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Formulation Development and Characterization Of Third Generation Cephalosporin Loaded Dry Injection and Dry Syrup: A Mixed Solvency Concept To Minimize Toxicity And Maximize Bioavailability

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Abstract:

The objective of present work was to explore the novel application of mixed solvency technique 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 the present study, poorly water insoluble drug cefixime was selected. Cefixime was tried to solubilize by using solubilizers which were physiologically compatible in an attempt to prepare its parenteral formulations (dry injection for reconstitution of cefixime) as well as oral liquid formulation (dry syrup).

In the present work, the procured cefixime drug sample was characterized by various characterization tests. Open capillary method was used to determine the melting point and it was found to be 218-225º C. Spectrophotometric method was used to analyze the drug which showed its peak at 288 nm. Further characterization of drug was done by FTIR spectroscopy. The characterization report of the procured sample of drug was found to be in concordance with that reported in the literature and was thus used for further studies.

1. Introduction

Many antibiotic materials are unstable when maintained in solution for an appreciable length of time, and therefore, from a stability standpoint, insoluble forms of the drug substances in aqueous suspensions or as dry powder for reconstitution are attractive to manufacturers [1]. Since decades among all the pharmaceutical products available, oral drug delivery has gained a higher scope and popularity and has been widely employed for the systemic delivery of drugs. The positive aspect regarding the oral dosage form which created its high level of acceptance was its ease of administration, patient compliance and stability of formulation [2]. The antibacterial oral suspensions include preparations of antibiotics substances (eg., erythromycin derivatives, and tetracyclines and its derivatives), sulfonamides (eg.,

sulfamethoxazole and sulfisoxazole acetyl), other anti-infective agents (eg., methenamine mandelate and nitrofurantoin), or combinations of these (eg., sulfamethoxazole-trimethoprim). The antibiotic oral suspension, including those prepared by reconstitution, provide a convenient way to administer dosages to infants and children and to adult patients who prefer liquid preparations to solid ones. Although studies have demonstrated that the dry oral suspension after constitution in a liquid is stable for 24 h after preparation, reconstituted solution remains stable when stored in the refrigerator for the labelled period, usually 7 to 14 d, depending on the preparation. This is a sufficient period for the patient to complete the regimen usually prescribed. However, in case the medication remains after the patient completes the course of therapy, the patient should be instructed to discard the remaining portion, which would be unfit for use at the later time [1].

Examples of dry powders mixtures intended for reconstitution to oral solutions are as follows:
i) Cloxacillin Sodium for Oral Solution, USP (Teva), an anti-infective antibiotic.
ii) Penicillin V Potassium for Oral Solution, USP (Veetids, Geneva), an anti-infective antibiotic.
iii) Potassium Chloride for Oral Solution, USP (K-LOR, Abbott), a potassium supplement.

2. Disadvantages of liquid oral suspensions [1, 4, 5]

- It is a bulk formulation, so there are chances of inaccuracy in single dosing.
- Drug dose depends on various physical factors of the dosage form such as the temperature of storage, sedimentation rate of the formulation, liquid flow properties like viscosity, pourability, redispersion, flocculation and content uniformity.
- Stability of the liquid suspension largely depends on the temperature of storage.
- Caking occurs upon storage.

3. Advantages of dry granules for oral suspension [1, 4, 5]

- There is accurate single dosing as the dose is packed in single dose sachets.
- Drug dose is comparatively independent of any physical factors like temperature, sedimentation rate and liquid flow properties.
- The packaging of the powder mixture is done in sachets making the formulation easy to carry.
- The enhanced convenience of the single dosage regimen.
- Colored, flavored, sweetened formulation is advantageous for administration to the pediatric population.
- Stable on storage and when reconstituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration for which the therapy is required.

4. Reasons for formulation of such suspensions [1, 4, 5]

The most common reason for the formulation of suspensions for reconstitution is the inadequate chemical stability of the drug in an aqueous vehicle. In such cases, dissolution or even suspension of the drug results in a very short shelf life. For example, reconstituted

suspensions of penicillin have a maximum shelf life of 14 d. The manufactured dry mixture, however, has a shelf life of at least 2 y.

Another reason for the formulating suspensions for reconstitution is to avoid the physical stability problems often encountered in conventional suspensions. These problems include possible increased drug solubility due to pH changes from chemical degradation, incompatibility of ingredients, viscosity changes, conversion of polymorphic form and crystal growth and caking.

Formulation for reconstitution reduces the weight of the final product because the aqueous vehicle is absent and consequently, transportation expenses may be reduced. The dry mixture may be shipped without regard to seasonal temperatures because its physical stability is less susceptible to temperature extremes as compared with conventional suspensions.

