 g	2.5 g
2.	Propylparaben	10 g	5 g
3.	Benzoic acid	5 g	2.5 g
4.	Methyl pyrrolidone	5 mL	2.5 mL
5.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 7: Composition of blend-6

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Glyceryl mono stearate	5 g	2.5 g
2.	Propylparaben	5 g	2.5 g
3.	Benzoic acid	5 g	2.5 g
4.	Methylparaben	2.5 g	1.25 g
5.	Methyl pyrrolidone	5 mL	2.5 mL
6.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Identification of amlodipine besylate

In the present investigation, melting point was determined by analog melting point apparatus after it was packed in capillary of amlodipine. Moreover, determine the melting point of another method was DSC (201–205) (differential scanning calorimetry).

Table 8: Composition of blend-7

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Glyceryl mono stearate	5 g	2.5 g
2.	Propylparaben	5 g	2.5 g
3.	Benzoic acid	2.5 g	1.25 g
4.	Benzyl alcohol	5 mL	2.5 mL
5.	Benzyl benzoate	5 mL	2.5 mL
6.	Valine	2.5 g	1.25 g
7.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 9: Composition of blend-8

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Glyceryl mono stearate	5 g	2.5 g
2.	Propylparaben	10 g	2.5 g
3.	Benzoic acid	2.5 g	1.25 g
4.	Valine	2.5 g	1.25 g
5.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 10: Composition of blend-9

S. No.	Solubilizer	For 100 mL	For 50 mL
1.	Methylparaben	2.5 g	1.25 g
2.	Propylparaben	2.5 g	1.25 g
3.	Glyceryl mono stearate	2.5 g	1.25 g
4.	Methyl pyrrolidone	10 mL	5 mL
5.	Benzyl benzoate	10 mL	5 mL
6.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Table 11: Composition of blend-10

S. No.	Solubilizers	For 100 mL	For 50 mL
1.	Glyceryl mono stearate	5 g	2.5 g
2.	Propylparaben	5 g	2.5 g
3.	Methylparaben	1.5 g	0.75 g
4.	Benzoic acid	5 g	2.5 g
5.	Valine	1.5 g	0.75 g
6.	Poloxamer407	1 g	0.5 g
7.	Ethyl oleate	Upto 100 mL	Upto 50 mL

Solubility determination procedure

Approximate solubility method: Solubility of drugs in ethyl oleate and different blends was determined by approximate solubility studies.

Table 12: Solubility studies of drug in blend-1 and ethyl oleate

S. No.	Approximate solubility of drug in blend-1	Approximate solubility of drug in ethyl oleate	Solubility enhancement
1.	Naproxen 14.57 mg/mL (1.46%w/v)	8.82 mg/mL (0.88%w/v)	1.66 fold
2.	Gatifloxacin 8.96 mg/mL (0.90%w/v)	2.44 mg/mL (0.24%w/v)	3.70 fold
3.	Aspirin 21.42 mg/mL (2.14%w/v)	10.73 mg/mL (1.07%w/v)	2.00 fold
4.	Ornidazole 83.33 mg/mL (8.33%w/v)	45.45 mg/mL (4.54%w/v)	1.80 fold
5.	Ibuprofen 153.84 mg/mL (15.38%w/v)	133.67 mg/mL (13.37%w/v)	1.15 fold
6.	Paracetamol13.23 mg/mL (1.32%w/v)	1.26 mg/mL (0.13%w/v)	10.15 fold
7.	Nimesulide6.67 mg/mL (0.67%w/v)	6.29 mg/mL (0.63%w/v)	1.06 fold
8.	Norfloxacin 4.80 mg/mL (0.48%w/v)	0.93 mg/mL (0.09%w/v)	5.30 fold
9.	Piroxicam 7.56 mg/mL (0.76%w/v)	4.13 mg/mL (0.41%w/v)	1.85 fold
10	Glipizide 3.33 mg/mL (0.33%w/v)	2.08 mg/mL (0.21%w/v)	1.57 fold
11.	Glimepiride 17.64 mg/mL (1.76%w/v)	2.63 mg/mL (0.26%w/v)	6.77 fold
12.	Hydrochlorothiazide3.12 mg/mL (0.31%w/v)	4.63 mg/mL (0.46%w/v)	0.67 fold
13	A mLodipine besylate 3.84 mg/mL (0.38%w/v)	1.83 mg/mL (0.18%w/v)	2.11 fold
14.	Furosemide 5.88 mg/mL (0.59%w/v)	2.17 mg/mL (0.22%w/v)	2.68 fold
15.	Acyclovir 0.19 mg/mL (0.02%w/v)	0.66 mg/mL (0.07%w/v)	0.28 fold
16.	Indomethacin 52.22 mg/mL (5.22%w/v)	36.92 mg/mL (3.69%w/v)	1.41 fold
17.	Diazepam 133.23 mg/mL (13.32%w/v)	73.57 mg/mL (7.36%w/v)	1.81 fold
18.	Ondansetron 2.68 mg/mL (0.27%w/v)	3.23 mg/mL (0.32%w/v)	0.84 fold
19.	Atenolol 34.80 mg/mL (3.48%w/v)	18.57 mg/mL (1.86%w/v)	1.87 fold
20.	Chlorthalidone 1.46 mg/mL (0.15%w/v)	1.11 mg/mL (0.11%w/v)	1.36 fold

