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FORMUATION AND EVALUATION OF DRY SUSPENSION OF ORNIDAZOLE AS PARENTERALS

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ABSTRACT

The main aim of present research study was to promote the novel application of mixed solvency concept in the formulation of dry dosage forms of poorly soluble drug and to minimize the toxic effects of solubilizers by reducing the concentration of individual solubilizer (used for solubility enhancement). In this research work, poorly water soluble drug ornidazole was selected. It was passed through solubility studies by using various physiologically compatible solubilizers to prepare its parenteral preparation (dry powder injection for reconstitution of ornidazole). In the present research work, the procured sample of ornidazole drug undergone by various characterization parameters. The melting range of drug was determined by the open capillary method and it was found to be 86-90º C. UV Spectrophotometric analysis was performed to obtain its maximum peak which was found to be at 320 nm.

KEYWORDS: Ornidazole, Mixed solvency, Soubelizers, Suspension, Dry Powder**.**

1. INTRODUCTION

Parenteral formulations may be categorised as solutions (aqueous or oil-based), suspensions (aqueous or oil-based) or emulsions. For the most part, these formulations use similar (or indeed identical) excipients but, as may be expected, there are certain excipients that are unique to each category. Details of the key formulation excipients for each formulation type are provided below. In addition, the reader will observe a similarity in the excipients used for the formulation of solutions, suspensions and emulsions for parenteral administration and those used for non-parenteral use. The main formulation considerations for parenteral formulations are described below.

In the pharmaceutical field, it is often required to prepare aqueous solutions of a variety of insoluble drugs. The ability to increase the aqueous solubility can be a valuable aid for increasing the efficacy and/or reducing adverse effects of certain drugs.

2. HYDROTROPIC SOLUBILIZATION

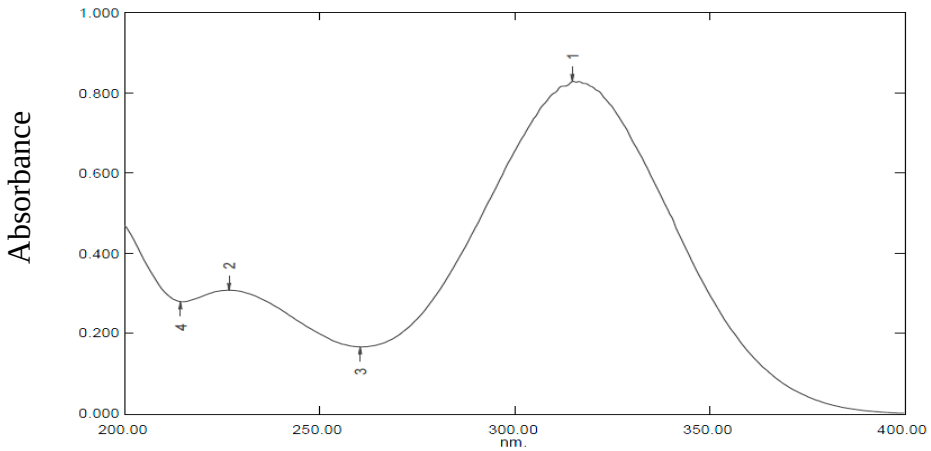
The mechanism by which the hydrotropic effect occurs is not clear. Some workers have speculated that hydrotropy is simply another type of solubilization, with the solute dissolved in oriented clusters of the hydrotropic agents. Hydrotropic solutions do not show colloidal properties, however. Others feel that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotropic agent and the solute. Still other reason that the phenomenon must be due to a change in solvent character because of a large amount of additive needed to bring about the increase in solubility.

3. MATERIAL AND METHODS

3.1. UV Spectrophotometric Analysis of Ornidazole

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

2.0 mL of the above solution was taken and diluted up to 100 ml to obtain the dilution of 20 µg/ml concentration. The resulting solution was scanned between 200-400 nm on Shimadzu-1700 UV spectrophotometer against demineralised water. The spectrum is shown in figure 5.1.



Wavelength (λ)

Fig. 1: UV spectra of ornidazole.