5. SPECTROPHOTOMETRIC ANALYSIS OF CEFIXIME

Accurately weighed quantity of cefixime (50 mg) was dissolved in about 400 ml of de mineralized water in a 500 ml volumetric flask and the volume was made upto 500 ml with demineralized water.
Aliquots of the above solution were taken and diluted to get cefixime concentration 10µg/ml. the resulting solution was scanned between 200-500 nm on Shimadzu-1700 UV spectrophotometer against distilled water. The spectrum is shown in figure 5.2

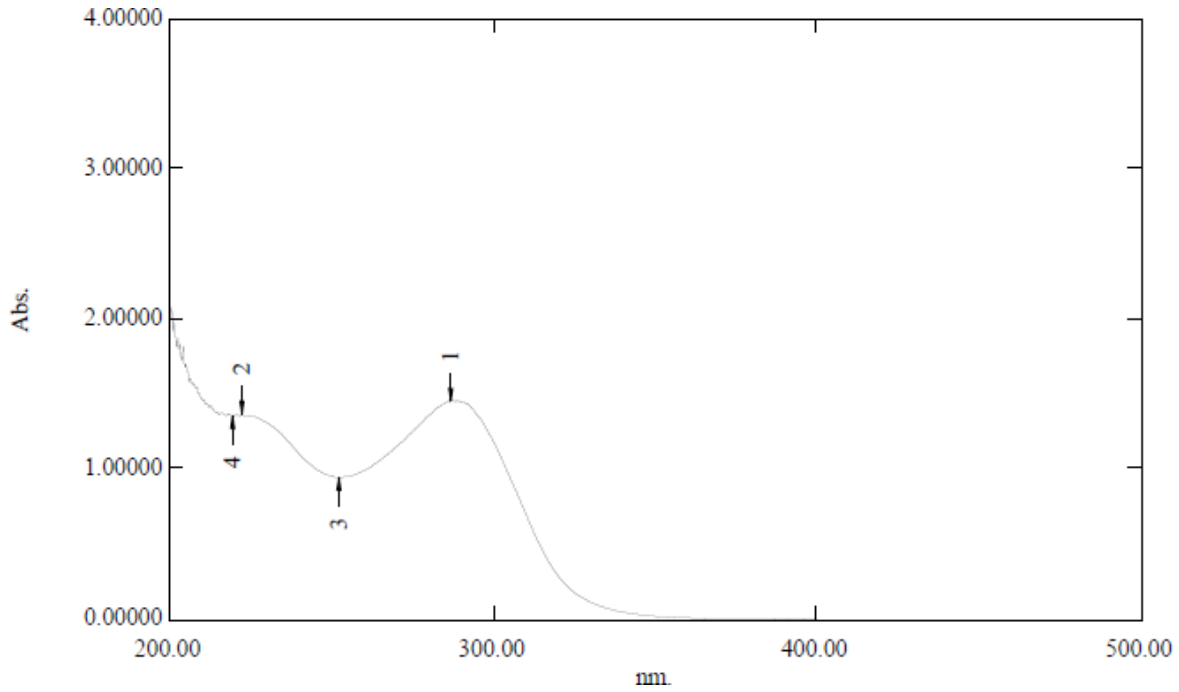

Fig. 5.2: UV spectra of cefixime

Result and discussion: The UV spectrum showed peak at 288nm for cefixime which is

concordant to that reported in literature.

6.1 Solubility studies

6.1.1 Preparation of various blends of solubilizers

Some solid solubilizers were screened on the basis of review of mixed solvency concept projects such as PVP k-30, lignocaine HCl, niacinamide, sodium benzoate, caffeine, sodium citrate, sodium acetate in concentration of 5% w/v of each solubilizer. To prepare 100 ml blend, 5 gm of each solubilizer was accurately weighed and taken in 100 ml volumetric flask and dissolved in 80 ml de-mineralized water by shaking. Volume was make upto the mark with de-mineralized water.

Table 6.1: Composition of various aqueous solutions containing blends of solid solublizers.

S. No.	Blend	5% w/v each solubilizer
1.	B1	PVP-K 30 + lignocaine + niacinamide
2.	B2	Niacinamide + lignocaine+ sodium citrate
3.	B3	Niacinamide + sodium citrate+ sodium acetate+ β cyclodextrin
4.	B4	Sodium acetate+ sodium citrate
5.	B5	Caffeine+ niacinamide
6.	B6	Sodium acetate+ sodium citrate+ β cyclodextrin

6.1.2 Approximate solubility determination in various aqueous solutions of blends of solubilizers.

To determine solubility 5 ml of solvent system was taken in a clear glass vial of 5ml capacity and accurately weighed drug (10 mg) was dissolved in the solvent system and the vial was shaken to dissolve the drug. As soon as clear solution is obtained, again 10 mg (accurately weighed) drug was added and the process was repeated till saturation (nearly). Total weighed quantity of drug dissolved in 5 ml solvent was considered to be approximate solubility of cefixime in respective solvent system. Amount dissolved per ml of solvent system was determined.

Table 6.2: Solubility results in various blends

S. No.	Blend	Solubility (mg/5ml)	Solubility (mg/ml)
1.	B1	Precipitation observed	Precipitationobserved
2.	B2	Precipitation observed	Precipitationobserved
3.	B3	190	38
4.	B4	430	86
5.	B5	50	10
6.	B6	280	56

6.2 Spectrophotometric calibration curve.

6.2.1 Preparation of calibration curve of cefixime in de-mineralized water.

50 mg of pure drug was accurately weighed and transferred into a 500 ml volumetric flask. It was dissolved in adequate amount of de-mineralized water and volume was made upto 500 mlwith demineralized water to obtain stock solution of 100 µg/ml. From 100 µg/ml solution, appropriate dilutions were prepared in the range of 5-25 µg/ml. Absorbances of resulting solutions were noted at 288 nm against demineralized water.