Table 13: Solubility study of drugs in blend-2 and Ethyl oleate

S. No.	Approximate solubility ofdruginblend-2	Approximate solubility in Ethyl oleate	Solubility enhancement
1.	Naproxen 14.23 mg/mL (1.42%w/v)	8.82 mg/mL (0.88%w/v)	1.61 fold
2.	Gatifloxacin 5.40 mg/mL (0.54%w/v)	2.44 mg/mL (0.24%w/v)	2.25 fold
3.	Aspirin 25.80 mg/mL (2.58%w/v)	10.75 mg/mL (1.07%w/v)	2.41 fold
4.	Ornidazole 102.63 mg/mL (10.26%w/v)	45.45 mg/mL (4.54%w/v)	2.26 fold
5.	Ibuprofen 146.67 mg/mL (14.67%w/v)	133.67 mg/mL (13.37%w/v)	1.10 fold
6.	Paracetamol 5.88 mg/mL (0.59%w/v)	1.26 mg/mL (0.13%w/v)	4.54 fold
7.	Nimesulide 6.27 mg/mL (0.63%w/v)	6.29 mg/mL (0.63%w/v)	Equal to the Ethyl oleate
8.	Norfloxacin 3.33 mg/mL (0.33%w/v)	0.93 mg/mL (0.09%w/v)	3.67 fold
9.	Piroxicam (3.94 mg/mL) 0.39%w/v	4.13 mg/mL (0.41%w/v)	0.95 fold
10.	Glipizide 1.12 mg/mL (0.11%w/v)	2.08 mg/mL (0.21%w/v)	0.52 fold
11.	Glimepiride 14.28 mg/mL (1.43%w/v)	2.63 mg/mL (0.26%w/v)	5.50 fold
12.	Hydrochlorothiazide1.23 mg/mL (0.12%w/v)	4.63 mg/mL (0.46%w/v)	0.26 fold
13.	A mLodipinebesylate 7.14 mg/mL (0.71%w/v)	1.83 mg/mL (0.18%w/v)	3.94 fold
14.	Furosemide 4.16 mg/mL (0.42%w/v)	2.17 mg/mL (0.22%w/v)	1.91 fold
15.	Acyclovir0.67 mg/mL (0.07%w/v)	0.66 mg/mL (0.07%w/v)	Equal to the Ethyl oleate
16.	Indomethacin 33.09 mg/mL (3.31%w/v)	36.92 mg/mL (3.69%w/v)	0.88 fold
17.	Diazepam 86.63 mg/mL (8.66%w/v)	73.57 mg/mL (7.36%w/v)	1.18 fold
18.	Ondansetron2.15 mg/mL (0.21%w/v)	3.23 mg/mL (0.32%w/v)	0.66 fold
19.	Atenolol 11.71 mg/mL (1.17%w/v)	18.57 mg/mL (1.86%w/v)	0.63 fold
20.	Chlorthalidone3.81 mg/mL (0.38%w/v)	1.11 mg/mL (0.11%w/v)	3.45 fold

Table 14: Solubility studies of drugs in blend-3 and Ethyl oleate

S. No.	Approximate solubility of drug in blend-3	Approximate solubility in Ethyl oleate	Solubility enhancement
1.	Naproxen 13.33 mg/mL (1.33%w/v)	8.82 mg/mL (0.88%w/v)	1.51 fold
2.	Gatifloxacin 6.66 mg/mL (0.67%w/v)	2.44 mg/mL (0.24%w/v)	2.79 fold
3.	Aspirin 13.33 mg/mL (1.33%w/v)	10.75 mg/mL (1.08%w/v)	1.24 fold
4.	Ornidazole115.43 mg/mL (11.54%w/v)	45.45 mg/mL (4.54%w/v)	2.53 fold
5.	Ibuprofen 197.62 mg/mL (19.76%w/v)	133.67 mg/mL (13.37%w/v)	1.48 fold
6.	Paracetamol 6.66 mg/mL (0.67%w/v)	1.26 mg/mL (0.13%w/v)	5.15 fold
7.	Nimesulide 5.32 mg/mL (0.53%w/v)	6.29 mg/mL (0.63%w/v)	0.84 fold
8.	Norfloxacin 6.66 mg/mL (0.67%w/v)	0.93 mg/mL (0.09%w/v)	7.44 fold
9.	Piroxicam 11.43 mg/mL (1.14%w/v)	4.13 mg/mL (0.41%w/v)	2.78 fold
10.	Glipizide 7.91 mg/mL (0.79%w/v)	2.08 mg/mL (0.21%w/v)	3.76 fold
11.	Glimepiride5.41 mg/mL (0.54%w/v)	2.63 mg/mL (0.26%w/v)	2.08 fold
12.	Furosemide 1.53 mg/mL (0.15%w/v)	2.17 mg/mL (0.22%w/v)	0.68 fold
13.	Hydrochlorothiazide 0.42 mg/mL (0.04%w/v)	4.63 mg/mL (0.46%w/v)	0.09 fold
14.	A mLodipinebesylate3.68 mg/mL (0.37%w/v)	1.83 mg/mL (0.18%w/v)	2.05 fold
15.	Acyclovir0.64 mg/mL (0.06%w/v)	0.66 mg/mL (0.07%w/v)	0.86 fold
16.	Indomethacin 36.23 mg/mL (3.62%w/v)	36.92 mg/mL (3.69%w/v)	0.98 fold
17.	Diazepam121.12 mg/mL (12.11%w/v)	73.57 mg/mL (7.36%w/v)	1.64 fold
18.	Ondansetron 1.57 mg/mL (0.16%w/v)	3.23 mg/mL (0.32%w/v)	0.50 fold
19.	Atenolol 31.17 mg/mL (3.12%w/v)	18.57 mg/mL (1.85%w/v)	1.68 fold
20.	Chlorthalidone7.33 mg/mL (0.73%w/v)	1.11 mg/mL (0.11%w/v)	6.64 fold

