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Formulation Development of a Model Dry Injection for Reconstitution of Poorly Water Soluble Drug Using Mixed Solvency Concept and its Evaluation

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Abstract: ***In this current era of pharmaceutical research, maximum newly invented drugs are found to be very poorly soluble in water. It poses difficulties in various developmental, manufacturing and administrating processes, which lead to the high failure of clinical trials of the drug due to poor pharmacokinetics. Parenteral dosage form could be expected to be an effective tool for avoiding the oral side effects and also achieving maximum bioavailability. Poor solubility of drugs in water is currently biggest challenge and limitation in injectable formulation developments. The prime purpose of any research work should be highly efficient and most effective in the pharmaceutics field to serve the society's needs by developing a formulation after literature survey and market review. The ultimate objective of this present research was to promote the use of mixed solvency concept by formulating the model dry injection of the poorlywater soluble drug and to decrease the concentration of individual solubilizers required to produce a substantial increase in solubility and thereby resulting in expected synergistic enhancement of solubility of the drug in water. In the present work, poorly water soluble drug, ornidazole was selected as a model drug and its dry injection for reconstitution was formulated. Ornidazole is the drug which belongs to the anti-protozoal category and used to treat infections caused by amoebic and trichomonas micro-organisms. It is nitro-imidazoline derivative which partially binds to plasma and also has a sensitizing action against radiation. (BCS class II: highly permeable and low soluble). Due to the poor water solubility of ornidazole, the products are available in the market in tablet form, infusion form and suspension form. In order to get expected synergistic enhancement on solubility, various blends of solubilizers can be tried thereby reducing the amount of individual solubilizer employed to achieve the desired solubility enhancement ratio. Thus, the successful completion of the research work will enable the preparation of stable dry injection for reconstitution of ornidazole.***

Keywords: Mixed solvency solubilization, ornidazole, solubility enhancement, synergistic enhancement effect

1. Introduction

Majority of drugs show the problem of poor solubility, whether in the case of their analytical estimations or in the field of liquid dosage forms in the form of solutions. Commonly used organic solvents for spectrophotometric analysis of water insoluble drugs include methanol, ethanol, chloroform, benzene, dichloromethane, dimethyl formamide, acetonitrile, ethyl acetate, toluene, carbon tetrachloride, acetone, hexane etc. The main drawbacks of organic solvents include high cost, toxicity and pollution. Organic solvents have innumerous adverse effects caused by single exposure like dermatitis, headache, drowsiness, nausea, eye irritation and long term exposure causes serious effects such as neurological disorders, chronic renal failure, liver damage, necrosis, mutagenesis disorder. They should be replaced by other eco-friendly alternative sources. The pollution and toxicity caused by most of the organic solvents is a big challenge. The researchers are doing much work to give eco-friendly solutions for this challenge. Maheshwari[1-5] has given a nice concept, known as mixed-solvency concept. By application of this concept, innumerable solvent systems can be developed. Maheshwari is of the opinion that each substance possesses solubilizing power. He has given several ecofriendly methods in the area of drug estimations and formulations precluding the use of toxic organic solvents. There are very few safe liquids e g propylene glycol, glycerin, tweens, ethanol, liquid polyethylene glycols (like PEG 200, 300 etc) which are employed by pharmaceutical industries in various dosage forms for making solution type dosage forms of poorly soluble drugs.

Mixed solvency concept, proposed by Maheshwari[1-3] provides a means to develop innumerable solvent systems employing combination of the pharmaceutical excipients in small concentrations. Each substance present on the earth has got solubilizing power. By combining the excipients, additive solvent actions and synergistic solvent actions can be obtained. The problem of toxicity issue due to high concentration of a single solvent can be solved in this manner. The solubility of a large number of poorly soluble drugs have been enhanced by mixed solvency concept[1-38]. In the present investigation, the poorly water-soluble drug, ornidazole, which is crystalline powder has been selected as a model drug for formulating its model dry injection for reconstitution by using mixed solvency approach.

2. Materials & Method

Ornidazole was obtained as gift sample from Alkem Laboratories Limited, Mumbai. All other chemicals and solvents employed were of analytical grade .