Table 6.3: Absorbance data for calibration curve of cefixime in demineralized water at 288nm

S. No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.267
3	10	0.509
4	15	0.756
5	20	0.992
6	25	1.222

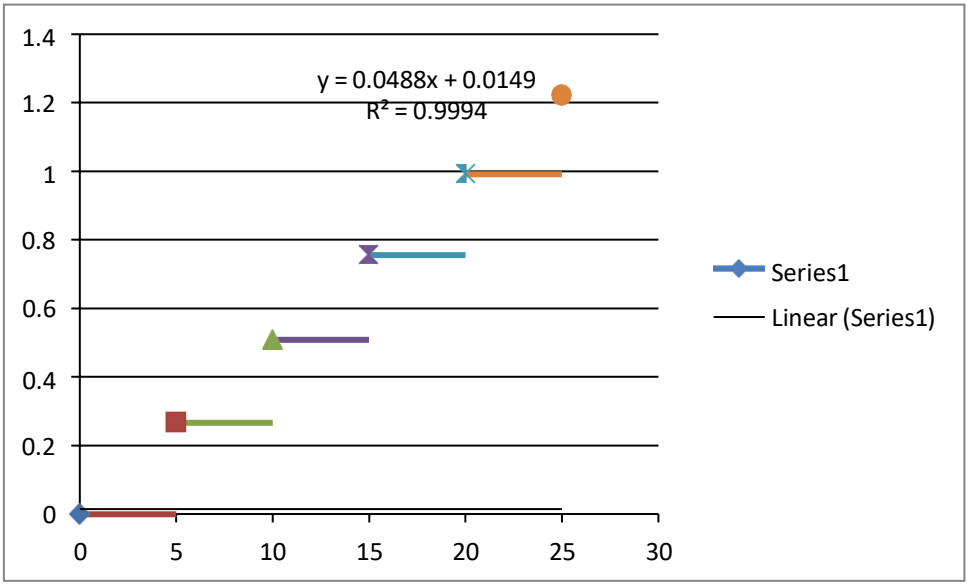

Fig 6.1: Calibration curve of cefixime in demineralized water

6.2.2 Study of interference of excipients in UV spectrophotometric estimation of cefixime.

Accurately weighed 100 mg of each excipient was taken in 100 ml volumetric flask and dissolved in 80 ml DM water and volume was made upto the mark to obtain stock solution of 1000 µg/ml. Similarly stock solution of cefixime was prepared. Then, 1 ml of drug solution and 1 ml of excipient solution was taken in 1000 ml volumetic flask and volume was made upto mark with DM water. Samples were analyzed on UV spectrophotometer at 288 nm against blank.

Table 6.4: Absorbance data for interference study

S. No.	Excipient 1000µg/ml	Absorbance at 288nm	Interference
1.	Plain drug solution 20µg/ml	0.992	-
2.	Cefixime + sodium acetate	0.987	No
3.	Cefixime + sodium citrate	0.974	No
4.	Cefixime + β CD	0.988	No
5.	Cefixime + Niacinamide	0.981	No

6.	Cefixime + Sodium benzoate	0.985	No

Result- No interference was shown by the excipients in the UV estimation of cefixime.

6.3 Thin layer chromatographic studies.

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 methanolic solution of cefixime alone, the aqueous solution containing cefixime in blend 4 and blend 6 were spotted with the aid of microdropper on the base line. To a solvent jar saturated with the solvent system butanol, ethanol and water (9:7:4), the plate already dried in air for 10 min was transferred. The solvent system was made 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 valueswere determined and recorded in table

Table 6.5: R_F values of cefixime and solubilized product

S. No.	Sovent system	R_F value
1.	Drug in methanol	0.45
2.	Drug in blend 4	0.42
3.	Drug in blend 6	0.41

Inference- The results of TLC study revealed that there is no significant change in RF values of cefixime solubilized in methanol and cefixime solubilized in solubilizer blend solutions. From the results of TLC study, it can be concluded that there is no salt formation or complexation of drug and solubilizer molecule.

6.4 Drug excipient interaction studies.

The compatibility of the drug with the excipient was assessed by drug-excipient interaction studies. The drug was mixed with excipient in 1:5 ratio in separate clear glass vials which were then properly sealed and kept undisturbed at different temperature conditions; at room temperature, at 40 C and in refrigerator for a period of one month. After every week, vials were withdrawn and contents were observed for any change in their physical appearance. The results so observed were recorded in table 6.6

Table 6.6: Observations of physical interaction between drug and excipients

S. No.	Drug-Excipients Mixture	Initial Appearance	Storage conditions											
			frigerator(2-8°C)				Room Temperature				40°C			
			Weeks				Weeks				Weeks			
			1	2	3	4	1	2	3	4	1	2	3	4
1	CEF	Yellowish powder	N	N	N	N	N	N	N	N	N	N	N	N
2	CEF+SA	Slight yellowish solid powder	N	N	N	N	N	N	N	N	N	N	N	N
3	CEF+SC	Slight yellowish solid powder	N	N	N	N	N	N	N	N	N	N	N	N
4	CEF+SB	Slight yellowish solid powder	N	N	N	N	N	N	N	N	N	N	N	N
5	CEF+β CD	Slight yellowish solid powder	N	N	N	N	N	N	N	N	N	N	N	N