Table 15: Solubility studies of drugs in blend-4 and Ethyl oleate

S. No.	Approximate solubility of drug in blend-4	Approximate solubility of drug in Ethyl oleate	Solubility enhancement
1.	Naproxen 13.33 mg/mL (1.33%w/v)	8.82 mg/mL (0.88%w/)	1.51 fold
2.	Gatifloxacin 4.12 mg/mL (0.41%w/v)	2.44 mg/mL (0.24%w/)	1.71 fold
3.	Aspirin 16.66 mg/mL (1.67%w/v)	10.75 mg/mL (1.07%w/v)	1.56 fold
4.	Ornidazole66.66 mg/mL (6.67%w/v)	45.45 mg/mL (4.54%w/v)	1.47 fold
5.	Ibuprofen 222.22 mg/mL (22.22%w/v)	133.67 mg/mL (13.37%w/v)	1.66 fold
6.	Paracetamol6.66 mg/mL (0.67%w/v)	1.26 mg/mL (0.13%w/)	5.15 fold
7.	Nimesulide7.69 mg/mL (0.77%w/v)	6.29 mg/mL (0.63%w/)	1.22 fold
8.	Norfloxacin 4.23 mg/mL (0.42%w/v)	0.93 mg/mL (0.09%w/)	4.67 fold
9.	Piroxicam4.63 mg/mL (0.46%w/v)	4.13 mg/mL (0.41%w/)	1.12 fold
10	Glipizide 5.43 mg/mL (0.54%w/v)	2.08 mg/mL (0.21%w/)	2.57 fold
11.	Glimepiride11.66 mg/mL (1.17%w/v)	2.63 mg/mL (0.26%w/)	4.50 fold
12.	Furosemide5.06 mg/mL (0.51%w/v)	2.17 mg/mL (0.22%w/v)	2.32 fold
13.	Hydrochlorothiazide 1.33 mg/mL (0.13%w/v)	4.63 mg/mL (0.46%w/v)	0.28 fold
14.	A mLodipine besylate 7.33 mg/mL (0.73%w/v)	1.83 mg/mL (0.18%w/v)	4.05 fold
15.	Acyclovir 1.20 mg/mL (0.12%w/v)	0.66 mg/mL (0.07%w/v)	1.71 fold
16.	Indomethacin 38.80 mg/mL (3.88%w/v)	36.92 mg/mL (3.69%w/v)	1.05 fold
17.	Diazepam97.50 mg/mL (9.75%w/v)	73.57 mg/mL (7.36%w/v)	1.32 fold
18.	Ondansetron 1.90 mg/mL (0.19%w/v)	3.23 mg/mL (0.32%w/v)	0.59 fold
19.	Atenolol 9.09 mg/mL (0.91%w/v)	18.57 mg/mL (1.85%w/v)	0.49 fold
20.	Chlorthalidone 3.16 mg/mL (0.32%w/v)	1.11 mg/mL (0.11%w/v)	2.91 fold

Table 16: Solubility studies of drugs in blend-5 and Ethyl oleate

S. No.	Approximate solubility of drug in blend-5	Approximate solubility of drug in Ethyl oleate	Solubility enhancement
1.	Naproxen 33.33 mg/mL (3.33%w/v)	8.82 mg/mL (0.88%w/v)	3.78 fold
2.	Gatifloxacin 8.33 mg/mL (0.83%w/v)	2.44 mg/mL (0.24%w/v)	3.46 fold
3.	Aspirin 4.29 mg/mL (0.43%w/v)	10.73 mg/mL (1.07%w/v)	0.40 fold
4.	Ornidazole 153.84 mg/mL (15.38%w/v)	45.45 mg/mL (4.54%w/v)	3.39 fold
5.	Ibuprofen 133.33 mg/mL (13.33%w/v)	133.67 mg/mL (13.68%w/v)	0.98 fold
6.	Paracetamol 16.66 mg/mL (1.67%w/v)	1.26 mg/mL (0.13%w/v)	12.85 fold
7.	Nimesulide 14.28 mg/mL (1.43%w/v)	6.29 mg/mL (0.63%w/v)	2.27 fold
8.	Norfloxacin 3.57 mg/mL (0.36%w/v)	0.93 mg/mL (0.09%w/v)	4.00 fold
9.	Piroxicam 13.33 mg/mL (1.33%w/v)	4.13 mg/mL (0.41%w/v)	3.24 fold
10.	Glipizide 10.32 mg/mL 1.03%w/v	2.08 mg/mL (0.21%w/v)	4.90 fold
11.	Glimepiride14.70 mg/mL (1.47%w/v)	2.63 mg/mL (0.26%w/v)	5.65 fold
12	Furosemide 19.54 mg/mL (1.95%w/v)	2.17 mg/mL (0.22%w/v)	8.86 fold
13.	Hydrochlorothiazide1.13 mg/mL (0.11%w/v)	4.63 mg/mL (0.46%w/v)	0.24 fold
14.	A mLodipinebesylate16.66 mg/mL (1.67%w/v)	1.83 mg/mL (0.18%w/v)	9.28 fold
15.	Acyclovir 2.14 mg/mL (0.21%w/v)	0.66 mg/mL (0.07%w/v)	3.00 fold
16.	Indomethacin 82.43 mg/mL (8.24%w/v)	36.92 mg/mL (3.69%w/v)	2.23 fold
17.	Diazepam 153.85 mg/mL (15.38%w/v)	73.57 mg/mL (7.36%w/v)	2.09 fold
18.	Ondansetron 4.54 mg/mL (0.45%w/v)	3.23 mg/mL (0.32%w/v)	1.41 fold
19.	Atenolol 42.22 mg/mL (4.22%w/v)	18.57 mg/mL (1.86%w/v)	2.27 fold
20.	Chlorthalidone17.85 mg/mL (1.78%w/v)	1.11 mg/mL (0.11%w/v)	16.18 fold