Preparation of calibration curve of ornidazole in distilled water.

Accurately weighed quantity of ornidazole (50 mg) and about 40 mL of demineralised water were taken in a 50 mL volumetric flask and then, it was shaken to dissolve the drug completely. After that the volume was made up to 50 mL with demineralised water to obtain the stock solution of 1000 µg/mL concentration.

The stock solution (0.5ml) was taken and diluted up to 100 ml with demineralised water to obtain the standard solution of 5 µg/mL concentration. Likewise 1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL solutions were taken and diluted up to 100 mL with demineralised water to obtain standard solutions of 10, 15, 20 and 25 µg/mL concentrations, respectively. The resulting dilutions were scanned between 200-400 nm on Shimadzu-1700 UV spectrophotometer against demineralised water. The data is graphically represented in figure 1& 2.

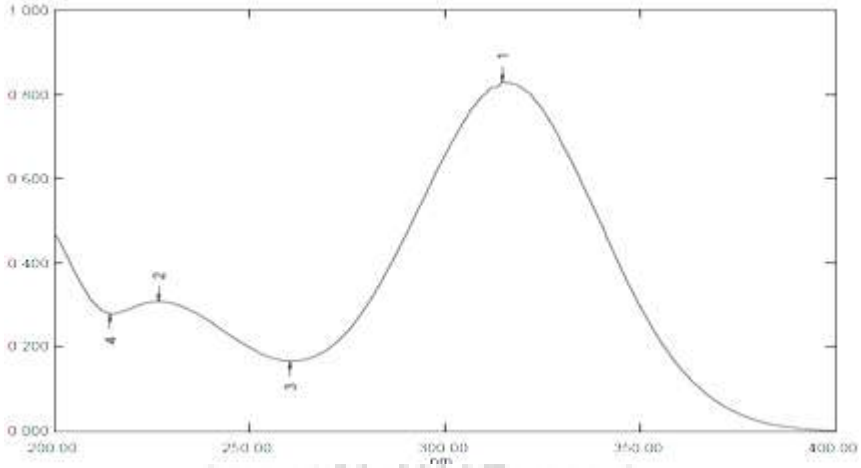

Figure 1: UV spectra of ornidazole

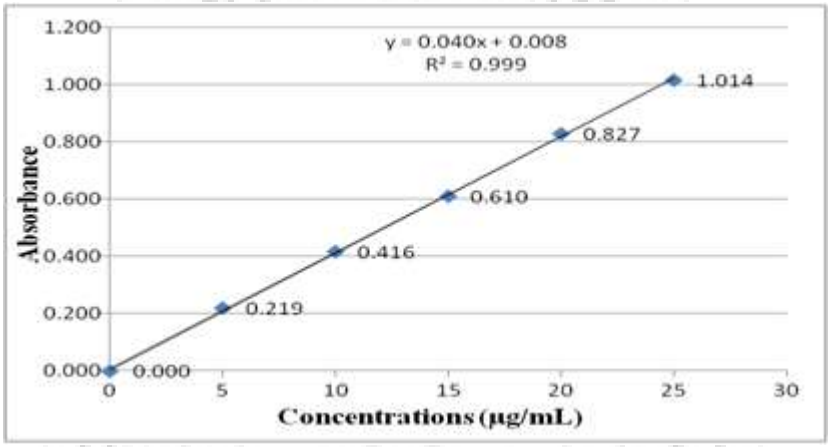

Figure 2: Calibration curve of ornidazole in demineralised water

FT-IR Spectroscopy study

The infrared spectroscopy of ornidazole was performed for identification of drug. Approximately 300 mg finely powdered dry KBr (Potassium Bromide) IR was triturated with about 1-5mg of the sample of drug and compressed as pellet and spectra was recorded on FTIR spectrophotometer (Shimadzu® IR Affinity-1). The IR spectrum is presented in fig. 3.