CEF =Cefixime N = No Change

SA =Sodium acetate SC= Sodium citrate

SB = Sodium benzoate β CD = β Cyclodextrin

7.1 DEVELOPMENT OF DRY PARENTERAL FORMULATION OF CEFIXIME

The present investigation was proposed to solubilize cefixime using combination of various physiologically compatible solubilizers. By increasing the solubility of drug, it might be possible to formulate the small volume parenteral, which will be useful in patient with

URTI's RTI's in which parenteral administration of cefixime may be required to achieve the required therapeutic plasma concentration rapidly.

7.1.1 VARIOUS PARAMETERS FOR DRY INJECTION FORMULATION OFCEFIXIME

7.1.1.1 Selection of solubilizer blend for injection formulation

On the basis of results obtained from solubility studies, the mixed blends in which solubility of cefixime was more than 50 mg/ml and have were selected, such selected mixed blends were B-4 and B6. To develop 3 ml of cefixime injection, the amount of solubilizers and drug that will be administered through each mixed blend was determined. Injection formulations were developed based on solubility of cefixime in individual blends. The proposed formulations are shown in table 7.1 and 7.2.

Table 7.1: Formulation DIB-4

S. No.	Ingredients	Formula for 100 mg cefixime/3ml	Formula for30 ml batch
1	Cefixime	100 mg	1 g
2	Sodium acetate anhydrous	150mg	1.5 g
3	Sodium citrate	150mg	1.5 g
4	sodium benzoate	15 mg	150 mg

Table 7.2: Formulation DIB-6

S. No.	Ingredients	Formula for 100mg cefixime/3 ml	Formula for 30 ml batch
1	Cefixime	100 mg	1 g
2	β cyclodextrin	100 mg	1 g
3	Sodium citrate	75 mg	0.75 g
4	Sodium acetate anhydrous	150 mg	1.5 g

5.	Sodium benzoate	15 mg	150

7.1.2 FORMULATION OF DRY POWDER INJECTION

7.1.2.1 Preparation of dry powder injection of cefixime

All the ingredients were passed through sieve number 80 to reduce the particle size separately. Then the required quantity of all excipients and drug was weighed and mixed by geometric dilution method with the help of mortar and pestle. The mixed blend was again passed through sieve and mixed manually in plastic bag of suitable size. The prepared formulation was then transferred to vials and vials were stoppered and sealed immediately.

7.1.3 FORMULATION OF READYMADE INJECTION

7.1.3.1 Preparation of readymade injection of cefixime

All the ingredients were passed through sieve number 80 to reduce the particle size separately. Then the required quantity of all excipients and drug was weighed and mixed by geometric dilution method with the help of mortar and pestle. The mixed blend was again passed through sieve and mixed manually in plastic bag of suitable size. This powder blend was transferred into suitable container. To the prepared blend 15 ml of demineralized water was added n the content was shaken to dissolve all the ingredients and finally the volume was made upto 30ml with demineralized water. The prepared formulation was then transferred to vials and vials were stoppered and sealed immediately.

7.2 EVALUATION OF DRY POWDER INJECTION

As soon as the formulation was developed it was subjected for various evaluations.

7.2.1 Determination of pH of reconstituted injection

The developed formulations were reconstituted by demineralized water and the pH was determined by using digital pH meter (Cyber Scan 510, Eutech Instruments, Singapore). The results are shown in table 7.3

Table 7.3: pH values of reconstituted injection formulations

Formulation code	pH
DIB-4	3.35
DIB-6	3.21

7.2.2 Determination of reconstitution time

For reconstitution of developed dry powder injection, 1 ml of demineralized water was injected into the vial through the rubber closure. The vial was then vigorously shaken for propermixing of the contents. The reconstitution time obtained were recorded in table 7.4

Table 7.4: Reconstitution time of various formulations

Formulation code	Reconstitution time (minutes)
DIB-4	1 min 30 sec
DIB-6	2min

7.2.3 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.

During the clarity testing of the reconstituted developed injection formulations, the results are shown in table 7.5.

Table 7.5: Clarity of various reconstituted injections

Formulation code	Clarity
DIB-4	Clear
DIB-6	Turbid

7.3 EVALUATION OF READYMADE INJECTION OF CEFIXIME

As soon as the formulation was developed it was subjected for various evaluations.

7.3.1 Determination of pH of readymade injection

The pH of the developed formulations was determined by using digital pH meter (Cyber Scan 510, Eutech Instruments, Singapore). The results are shown in table 7.6.

Table 7.6: pH values of readymade injection formulations

Formulation code	pH
RIB-4	3.33
RIB-6	3.23

7.3.2 Clarity testing of readymade injection

Clarity test of readymade injection was performed by visually inspecting the externally clean vial viewed against black and white background under good light.

During the clarity testing of the reconstituted developed injection formulations, the

results are shown in table 7.7.