Table 17: Solubility studies of drugs in blend-6 and Ethyl oleate

S. No.	Approximate solubility of drug in blend-6	Approximate solubility of drug in Ethyl oleate	Solubility enhancement
1.	Glipizide 9.13 mg/mL (0.91%w/v)	2.08 mg/mL (0.21%w/v)	4.33 fold
2.	Glimepiride 12.22 mg/mL (1.22%w/v)	2.63 mg/mL (0.26%w/v)	4.69 fold
3.	Furosemide 23.84 mg/mL (2.38%w/v)	2.17 mg/mL (0.22%w/v)	10.82 fold
4.	Hydrochlorothiazide 0.83 mg/mL (0.08%w/v)	4.63 mg/mL (0.46%w/v)	0.38 fold
5.	A mLodipinebesylate 20.62 mg/mL (2.06%w/v)	1.83 mg/mL (0.18%w/v)	11.44 fold
6.	Piroxicam 25.50 mg/mL (2.55%w/v)	4.13 mg/mL (0.41%w/)	6.22 fold
7.	Acyclovir 1.11 mg/mL (0.11%w/v)	0.66 mg/mL (0.07%w/v)	1.57 fold
8.	Indomethacin 86.47 mg/mL (8.65%w/v)	36.92 mg/mL (3.69%w/v)	2.34 fold
9.	Diazepam 131.12 mg/mL (13.11%w/v)	73.57 mg/mL (7.36%w/v)	1.78 fold
10.	Ondansetron 4.87 mg/mL (0.49%w/v)	3.23 mg/mL (0.32%w/v)	1.53 fold
11.	Atenolol 36.36 mg/mL (3.64%w/v)	18.57 mg/mL (1.86%w/v)	1.96 fold
12.	Chlorthalidone 4.11 mg/mL (0.41%w/v)	1.11 mg/mL (0.11%w/v)	3.73 fold

1 mL of blend-1 was taken in a test tube and 50 mg naproxen drug was weighed on a tared butter paper. Little quantity of naproxen drug (about 2–3 mg) was transferred in the test tube. Test tube was shaken for 20 min. When a clear solution was obtained, again little quantity of naproxen drug (about 2–3 mg) was transferred in the test tube and test tube was shaken for 20 min. When a clear solution was obtained, again same procedure was repeated till a suspension was obtained

Table 18: Solubility studies of drugs in blend-7 and ethyl oleate

S. No.	Approximate solubility of drug in blend-7	Approximate solubility of drug in ethyl oleate	Solubility enhancement
1.	Glipizide 10.71 mg/mL (1.07%w/v)	2.08 mg/mL (0.21%w/v)	5.09 fold
2.	Glimepiride 16.15 mg/mL (1.61%w/v)	2.63 mg/mL (0.26%w/v)	6.19 fold
3.	Furosemide 10.58 mg/mL (1.06%w/v)	2.17 mg/mL (0.22%w/v)	4.82 fold
4.	Hydrochlorothiazide 1.20 mg/mL (0.12%w/v)	4.63 mg/mL (0.46%w/v)	0.26 fold
5.	A mLodipine besylate 13.84 mg/mL (1.38%w/v)	1.83 mg/mL (0.18%w/v)	7.67 fold
6.	Piroxicam 18.13 mg/mL (1.81%w/v)	4.13 mg/mL0.41%w/v	4.41 fold
7.	Acyclovir1.53 mg/mL (0.15%w/v)	0.66 mg/mL (0.07%w/v)	2.14 fold
8.	Indomethacin 78.88 mg/mL (7.89%w/v)	36.92 mg/mL (3.69%w/v)	2.14 fold
9.	Diazepam154.61 mg/mL (15.46%w/v)	73.57 mg/mL (7.36%w/v)	2.10 fold
10.	Ondansetron 5.93 mg/mL (0.59%w/v)	3.23 mg/mL (0.32%w/v)	1.84 fold
11.	Atenolol 39.20 mg/mL (3.92%w/v)	18.57 mg/mL (1.86%w/v)	2.11 fold
12.	Chlorthalidone 3.46 mg/mL (0.35%w/v)	1.11 mg/mL (0.11%w/v)	3.18 fold