3.2. Preparation of Calibration Curve of Ornidazole in De-Mineralised 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. 0.5 mL of the above solution was taken and diluted up to 100 mL to obtain the dilution 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 to obtain dilutions 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 recorded in table 6.1 and graphically represented in figure 6.1.

Table 1: Absorbance data for calibration curve of ornidazole in DM water at 320nm.

S.No.	Concentration (µg/mL)	Absorbance			Average	Standard Deviation
		1st Time	2nd Time	3rd Time		
1	0	0.000	0.000	0.000	0.000	0.000
2	5	0.216	0.222	0.220	0.219	0.003
3	10	0.416	0.417	0.415	0.416	0.001
4	15	0.601	0.619	0.609	0.610	0.009
5	20	0.825	0.829	0.827	0.827	0.002
6	25	1.010	1.018	1.015	1.014	0.004

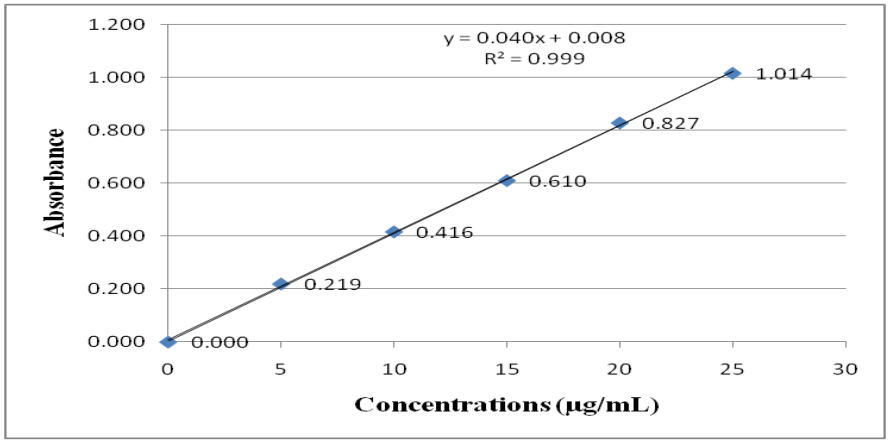


Fig 2: Calibration curve of ornidazole in demineralised water.

3.3. Study of Interference of Excipients in UV Spectrophotometric Estimation of Ornidazole

For determination of interference of additives in the spectrophotometric estimation of ornidazole, the absorbances of the standard solutions of ornidazole were determined in DM water alone and in the presence of fairly large concentrations of additives.

To obtain 1000 µg/mL stock solution of ornidazole drug, accurately weighed 100 mg of drug was taken in a 100 mL vol. flask and dissolved by using DM water and volume made up to 100 mL with DM water. Similarly, the same concentration (1000 µg/mL) of stock solution of each excipient was prepared.

Then, 2 ml of drug stock solution and 10 ml of excipient stock solution were withdrawn and taken in 100 ml volumetric flask and volume was made up to the mark with DM water to obtain the concentration of 20 µg/mL and 100 µg/mL of drug and excipients, respectively. Samples were analysed on UV spectrophotometer at 320 nm against the blank.

Table 2: Absorbance data for interference study.

Drug	Excipients	Drug conc. (µg/ml)	Additives conc.(µg/ml)	λ_{max} (nm)	Absorbance
Ornidazole		20	-	320	0.830
Ornidazole	Sod benzoate	20	100	320	0.829
Ornidazole	Niacinamide	20	100	320	0.838
Ornidazole	Caffeine	20	100	320	0.835
Ornidazole	Sod caprylate	20	100	320	0.824
Ornidazole	Sod citrate	20	100	320	0.827
Ornidazole	Sod acetate	20	100	320	0.836
Ornidazole	PVP K30	20	100	320	0.832
Ornidazole	PEG 4000	20	100	320	0.826

Result- No interference was shown by the excipients in the UV estimation of ornidazole at 320 nm.

3.4. Development of Dry Powder Injection for Reconstitution of Ornidazole

The present research study was intended to enhance the solubility of ornidazole using a combination of various physiologically compatible solubilizers. After increasing the solubility of the drug, it might be possible to formulate the small volume parenteral as dry powder injection for reconstitution to produce a solution, which will be stable and fulfill the requirements to achieve the required therapeutic plasma concentration rapidly.