Table 7.7: Clarity of various readymade injections

Formulation code	Clarity
RIB-4	Clear
RIB-6	Turbid

% Residual drug

7.4 ACCELERATED STABILITY STUDY AND DEGRADATION KINETICS OF CEFIXIME IN DRY POWDER INJECTION

The stability of cefixime was studied in order to investigate the kinetics of degradation of this drug in powder for injection.

Accelerated thermal degradation study was performed by subjecting the prepared cefixime dry powder injection sample (138 mg in each vial for B-4 & 146mg in each vial for B-6) at 40 ◦C for 28 days. At time intervals of 7 days, aliquots of degraded samples were diluted with demineralized water up to 1000 ml and analyzed by UV/Visible spectrophotometer (Shimadzu 1700) against respective reagent blanks at 288 nm. The % residual drug was calculated and shown in table 7.8 to 7.9 and fig. 7.1 to 7.2.

Table 7.8: Chemical stability data of cefixime in formulation DIB-4

Time (days)	% Residual drug		
	Room temperature	40 ºC	50 °C
0	100.00	100.00	100.00
7	99.51	99.40	98.82
14	98.75	98.54	97.42
21	98.01	97.72	96.13
28	97.25	96.83	94.54

Table 7.9: Chemical stability data of cefixime in formulation DIB-6

Time (days)	% Residual drug		
	Room temperature	40 ºC	50 °C
0	100.00	100.00	100.00
7	98.87	97.79	97.02
14	97.55	95.81	93.65
21	96.71	94.05	90.18
28	95.36	91.22	87.15

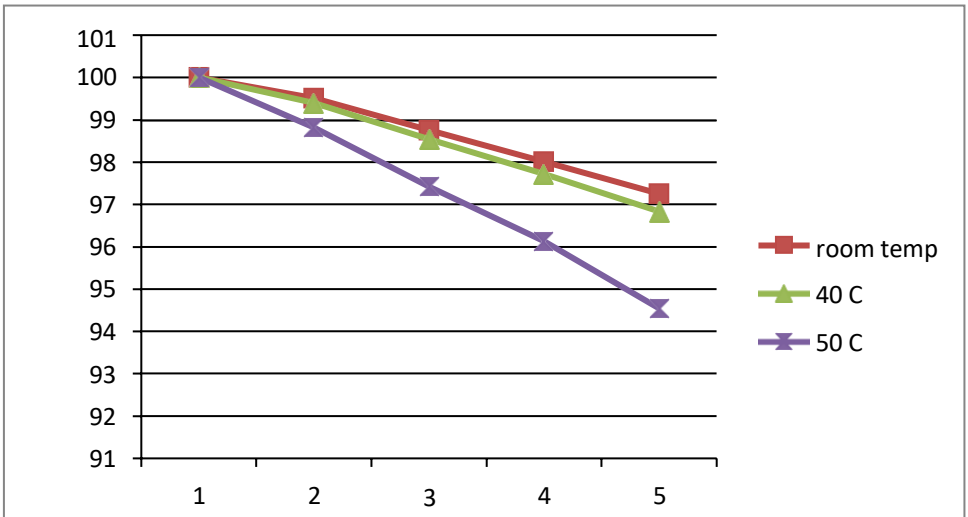

Fig. 7.1: Degradation curve for the formulation DIB-4

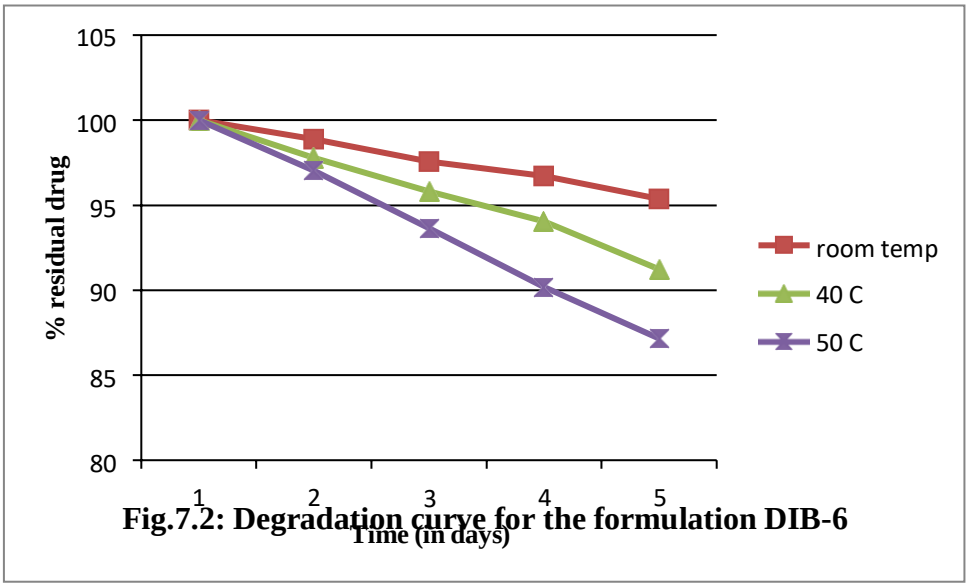

Fig.7.2: Degradation curve for the formulation DIB-6

7.5 ACCELERATED STABILITY STUDY AND DEGRADATION KINETICS OF CEFIXIME IN READYMADE INJECTION

The stability of cefixime was studied in order to investigate the kinetics of degradationof this drug in powder for injection.