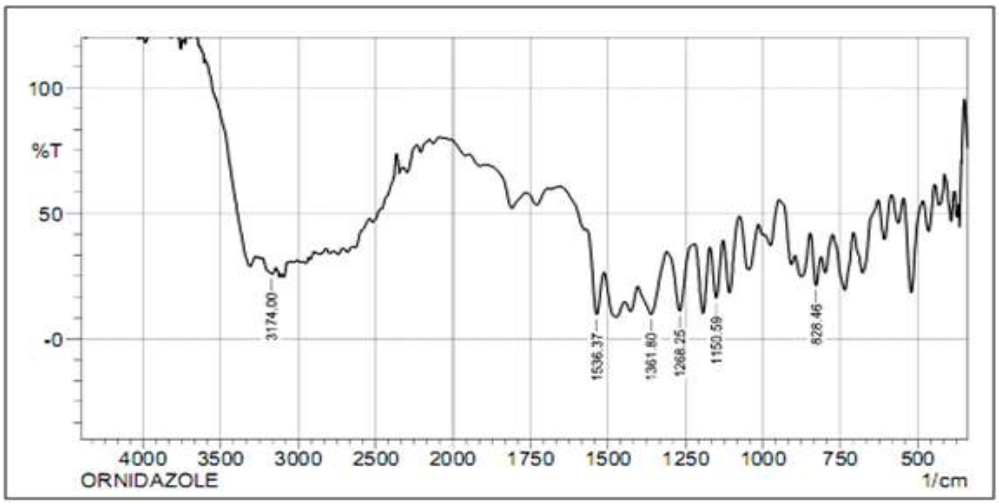

Figure 3: FTIR spectra of ornidazole

DSC of Drug Sample

The DSC study was carried out on a Perkin Almer differential scanning calorimeter with thermal analyzer. The drug sample (3.8 mg) was placed in an aluminium pan. The pan was placed on the heating cell after sealing. Heating at a rate of 10°C/min with a continuous purge of nitrogen (45 CC/min) was done with recording of energy changes in the sample with respect to an empty aluminium pan as reference in the temperature range of 40-200°C. Obtained DSC thermogram (melting isotherm) is shown in fig. 4.

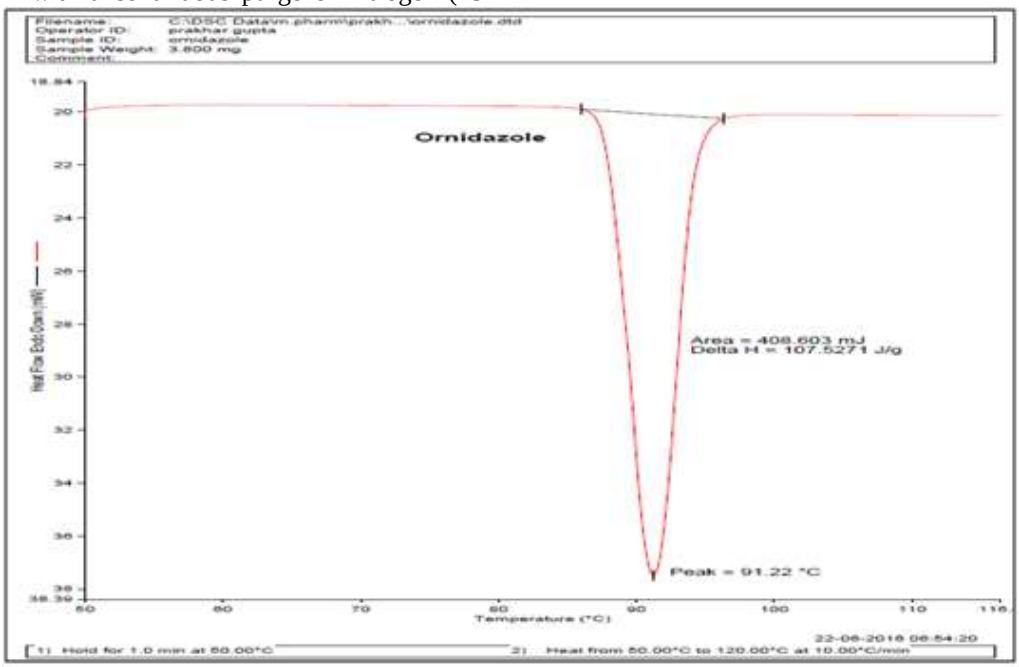

Figure 4: DSC spectrum of ornidazole drug sample

Solubility Determination of Drug in Various Aqueous solutions of solubilizers (Mixed Blends)