3.5. Selection of Solubilizers Blends for Injection Formulation

On the basis of results obtained from solubility studies, the mixed blends in which solubility of ornidazole was more than 100 mg/ml achieved 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 7.1, 7.2 and 7.3.

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

4. Formulation of Dry Powder Injection for Reconstitution

The dry powder injections for reconstitution were formulated according to the formulation detail given in above tables, following the procedure is given below.

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.*

5. Evaluation of Dry Powder Injection for Reconstitution

The prepared formulations were subjected for various evaluation parameters.

5.1. 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 7.4.

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

5.2. 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 7.5.

Table 7: Reconstitution time 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

5.3. Clarity Testing of Reconstituted Injection

Clarity test of 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 formulation are shown in table 7.6.

Table 8: Clarity of various reconstituted injections.

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

5.4. 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 saturated aqueous solution of sodium chloride. 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, 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 table 7.8 to 7.9 and fig. 7.1 to 7.2.

Table 9: Chemical stability data of Ornidazole in formulation DPI-B-F.

Weeks	% Residual drug	
	Room temperature	40 ºC/75% RH
0	100.00	100.00
1	99.64	99.52
2	99.39	99.27
3	99.03	98.91
4	98.55	98.42
5	98.30	98.18
6	97.94	97.82
7	97.09	96.97
8	96.61	96.36
9	96.24	96.00
10	95.88	95.52
11	95.39	95.15
12	95.03	94.67

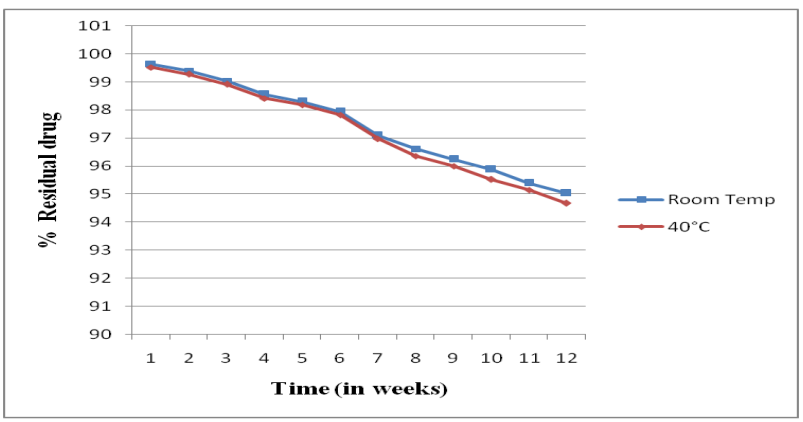


Fig. 3: Degradation curve for the formulation DPI-B-F.

Table 10: Chemical stability data of Ornidazole in formulation DPI-B-I.

Weeks	% Residual drug	
	Room temperature	40 ºC/75% RH
0	100.00	100.00
1	99.76	99.64
2	99.40	99.28
3	99.04	98.80
4	98.80	98.55
5	98.43	98.19
6	98.07	97.95
7	97.71	97.35
8	97.47	97.23
9	97.11	96.87
10	96.75	96.39
11	96.51	96.14
12	96.39	95.78

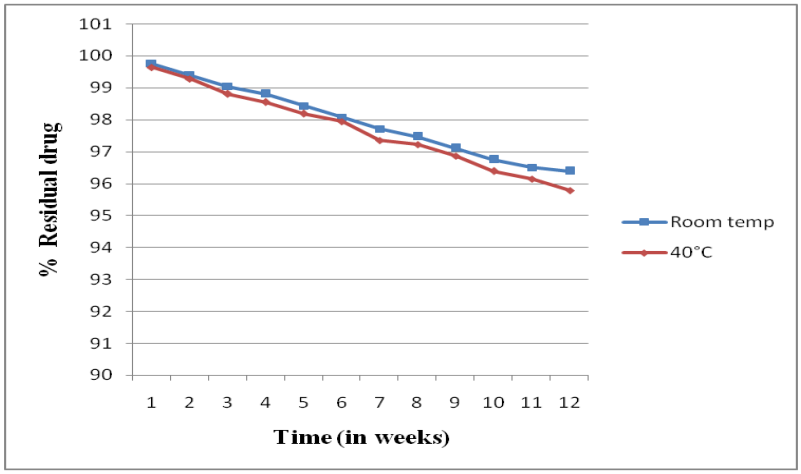


Fig. 4: Degradation curve for the formulation DPI-B-I.