Accelerated thermal degradation study was performed by subjecting the prepared cefixime readymade injection (1ml in each vial for both RIB-4 & RIB-6) at 40 ◦C for 14 days.Daily for a period of 14 days, aliquots of degraded samples were diluted with demineralized water up to 1000 ml and analyzed by UV/Visible spectrophotometer (Shimadzu 1700) against respective reagent blanks at 288 nm. The % residual drug was calculated and shown in table 7.10 to 7.11 and fig 7.3 to 7.4

Time (days)	% Residual drug		
	Room temperature	**40 °C**	**50 °C**
1	100.00	100.00	100.00

Table 7.815: Chemical stability data of cefixime in formulation RIB-

2	99.32	99.45	98.87
3	98.70	98.56	97.46
4	98.10	97.75	96.13
5	97.28	96.79	94.54
6	96.98	95.95	93.58
7	96.43	94.78	93.01
8	96.11	94.21	92.98
9	95.78	93.81	91.84
10	95.28	92.74	90.87
11	94.65	91.69	89.18
12	94.21	90.52	88.45
13	93.89	90.16	87.92
14	93.05	88.73	86.81

Table 7.11: Chemical stability data of cefixime in formulation RIB-6

Time (days)	**% Residual drug**		
	Room temperature	**40 °C**	**50 °C**
1	100.00	100.00	100.00
2	98.86	97.74	97.10
3	97.59	95.79	93.69
4	96.75	94.11	90.11
5	95.31	91.23	87.13
6	94.45	90.38	84.36
7	93.84	89.63	83.98
8	92.22	88.70	81.78
9	91.85	87.59	78.98
10	90.42	86.54	75.13
11	89.53	85.93	72.54
12	88.17	84.28	70.04
13	87.27	83.34	67.25
14	86.63	82.15	65.37