In order to carryout the equilibrium solubility of ornidazole in various blends (Table 1), 5ml of each blend was taken in the appropriate vials and then some excess amount of drug was added into each vials. Then vials were subjected to continuous shaking in water bath incubator shaker for 24 hrs. Then, vials were kept undisturbed for 12 hrs. After filteration through Whatman filter paper number 41, the filterates were suitably diluted with distilled water and absorbances were measured at 320nm. Then equilibrium solubility of drug in each blends were calculated by using calibration curve. Results are shown in the table 1.

Table 1: Results of solubility studies of ornidazole in various aqueous solutions of solubilizers

S. No.	Blends	Composition of aqueous blends (w/v)	Equilibrium solubility (%)
1.	A	Sodium benzoate - 10% Niacinamide - 10% Caffeine - 10% Sodium caprylate - 10%	8.8125%
2.	B	Sodium benzoate - 5% Niacinamide - 5% Caffeine - 5% Sodium citrate - 5%	3.6375%
3.	C	Sodium benzoate - 5% Niacinamide - 5% Caffeine - 5% Sodium acetate - 5%	3.6000%
4.	D	Sodium benzoate - 5% Niacinamide - 5% Sodium acetate - 5% Sodium caprylate - 5%	4.5500%
		Sodium citrate - 5% PVP K30 - 5%	
5.	E	Sodium benzoate - 10% Niacinamide - 10% Sodium caprylate - 10% Sodium citrate - 10%	6.1500%
6.	F	Sodium benzoate - 10% Niacinamide - 10% Caffeine - 6% Sodium caprylate - 10%	11.3750%
7.	G	Sodium benzoate - 10% Niacinamide - 10% Sodium acetate - 5% Sodium citrate - 5% Caffeine - 6% Sodium caprylate - 4%	5.5875%
8.	H	Sodium benzoate - 10% Niacinamide - 5% Caffeine - 5% Sodium acetate - 5% Sodium citrate - 5% PEG 4000 - 10%	4.1750%
9.	I	Sodium benzoate - 10% Niacinamide - 10% Sodium acetate - 5% Sodium citrate - 5% Caffeine - 6% Sodium caprylate - 4% PEG 4000 - 10%	11.7125%
10.	J	Sodium benzoate - 10% Niacinamide - 10% Caffeine - 6% PEG 4000 - 10%	6.3000%
11.	K	Sodium benzoate - 10% Niacinamide - 10% Caffeine - 6% PEG 4000 - 20%	10.3625%

12.	L	Sodium benzoate - 10% Niacinamide - 10% Caffeine - 10% Sod. caprylate - 10% PEG 4000 - 10%	9.1250%

Chromatographic Study of Solubilized Drug product

In order to examine the possibility of interaction between drug and solublisers, thin layer chromatographic studies were performed. A plate of silica gel GF 254 was activated at 110°C for 1 hour and then used. The aqueous solution of ornidazole alone and the aqueous solution solubilizers containing ornidazole in Blend-F, Blend-I, Blend-K were spotted with the aid of microdropper on the base line. Then, the plate was left in air for sufficient time to dry and transferred to a solvent jar saturated with the solvent system butanol, ethanol and water (9:7:4)

The solvent system was allowed to run for about 4 cm. Finally, the plate was allowed to air dry for 5 min and was observed for visualization of spots under UV light. The respective RF values were determined and recorded in table 2.

Table 2: Results of TLC studies

Solvent System	Adsorbent	R_F Value for ornidazole			
Butanol+ethanol +water (9:7:4)	Silica Gel GF 254	OZ/ H_2O	B-F	B-I	B-K
		0.925	0.925	0.925	0.924

Physical stability of drug in the presence of solubilizers

This study was performed to determine any physical change in the drug when kept in contact with various formulation excipients. The drug was mixed with excipients in the 1:1 ratio and was kept in separate glass vials properly capped and sealed with teflon tape. The vials were kept at different temperature conditions; at room temperature, at 40°C for a period of one month. After every week, vials were withdrawn and contents were observed for any change in their physical appearance and colour of the contents.