Table 19: Solubility studies of drugs in blend-8 and ethyl oleate

S. No.	Approximate solubility of drug in blend-8	Approximate solubility of drug in ethyl oleate	Solubility enhancement
1.	Glipizide 8.26 mg/mL (0.83%w/v)	2.08 mg/mL (0.21%w/v)	3.95 fold
2.	Glimepiride 16.92 mg/mL (1.69%w/v)	2.63 mg/mL (0.26%w/v)	6.50 fold
3.	Furosemide 10.67 mg/mL (1.07%w/v)	2.17 mg/mL (0.22%w/v)	4.86 fold
4.	Hydrochlorothiazide 1.35 mg/mL (0.13%w/v)	4.63 mg/mL (0.46%w/v)	0.28 fold
5.	A mLodipine besylate 14.44 mg/mL (1.44%w/v)	1.83 mg/mL (0.18%w/v)	8.00 fold
6.	Piroxicam 16.42 mg/mL (1.64%w/v)	4.13 mg/mL 0.41%w/v	4.00 fold
7.	Acyclovir1.79 mg/mL (0.18%w/v)	0.66 mg/mL (0.07%w/v)	2.57 fold
8.	Indomethacin 71.14 mg/mL (7.11%w/v)	36.92 mg/mL (3.69%w/v)	1.93 fold
9.	Diazepam 147.86 mg/mL (14.79%w/v)	73.57 mg/mL (7.36%w/v)	2.00 fold
10.	Ondansetron 9.13 mg/mL (0.91%w/v)	3.23 mg/mL (0.32%w/v)	2.84 fold
11.	Atenolol 62.10 mg/mL (6.21%w/v)	18.57 mg/mL (1.86%w/v)	3.34 fold
12.	Chlorthalidone6.25 mg/mL (0.62%w/v)	1.11 mg/mL (0.11%w/v)	5.64 fold

Table 20: Solubility studies of drugs in blend-9 and Ethyl oleate

S. No.	Approximate solubility of drug in blend-9	Approximate solubility of drug in Ethyl oleate	Solubility enhancement
1.	Glipizide 13.33 mg/mL (1.33%w/v)	2.08 mg/mL (0.21%w/v)	6.33 fold
2.	Glimepiride20.76 mg/mL (2.08%w/v)	2.63 mg/mL (0.26%w/v)	8.00 fold
3.	Furosemide 24.73 mg/mL (2.47%w/v)	2.17 mg/mL (0.22%w/v)	11.23 fold
4.	Hydrochlorothiazide56.15 mg/mL (5.61%w/v)	4.63 mg/mL (0.46%w/v)	12.19 fold
5.	A mLodipine besylate 64.61 mg/mL (6.46%w/v)	1.83 mg/mL (0.18%w/v)	35.89 fold
6.	Piroxicam 17.85 mg/mL (1.78%w/v)	4.13 mg/mL 0.41%w/v	4.34 fold
7.	Acyclovir 2.14 mg/mL (0.21%w/v)	0.66 mg/mL (0.07%w/v)	3.00 fold
8.	Indomethacin 139.28 mg/mL (13.93%w/v)	36.92 mg/mL (3.69%w/v)	3.77 fold
9.	Diazepam 204.44 mg/mL (20.44%w/v)	73.57 mg/mL (7.36%w/v)	2.78 fold
10.	Ondansetron 91.54 mg/mL (9.15%w/v)	3.23 mg/mL (0.32%w/v)	28.59 fold
11.	Atenolol 64.80 mg/mL (6.48%w/v)	18.57 mg/mL (1.86%w/v)	3.48 fold
12.	Chlorthalidone56.46 mg/mL (5.65%w/v)	1.11 mg/mL (0.11%w/v)	51.36 fold

Table 21: Solubilitystudiesofdrugsinblend-10 and Ethyl oleate

S. No.	Approximate solubility of drug in Ethyl oleateblend-10	Approximate solubility of drug in Ethyl oleate	Solubility enhancement
1.	Glipizide 7.14 mg/mL (0.71%w/v)	2.08 mg/mL (0.21%w/v)	3.38 fold
2.	Glimepiride7.53 mg/mL (0.75%w/v)	2.63 mg/mL (0.26%w/v)	2.88 fold
3.	Furosemide11.23 mg/mL (1.12%w/v)	2.17 mg/mL (0.22%w/v)	5.09 fold
4.	Hydrochlorothiazide 1.12 mg/mL (0.11%w/v)	4.63 mg/mL (0.46%w/v)	0.24 fold
5.	A mLodipine besylate 14.61 mg/mL (1.46%w/v)	1.83 mg/mL (0.18%w/v)	7.11 fold
6.	Piroxicam 24.43 mg/mL (2.44%w/v)	4.13 mg/mL0.41%w/v	5.95 fold
7.	Acyclovir 1.43 mg/mL (0.14%w/v)	0.66 mg/mL (0.07%w/v)	2.00 fold
8.	Indomethacin 31.25 mg/mL (3.12%w/v)	36.92 mg/mL(3.69%w/v)	0.84 fold
9.	Diazepam 19.63 mg/mL (1.96% w/v)	73.57 mg/mL (7.36%w/v)	0.27 fold
10.	Ondansetron 5.54 mg/mL (0.55%w/v)	3.23 mg/mL (0.32%w/v)	1.72 fold
11.	Atenolol 24.44 mg/mL (2.44%w/v)	18.57 mg/mL(1.86%w/v)	1.31 fold
12.	Chlorthalidone 4.17 mg/mL (0.42%w/v)	1.11 mg/mL (0.11%w/v)	3.82 fold

after shaking for 20 min. Then, butter paper together with drug was reweighed. Difference of two reading gives the approximate solubility of naproxenin 1 mL of blend-1.