Table 11: Chemical stability data of Ornidazole in formulation DPI-B-K.

Weeks	% Residual drug	
	Room temperature	40 ºC/75% RH
0	100.00	100.00
1	99.76	99.64
2	99.39	99.27
3	99.03	98.91
4	98.54	98.42
5	98.18	97.93
6	97.81	97.45
7	97.32	96.96
8	96.84	96.23
9	96.35	95.74
10	95.86	95.01
11	95.26	94.53
12	94.77	93.80

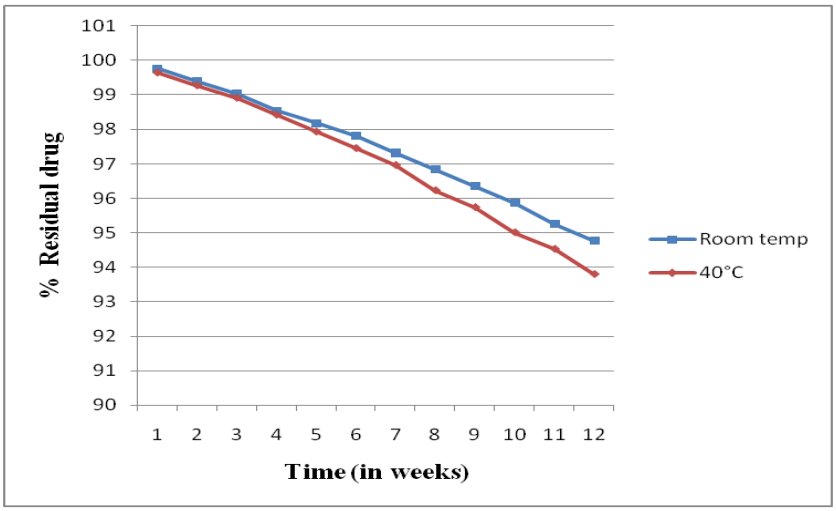


Fig. 5: Degradation curve for the formulation DPI-B-K.

RESULT AND DISCUSSION

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 and 95.78% 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.

5.5. 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 7.10, 7.11 and 7.12.

Table 12: 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 13: 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 14: 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.

Result and discussion: The above results indicate that the formulations (DPI-B-I, DPI-B-F, and DPI-B-K) were observed to have stability (up to 24 hours) towards 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.

Result and discussion: The results showed that, at the end of 3 months accelerated stability study of the dry power syrup for reconstitution the % residual drug content was found to be 96.14% at room temperature and 95.66% at 40^{o}C in DPS-B-I. But the % residual drug content was found to be in the formulation DPS-B-F is 95.07% at room temperature and

94.59% at 40°C, and the % residual drug content was found to be in the formulation DPS-B-K is 95.04% at room temperature and 94.20% at 40°C.

The results for the chemical stability testing of the reconstituted syrup at the end of 14 days, the % residual drug content of formulation DPS-B-I was found to be 99.16% at room temperature and 98.19% at 40°C. But in the formulation DPS-B-F, the % residual drug content was found to be 98.44% at room temperature and 97.96% at 40º C and in the formulation DPS-B-K, the % residual drug content was found to be 98.43% at room temperature and 97.95% at 40º C.

On the basis of results obtained it was concluded that the dry powder syrup for reconstitution formulation DPS-B-I is more stable as compared to other formulations.

The main aim of present research study was to promote the novel application of mixed solvency concept in the formulation of dry dosage forms of poorly soluble drug and to minimize the toxic effects of solubilizers by reducing the concentration of individual solubilizer (used for solubility enhancement).

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