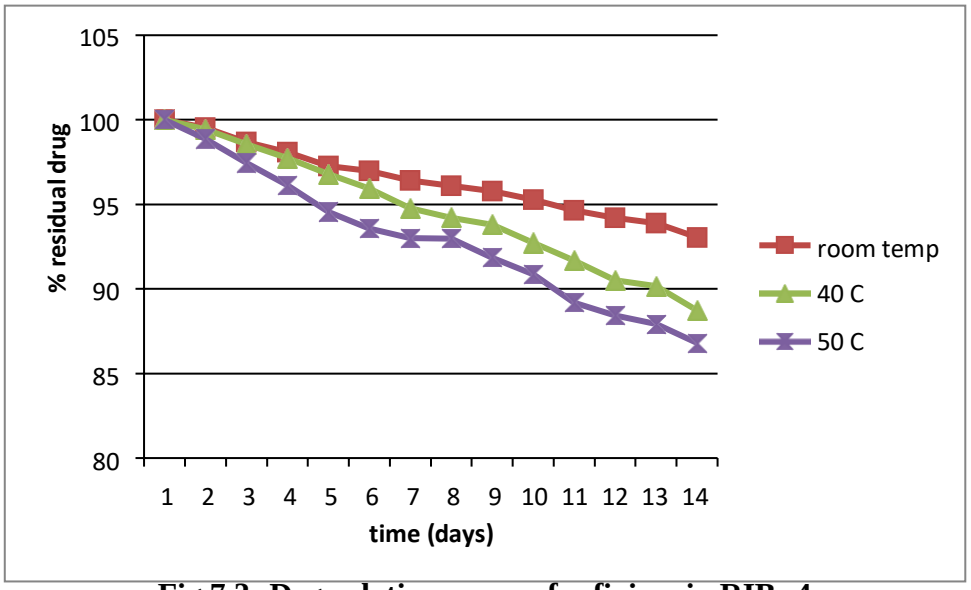

Fig 7.3: Degradation curve of cefixime in RIB- 4

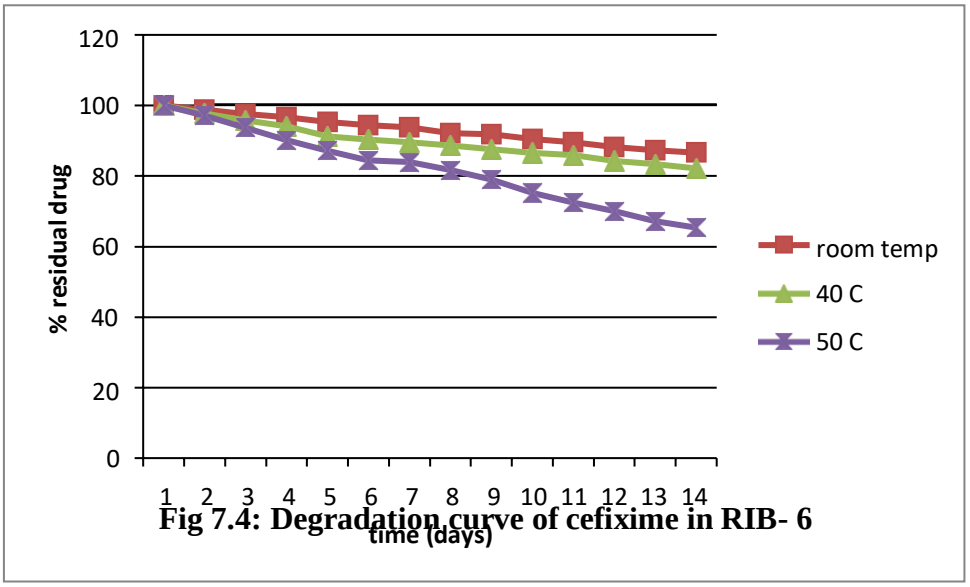

Fig 7.4: Degradation curve of cefixime in RIB- 6

Result and discussion: The results of chemical stability studies showed that the residual drug content at the end of 1 month was found to be 97.25% at 30°C in DIB-4 formulations whereas for DIB-6 it was found to be 95.36%. The residual drug content at 1 month time period in the formulation DIB-4 was 96.83% at 40°C and 94.54% at 50°C whereas in formulation DIB-6, 91.22% at 40°C and 87.15% at 50°C, which indicates that the formulationDIB-4 will have longterm stability at room temperature as compared to DIB-6.

The results for the chemical stability of the readymade syrup at the end of 14 days was found to be 93.05% at 30º C in RIB-4 formulations whereas for RIB- 6 formulation it was found to be 86.63%. The residual drug content at the end of 14days in the formulation RIB- 4 was 88.73% at 40º C and 86.81% at 50º C. The residual drug content at the end of 14 days in the formulation RIB- 6 was 82.15% at 40º C and 65.37% at 50º C, which indicates that the formulation RIB-4 will have long term stability at room temperature as compared to RIB-6.

7.6 DILUTION PROFILE OF RECONSTITUTED INJECTION

Series of dilutions were done by diluting reconstituted injection of cefixime (Formulation B-4 and B-6) 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 7.12 and 7.13

Table 7.12: Dilution profile of reconstituted solution of formulation (B-4)

	Time (hrs.)											
	Normal saline solution						**5% dextrose solution**					
Dilution	**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 7.13: Dilution profile of reconstituted solution of formulation (B-6)

	Time (hrs.)											
	Normal saline solution						**5% dextrose solution**					
Dilution	**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 (DIB-4 and DIB-6) were observed to have stability (up to 6 hours) towards precipitate formation in normal saline solution and 5% dextrose solution. In case of blend 6, as the dilution ratio was increased, the appearance of

precipitate was faster, but after much higher dilution (e.g. 1:100), the precipitate partly disappeared. This might be due to the redissolution of precipitate formed.

8.1 DEVELOPMENT OF DRY SYRUP FORMULATION

The oral liquid dosage form of poorly water-soluble drugs available in market are mostly in the form of solid dosage form like tablets, capsules etc. Liquid oral solutions (syrups) show better availability and quick onset of action in comparison to the tablet dosage form. In the present investigation, the poorly water-soluble drug cefixime has been selected for formulating its dry syrup with the help of β cyclodextrin, sodium citrate and sodium acetate as solubilizing agents. As of now, cefixime is available in the market in the form of suspension (after reconstitution). In the present study, the use of mixed solvency has been explored to develop syrup of poorly water-soluble drug (in solution form after reconstitution) by employing the combination of physiologically compatible solubilizing agents at reduced concentrations to provide quick onset of action and better availability (in comparison to its suspension form).

On the basis of the results obtained from the solubilization studies, both dry and readymade syrup of poorly water-soluble drug cefixime have been developed.

8.1.1 Syrup formula

The formula for the formulation of syrup is as follows:

Table 8.1: Formula of cefixime oral liquid formulation (Syrup)

S. No.	Ingredients	Formulation code
		DSB-6
1.	Cefixime	2 g
2.	Sodium citrate	2.5 g
3.	Sodium acetate	5 g
4.	β cyclodextrin	3.5 g
5.	Sodium benzoate	0.5 g
6.	Sucrose	40 g
7.	Distilled water (q.s.)	100 ml

8.1.2 FORMULATION OF DRY SYRUP FORMULATION

The syrup was formulated according to the formulation details given in table, following the procedure given below.

All the ingredients were weighed appropriately and were mixed by geometric dilution method for proper mixing in a pestle mortar. The resultant mixture was mixed thoroughly ina pestle mortar for uniform mixing.

The prepared formulation was then transferred to vials and vials were stoppered and sealed

immediately.

8.1.3 FORMULATION OF READYMADE SYRUP FORMULATION

The syrup was formulated according to the formulation details given in table, following the procedure given below.

All the ingredients were weighed appropriately and were mixed by geometric dilution method for proper mixing in a pestle mortar. The resultant mixture was mixed thoroughly in a pestle mortar for uniform mixing. The resultant powder mixture was transferred into appropriate container and 15ml demineralized water was added to dissolve the content and later volume was made upto 30ml with demineralized water. The prepared formulation was then transferred to vials and vials were stoppered and sealed immediately.

8.1.4 DETERMINATION OF pH OF DEVELOPED LIQUID SYRUP

The pH of formulated syrups was determined using digital pH meter (Cyber Scan 510, Eutech Instruments Singapore).