Same procedure was used for determination of approximate solubility of all drugs in ethyl oleate and different blends.

Preparation of blend (blend-1)

Firstly 5 g of propyl paraben was weighed accurately and transferred it to a 50 mL volumetric flask. Then, 30 mL of ethyl oleate was added to dissolve it at 50–60°C with vigorously shaking for 20 min. The temperature was maintained with the help of water bath. After complete dissolution of propylparaben, 5 mL of Benzyl alcohol was added. Then, volume was made up to 50 mL with Ethyl oleate.

Same procedure (forblend-1) was used to prepare blends 2, 3, 4, 5, 6, 7, 8, 9, and 10. Tables 2-11 gives the composition of blends 2, 3, 4, 5, 6, 7, 8, 9, and 10, respectively.

Preparation of oily intramuscular injection

Preparation of aseptic area

Before formulating and filling injections into vials. The aseptic was created by firstly scrubbing and cleaning the room walls and floor using water, followed by mopping with 2.5%v/v Dettol solution to disinfect the room. After that benches were cleaned we 70% Isopropyl alcohol and also sprayed in air. The solubility of various drugs was determined individually in ethyl oleate and each of the prepared blends.

The result of solubility and solubility fold enhancement is determined in Tables 12-21.

Treatment of packing material

10 mL glass vials were cleaned with water several times with distilled water. All of these vials were positioned upside-down in an oven set to 180°C for 2 h to sterilize them using dry heat. Rubber stoppers were used to plug the vials, and they were first shaken in a 0.2% liquid detergent solution for 2 h. After that, they were repeatedly rinsed with distilled water to remove any detergent residue. The possibilities of formulation of injections are determined by considering the dose of each drug and its solubility in each blend. Then, the blends and drugs selected were determined in Table 22.

Preparation of oily injection

Methyl paraben (50 mg), Propyl paraben (50 mg), Glyceryl mono stearate (50 mg), and Benzyl benzoate (0.2 mL) were transferred in a 10 mL volumetric flask and about 7 mL of ethyl oleate was added. The flask was shaken to dissolve the components to get a clear solution. Then, volume was made up to the mark with ethyl oleate. Thus, a blend was obtained. Now, 20 mg Amlodipine besylate was transferred in another 10 mL volumetric flask and about 8 mL of prepared blend was added. The flask was shaken to get clear solution. Then, sufficient ethyl oleate was added to make up the volume. In this way, the oily injection of Amlodipine besylate was prepared. The solubility of amlodipine besylate was found to be maximum in Blend- 9. So, its injection was prepared using blend-9. The composition of the amlodipine besylate oily IM injection is given in Table 23.

Table 22: Result: Possibilities of oily intramuscular injection preparation

S. No.	Names of drugs	Usual dose (mg)	Approximate solubility in ethyl oleate (mg/m)	Approximatesolubility in blends	Possibility of IM oily injections
Blend-1					
1.	Atenolol	25–50	18.57	34.80	25 mg/mL
Blend-2					
1.	A mLodipine besylate	5–10	1.83	14.61	10 mg/mL
2.	Piroxicam	20	4.13	24.43	20 mg/mL
Blend-3					
1.	Piroxicam	20	4.13	11.43	20 mg/2 mL
2.	Glipizide	5–20	2.08	7.91	5 mg/mL
3.	Atenolol	25–50	18.57	31.17	25 mg/mL
Blend-4					
1.	Ibuprofen	400–600	133.67	222.22	400 mg/2 mL
2.	Glipizide	5–20	2.08	5.43	5 mg/mL
3.	A mLodipine besylate	5–10	1.83	7.33	5 mg/mL
Blend-5					
1.	Piroxicam	20	4.13	13.33	20 mg/2 mL
2.	Glipizide	5–20	2.08	10.32	10 mg/mL
3.	Furosemide	20–80	2.63	14.70	20 mg/mL
4.	A mLodipine besylate	5–10	1.83	16.66	10 mg/mL
5.	Atenolol	25–50	18.57	42.22	25 mg/mL
6.	Chlorthalidone	25–100	1.11	17.85	25 mg/mL
Blend-6					
1.	Glipizide	5–20	2.08	9.13	5 mg/mL
2.	Furosemide	20–80	2.63	23.84	20 mg/mL
3.	A mLodipine besylate	5–10	1.83	20.62	20 mg/mL
4.	Piroxicam	20	4.13	25.50	20 mg/mL
5.	Atenolol	25–50	18.57	36.36	25 mg/mL
Blend-7					
1.	Glipizide	5–20	2.08	10.71	10 mg/mL
2.	Furosemide	20–80	2.63	10.58	20 mg/2 mL
3.	Piroxicam	20	4.13	18.13	20 mg/2 mL
4.	Atenolol	25–50	18.57	39.20	25 mg/mL
Blend-8					
1.	Glipizide	5–20	2.08	8.26	5 mg/mL
2.	Furosemide	20–80	2.63	10.67	20 mg/mL
3.	A mLodipine besylate	5–10	1.83	14.44	10 mg/mL
4.	Atenolol	25–50	18.57	62.10	50 mg/mL
Blend-9					
1.	Glipizide	5–20	2.08	13.33	10 mg/mL
2.	Furosemide	20–80	2.63	24.73	20 mg/mL
3.	Hydrochlorothiazide	12.5–100	4.63	56.15	50 mg/mL
4.	A mLodipine besylate	5–10	1.83	64.61	10 mg/mL
5.	Piroxicam	20	4.13	17.85	20 mg/mL
6.	Atenolol	25–50	18.57	64.80	50 mg/mL
7.	Chlorthalidone	25–100	0.11	56.46	50 mg/mL
Blend-10					
1.	Glipizide	5–20	2.08	7.14	5 mg/mL
2.	Furosemide	20–80	2.63	11.23	20 mg/2 mL
3.	A mLodipine besylate	5–10	1.83	14.61	10 mg/mL
4.	Piroxicam	20	4.13	24.43	20 mg/mL
5.	Atenolol	25–50	18.57	24.44	25 mg/2 mL