Optimization of blend for preparation of dry powder for injection

On the basis of results obtained from solubility studies, the mixed blends in which solubility of ornidazole was more than 100 mg/ml were selected. Such selected mixed blends were B-F, B-I, and B-K. To develop 5 ml of ornidazole injection, the amount of solubilizers and drug that will be administered through each mixed blend was determined. Injection formulations were developed based on the solubility of ornidazole in individual blends. The proposed formulations are shown in table 3, 4 and 5.

Table 3: Formulation DPI- B-F

S. No.	Ingredients	Formula for 500 mg OZ/5 ml	Formula for 30 ml batch
1	Ornidazole	500 mg	3 g
2	Sodium benzoate	500 mg	3 g
3	Niacinamide	500 mg	3 g
4	Caffeine	300 mg	1.8 g
5	Sodium caprylate	500 mg	3 g

Table 4: Formulation DPI-B-I

S. No.	Ingredients	Formula for 500 mg OZ/5 ml	Formula for 30 ml batch
1	Ornidazole	500 mg	3 g
2	Sodium benzoate	500 mg	3 g
3	Niacinamide	500 mg	3 g
4	Sodium acetate	250 mg	1.5 g
5	Sodium citrate	250 mg	1.5 g
6	Caffeine	300 mg	1.8 g
7	Sodium caprylate	200 mg	1.2 g
8	PEG 4000	500 mg	3 g

Table 5: Formulation DPI- B-K

S. No.	Ingredients	Formula for 500 mg OZ/5 ml	Formula for 30 ml batch
1	Ornidazole	500 mg	3 g
2	Sodium benzoate	500 mg	3 g
3	Niacinamide	500 mg	3 g
4	Caffeine	300 mg	1.8 g
5	PEG 4000	1 g	6 g

Formulation of dry powder injection for reconstitution

The dry powder injections for reconstitution were formulated according to the formulation detail given in above tables. All the solubilizers were passed through sieve no 80 to reduce the particle size individually. Then, the required quantities of all excipients and drug were weighed and mixed by geometric dilution method with the help of mortar and pestle. The mixed blend was again passed through sieve no 80 and mixed manually in a plastic bag of suitable size. The prepared formulation was then transferred to vials in required amount for stability study and vials were capped and sealed immediately.

Evaluation of dry injection for reconstitution

The prepared formulations were subjected for various evaluation parameters

- **Determination of pH of reconstituted injection** The developed formulations were reconstituted by DM water and approximate 10 mL volume was taken to determine the pH by using digital pH meter (Cyber Scan 510, Eutech Instruments, Singapore). The results are shown in table 6.

Table 6: pH values of reconstituted injection formulations

Formulation code	pH
DPI-B-F	8.40
DPI-B-I	7.79
DPI-B-K	7.40

- **Determination of reconstitution time**To determine the reconstitution time, DM water was used to dilute the dry injection formulation for all the batches and time were noted to obtain a clear solution. The reconstitution times obtained were recorded in table 7.

Table 7: Reconstitution times of various formulations

Formulation code	Reconstitution time (minutes)
DPI-B-F	2 min 50 sec
DPI-B-I	2 min 15 sec
DPI-B-K	3 min 25 sec

- **Clarity testing of reconstituted injections** Clarity test for reconstituted product was performed by visually inspecting

the externally clean vial viewed against black and white background under good light. Results of the clarity testing of the reconstituted developed injection formulations are shown in table 8.

Table 8: Clarity of various reconstituted injections

Formulation code	Clarity
DPI-B-F	Clear
DPI-B-I	Clear
DPI-B-K	Clear

Accelerated stability study and degradation kinetics of ornidazole in dry powder injection

In order to investigate the degradation kinetics of this drug in dry powder for injection, the stability studies of ornidazole were performed by using desiccator method. Accelerated thermal degradation study was performed by keeping all the three above formulated batches of ornidazole dry powder injection samples in desiccators at the two different temperatures (room temperature and 40^{o} C) for 3 months by maintaining humidity by the use of NaCl saturated solution. For DPI-B-F, 92 mg filled in each vial, For DPI-B-I, 120 mg filled in each vial, For DPI-B-K, 112 mg filled in each vial.