Table 23: Formulation for A mL odipine besylate IM injection

S. No.	Ingredients	Formula for 2 mL 10 mg/mL	Formula for 10 mL batch
1.	Methylparaben	50 mg	250 mg
2.	Propylparaben	50 mg	250 mg
3.	Glyceryl mono stearate	50 mg	250 mg
4.	Methyl pyrrolidone	0.2 mL	1 mL
5.	Benzyl benzoate	0.2 mL	1 mL
6.	A mLodipine besylate	20 mg	100 mg
7.	Ethyl oleate	Quantity sufficient	Quantity sufficient

Table 24: Physical stability data for formulation

No. of weeks	Room temperature (30–35°C)	
	Colour development	Precipitation
1	Nil	Nil
2	Nil	Nil
3	Nil	Nil
4	Nil	Nil
5	Nil	Nil
6	Nil	Nil
7	Nil	Nil
8	Nil	Nil

Evaluation of intramuscular injection

Physical stability studies

To observe physical instability, various storage conditions were applied to properly sealed vials of the prepared formulation. At intervals of 1 weeks, the samples were visually inspected for changes in color, clarity, and precipitation in 30–35°C room environment up to 8 weeks. The stability study was performed for 8 weeks for a prepared IM oily injection of amlodipine besylate, and the observations were made [as given in Table 24].

CONCLUSION

From the present research work, it can be concluded that a large number of oily intramuscular injections (in the solution form) of poorly oil soluble drugs can be developed utilizing the solubilizing properties of oil soluble safe excipients. Since, safe concentration (as per Inactive Ingredient guide 2020) of oil soluble additives has been employed in various blends, the formulations shall be expectedly safe from the point of view of toxicity.

ACKNOWLEDGMENT

I would like to thanks head of the department, Department of Pharmacy, SGSITS, Indore for providing all the facilities. And also a profound thanks to Dr. R.K. Maheshwari for his guidance and support throughout my research and also to librarians for providing E-resources.

REFERENCES

1. Gulati NG, Gupta H. Parenteral drug delivery: A review. Rec Pat Drug Deliv Formul 2011;5:133-45.
2. Available from: https://www.healthline.com/health/intramuscular-injection#purpose [Last accessed on 2021 Dec 15].
3. Maheshwari RK, Shipkar R. Formulation development and evaluation of injection of poorly soluble drug using mixed solvency concept. Int J Pharm Biosci 2012;3:179-89.
4. Bhawsar N, Maheshwari RK, Ansari A, Saktawat Y. New spectrophotometric estimation of gatifloxacin in the tablets using mixed solvency approach. Int J Pharm Sci 2011;2:270-4.
5. Maheshwari RK, Upadhyay N, Jain J, Patani M, Mathuria KC. New spectrophotometric estimation of naproxen tablet formulations employing mixed solvency concept (AT 331NM). Int J Pharm Technol 2011;3:3618-23.
6. Maheshwari RK, Jain R, George P. Formulation development and evaluation of controlled release tablets of lamotrigine using mixed solvency concept. Bull Pharm Res 2015;5:14-9.
7. Soni LK, Solanki SS, Maheshwari RK. Studies on mixed solvency concept in formulation development of oral solution (syrup) of poorly water soluble drug. J Harmon Res Pharm 2015;4:305-15.
8. Chandna C, Maheshwari RK. Mixed solvency concept in reducing surfactant concentration of self emulsifying drug delivery systems of candesartan cilexetil using D-optimal mixture design. Asian J Pharm 2013;7:83-91.
9. Prashant PB, Rawat SS, Mahajan YY, Galgatte UC, Maheshwari RK. Formulation development and evaluation of aqueous injection of poorly soluble drug made by novel application of mixed solvency concept. Int J Drug Deliv 2013;2:152-66.
10. Maheshwari RK. Mixed-solvency-a novel concept for solubilization of poorly water-soluble drugs. Delving J Tech Eng Sci 2009;1:39-43.
11. Jain S, Maheshwari RK, Nema RK, Singhvi I. New spectrophotometric estimation frusemide in the tablets