At time intervals of 1 week, aliquots of degraded samples were diluted with DM water up to 1000 ml and analyzed by UV/Visible spectrophotometer (Shimadzu 1700) against respective reagent blanks at 320 nm. The % residual drug was calculated and shown in fig. 5 to 7.

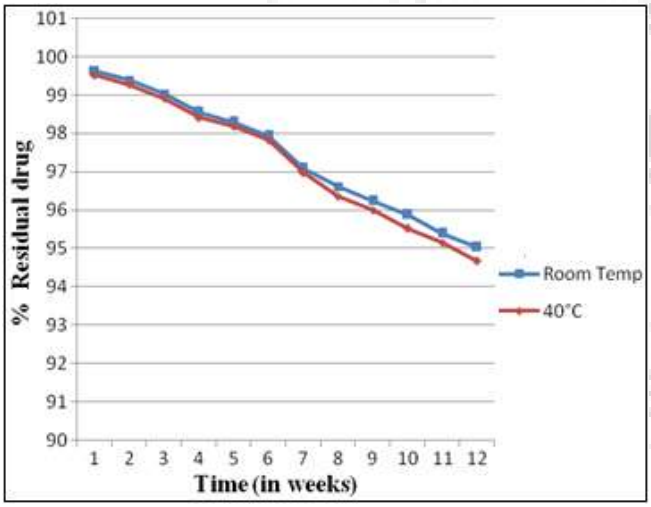

Figure 5: Degradation curve for the formulation DPI-B-F

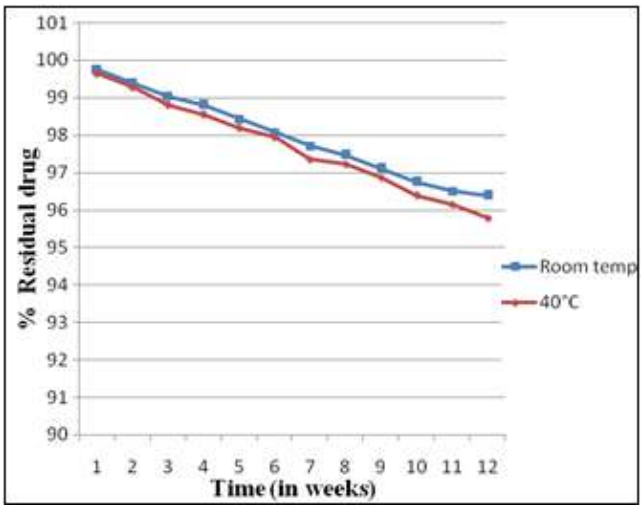

Figure 6: Degradation curve for the formulation DPI-B-I

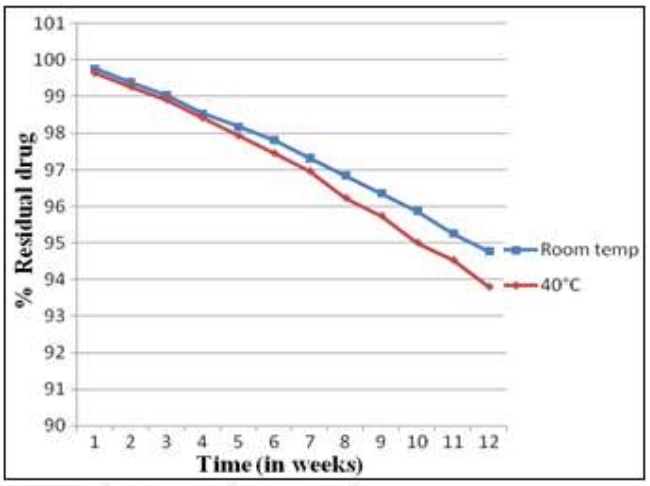

Figure 7: Degradation curve for the formulation DPI-B-K

Dilution study of reconstituted injection

Series of dilutions were done by diluting reconstituted injection of ornidazole (Formulation DPI-B-I, DPI-B-F, and DPI-B-K) with different diluents, normal saline (0.9% NaCl) and 5% dextrose solution. The diluted products were observed for any precipitation up to 24 hours. The observations were recorded in Table 9,10 and 11.

Table 9: Dilution profile of reconstituted solution of formulation (DPI-B-F)

Dilution	Time (hrs.)											
	Normal saline solution						5% dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	-	-	-	-	-	-	-	-	-	-	-	-
1:5	-	-	-	-	-	-	-	-	-	-	-	-
1:10	-	-	-	-	-	-	-	-	-	-	-	-
1:20	-	-	-	-	-	-	-	-	-	-	-	-
1:30	-	-	-	-	-	-	-	-	-	-	-	-
1:40	-	-	-	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	-
1:500	-	-	-	-	+	+	-	-	-	-	+	+

(-) No precipitation, (+) Precipitation

Table 10: Dilution profile of reconstituted solution of formulation (DPI-B-I)

Dilution	Time (hrs.)											
	Normal saline solution						5% dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	-	-	-	-	-	-	-	-	-	-	-	-
1:5	-	-	-	-	-	-	-	-	-	-	-	-
1:10	-	-	-	-	-	-	-	-	-	-	-	-
1:20	-	-	-	-	-	-	-	-	-	-	-	-
1:30	-	-	-	-	-	-	-	-	-	-	-	-
1:40	-	-	-	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	-
1:500	-	-	-	-	-	-	-	-	-	-	-	-

(-) No precipitation, (+) Precipitation

Table 11: Dilution profile of reconstituted solution of formulation (DPI-B-K)

Dilution	Time (hrs.)											
	Normal saline solution						5% dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	-	-	-	-	-	-	-	-	-	-	-	-
1:5	-	-	-	-	-	-	-	-	-	-	-	-
1:10	-	-	-	-	-	-	-	-	-	-	-	-
1:20	-	-	-	-	-	-	-	-	-	-	-	-
1:30	-	-	-	-	-	-	-	-	-	-	-	-
1:40	-	-	-	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	+
1:500	-	-	-	-	+	+	-	-	-	-	-	+

(-) No precipitation, (+) Precipitation

3. Results and Discussion

The UV visible spectroscopy of ornidazole showed peak at 320 nm, which issame as reported in literature (fig. 01). From the calibration curve equation isgiven as y = 0.040x + 0.008. The value of $R^2$is 0.999. On the basisof obtained result it was concluded that ornidazole, obeyed Beers Lamberts law in the range of 5 mcg/ml to 25 mcg/ml. The infrared spectrum of ornidazole was concordant with the reference spectrum of ornidazole and the major peaks are shown in fig 3. The DSC spectrum of ornidazole was same as reported in literature and principal peak was obtained at 91.22^o C. Hence, it was inferred that the procured drug sample was pure ornidazole and hence used for further studies. DSC curve was shown in figure 4. Desired solubility was observed in three blends which are **Blend-F, Blend-I, Blend-K.** These blends were selected for the batch formation and will be examined for stability and other parameters and solubility recorded in table 1. The results of TLC study from table 2, revealed that there is no significant change in RF values of ornidazole solubilized in water and ornidazole solubilized in solubilizers blend solutions. From the results of TLC study, it can be concluded that there is no salt formation or complexation of drug with solubilizer molecules. All solubilizers were found compatible with ornidazole. The results of chemical stability studies showed that the residual drug content at the end of 3 months was found to be 95.03% at room temperature and 94.67% at 40°C in DPI-B-F formulations, for DPI-B-I formulation it was found to be 96.39% at room temperature and95.78% at 40^o C and for DPI-B-K it was found to be 94.77% at room temperature and 93.80% at 40^o C. This indicates that the formulation DPI-B-I will have longer-term stability at room temperature as compared to that of DPI-B-F and DPI-B-K formulations. Dilution Studies indicated that the formulations (DPI-B-I, DPI-B-F, and DPI-B-K) were stable (up to 24 hours) against precipitate formation in normal saline solution and 5% dextrose solution. In the case of batch formulation DPI-B-F and DPI-B-K, as the dilution ratio was increased, the appearance of precipitate was observed but in batch formulation DPI-B-I, there is no precipitation found in any dilution ratio and results are shown in table 9,10 and 11.

4. Acknowledgement

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