using mixed solvency concept. Int J Curr Adv Res 2017;6:8510-3.
12. Maheshwari RK. Mixed-solvency approach-Boon for solubilization of poorly soluble-drugs. Asian J Pharm 2010;4:60-3.
13. Maheshwari RK, Jain S, Padria, A, Mulani, P, Baghel, JS, Maheshwari, N. Eco-friendly extraction using solids-a novel application of mixed solvency concept. J Drug Deliv Ther 2019;9:244-9.
14. Maheshwari RK, Chandna C. Mixed solvency concept in reducing surfactant concentration of self-emulsifying drug delivery systems of candesartan cilexetil using D-optimal mixture design. Asian J Pharm 2013;7:83-91.
15. Rathod M, Agarwal S. Development and evaluation of furosemide microspheres made by mixed solvency concept. Int J Pharm Erudition 2013;2:22-31.
16. Jain S, Maheshwari RK. Formulation development of oral liquisolid system of poorly water soluble drug, piroxicam, using mixed solvency concept and their evaluations. Int J Sci Res 2018;8:1703-11.
17. Barua D, Indurkhya A, Maheshwari RK, Patel PK. Formulation of Rifabutin Liquisolid system using mixed solvency concept and their evaluation. Int J Pharm Pharm Sci 2019;4:2455-698.
18. Agrawal R, Maheshwari RK. Novel application of mixed solvency concept in the development of oral liquisolid system of a poorly soluble drug, cefixime and its evaluation. J Drug Deliv Ther 2018;8:5-8.
19. Bagel J, Maheshwari RK. Novel application of mixed solvency concept in the development of fast dissolving solid dispersion of poorly water-soluble drug, torsemide and its evaluations. World J Pharm Res 2020;9:1820-39.
20. Mansuk AG, Deshmukh D, Maheshwari RK, Pachpute T. Formulation optimization and characterization of solid dispersion of piroxicam prepared by novel application of mixed solvency concept. Pharm Resonance 2020;2:41-6.
21. Maheshwari RK, Chaklan N, Singh S. Novel pharmaceutical application of mixed solvency concept for development of solid dispersions of piroxicam. Eur J Biomed Pharm Sci 2015;1:578-91.
22. Singh S, Maheshwari RK, Gahlot N. Formulation development of topical solutions of poorly water-soluble drug indomethacin employing novel application of mixed solvency concept and their evaluation. Int J Green Pharm 2018;12:S373-9.
23. Mulani P, Maheshwari RK. Formulation development of aqueous topical solutions and gels of poorly water soluble drug nimesulide, using novel application of mixed solvency concept and their evaluations. Int J Sci Res 2018;8:1521-9.
24. Carpenter G, Maheshwari RK. Formulation and development of fast dissolving oral film of a poorly soluble drug, frusemide with improved drug loading using mixed solvency concept and its evaluation. J Drug Deliv Ther 2018;8:132-41.
25. Gahlot N, Maheshwari RK. Formulation and development of vaginal films of poorly water soluble drug, metronidazole, using mixed solvency concept and their evaluations. J Drug Deliv Ther 2018;8:41-8.
26. Soni LK, Solanki SS, Maheshwari RK. Evaluation of analgesic, anti-inflammatory and ulcerogenic liability of oral solution (syrup) formulation developed by novel mixed solvency concept. Adv Pharmacol Toxicol 2015;16:21-30.
27. Maheshwari RK, Rajagopalan R. Formulation and evaluation of tinidazole syrup made by mixed solvency concept technique. Der Pharm Lett 2011;3:266-71.
28. Maheshwari RK, Rajagopalan R. Formulation and evaluation of paracetamol syrup made by mixed-solvency concept. Der Pharm Lett 2012;4:170-4.
29. Agrawal A, Maheshwari RK. Formulation development and evaluation of *in situ* nasal gel of poorly water soluble drug using mixed solvency concept. Asian J Pharm 2014;5:131-40.
30. Jain S, Khan A, Jain SD, Maheshwari RK. Solubility enhancement of paracetamol by mixed solvency method. Res Rev J Comput Biol 2019;8:19-22.
31. Gadade DD, Lohade TS, Lahoti SR, Rawat SS, Maheshwari RK. Solubility enhancement of ofloxacin by mixed solvency approach. Indian Drugs 2018;55:34-40.
32. Kumar CJ, Kumar MD. Solubility enhancement of theophylline drug using mixed solvency approach. Int J Chem Sep Technol 2015;1:1-4.
33. Khan MA. Enhancement of solubility of poorly water soluble drugs diclofenac sodium by mixed solvency approach. Res J Pharm Dosage Forms Technol 2013;5:39-41.
34. Maheshwari N, Maheshwari RK. Formulation development of dry injection for reconstitution of a poorly water soluble drug, candesartan cilexetil, using mixed solvency concept and their evaluations. Int J Sci Res 2018;8:1313-20.
35. Solanki SS. Development of parenteral formulation of poorly water soluble drugs: The role of novel mixed-solvency concept. Asian J Pharm 2017;11:1-10.
36. Gayakwad PS, Gavit AJ, Rajput PV, Bari MM, Barhate SD, Maheshwari RK. Formulation development and evaluation of an aqueous injection of gatifloxacin by novel mixed solvency technique. World J Pharm Res 2014;3:1642-64.
37. Gour V, Garg A, Shukla A, Yadav AK. Development and evaluation of metronidazole injection by mixed solvency approach. Asian J Biomater Res 2016;2:38-45.
38. Solanki SS, Soni LK, Maheshwari R.K. Solubilization of poorly water soluble drug using mixed solvency approach for aqueous injection. Br J Pharm Res 2014;4:549-68.
39. Pawar PB, Rawat SS, Mahajan YY, Galgatte UC, Maheshwari RK. Formulation development and evaluation of aqueous injection of poorly soluble drug made by novel application of mixed solvency concept. Int J Drug Delivery 2013;5:152-66.
40. Solanki SS, Soni LK, Maheshwari RK. Study on mixed solvency concept in formulation development of aqueous injection of poorly water soluble drug. J Pharm (Cairo) 2013;2013:678132.

Source of Support: Nil. **Conflicts of Interest:** None declared.