Table 8.2: pH values of reconstituted syrup formulations

Formulation code	pH
DSB-6	4.18
RSB-6	4.23

Result: The pH of the formulations DSB-6 was found to be 4.18 and that of the readymade syrup RSB-6 was found to be 4.23 respectively.

8.1.5 DETERMINATION OF RECONSTITUTION TIME

For reconstitution of developed dry syrup, 1 ml of demineralized water was injected into the vial through the rubber closure. The vial was then vigorously shaken for proper mixing of the contents. The reconstitution times were recorded in table 8.3.

Table 8.3: Reconstitution time of formulation

Formulation code	Reconstitution time (minutes)
DSB-6	4min 32 sec

8.1.6 PHYSICAL AND CHEMICAL STABILITY TESTING OF FORMULATEDSYRUPS

The formulated syrups were subjected to physical and chemical stability testing at three different temperatures (ambient, moderate and relatively higher temperature).

8.1.6.1 Physical stability testing of formulated syrups

The dry powder for syrups were filled in 5 ml glass vials and vials were plugged and sealed. The vials were kept at room temperature, 40°C/75% RH and 50°C. For physical stability studies, the syrups were observed at definite time intervals for colour change and clarity (to observe any turbidity or precipitation). Observations are recorded in table 8.4 and 8.5.

Table 8.4 : Physical stability testing data for syrup formulation DSB-6

Conditions	Time (days)	Physical Parameters	
		Color	Clarity
RTD	0	Slight yellow	Clear solution
RTD	15	Slight yellow	Clear solution
RTD	30	Slight yellow	Clear solution
40°C/75% RH	0	Slight yellow	Clear solution
40°C/75% RH	15	Slight yellow	Clear solution
40°C/75% RH	30	Slight yellow	Clear solution
50°C	0	Slight yellow	Clear solution
50°C	15	Slight yellow	Clear solution
50°C	30	Slight yellow	Clear solution

Table 8.5: Physical stability testing data for syrup formulation RSB-6

Conditions	Time (days)	Physical parameters		
		Color	Clarity	Precipitation
RTD	0	Slight yellow	Clear solution	No precipitation
RTD	15	Slight yellow	Clear solution	No precipitation
RTD	30	Slight yellow	Turbid	Precipitation
40°C/75% RH	0	Slight yellow	Clear solution	No precipitation
40°C/75% RH	15	Slight yellow	Clear solution	No precipitation
40°C/75% RH	30	Slight yellow	Turbid	Precipitation
50°C	0	Slight yellow	Clear solution	No precipitation
50°C	15	Slight yellow	Turbid	Precipitation
50°C	30	Slight yellow	Turbid	Precipitation

Result and discussion: It was found that the batch DSB-6, showed no significant color change or precipitate formation.

Similarly, RSB-6 showed little opalescence upon storage. The opalescence was found due to the precipitation of β-cyclodextrin.

8.1.7 Freeze Thaw cycling

In case of products that are susceptible to phase separation, loss of viscosity, precipitation and aggregation an extra investigation involving thermal cycling is carried out to establish the influence of temperature variation during distribution. Under this, the packaged product is cycled through temperature conditions that simulate the changes likely to be encountered once the drug product is in distribution.

8.1.7.1 Procedure for Freeze Thaw cycling testing of syrups

The vials were kept alternately at 40±1°C and 4±1°C for 24 hour each, and shaken everyday for 5 minutes on a touch type vortex mixer. Two vials of formulation were taken, one of which was kept at 40±1°C and the other at 4±1°C for first day, followed by subsequent temperature cycling and shaking as described. After 7-7 such cycles at 4±1°C and 40±1°C (alternately), the vials were observed to check turbidity and precipitation, if any.

Result and discussion: There was no precipitation and no turbidity in syrup DSB-6 formulation upon reconstitution at the end of testing. Little opalescence was found in RSB-6 formulation at the end of this testing.

8.2 Chemical stability testing of dry syrup

In order to study the chemical stability of syrups, the samples were collected at seven days interval upto one month and analyzed by UV Visible spectrophotometer to calculate the residual drug content of the syrups. The initial drug content for each formulation was taken as 100%. The values of percent residual drug for the formulation at different time intervals as well as at different temperatures are noted in table 8.6 and 8.7 and fig 8.1 and 8.2.

Table 8.6: Chemical stability testing data for syrup formulationsDSB6

Conditions	Time (days)	Percent residual drug in formulation
		DSB-6
Room temperature	0	100
Room temperature	7	96.12
Room temperature	14	92.34
Room temperature	21	90.82
Room temperature	28	90.14
Room temperature	35	88.38
Room temperature	42	85.21
40±2°C/75% RH	0	100
40±2°C/75% RH	7	96.01
40±2°C/75% RH	14	91.37
40±2°C/75% RH	21	90.17
40±2°C/75% RH	28	87.52
40±2°C/75% RH	35	81.63
40±2°C/75% RH	42	79.52
50°C	0	100
50°C	7	95.48
50°C	14	89.62
50°C	21	83.79
50°C	28	78.12
50°C	35	72.84
50°C	42	65.39

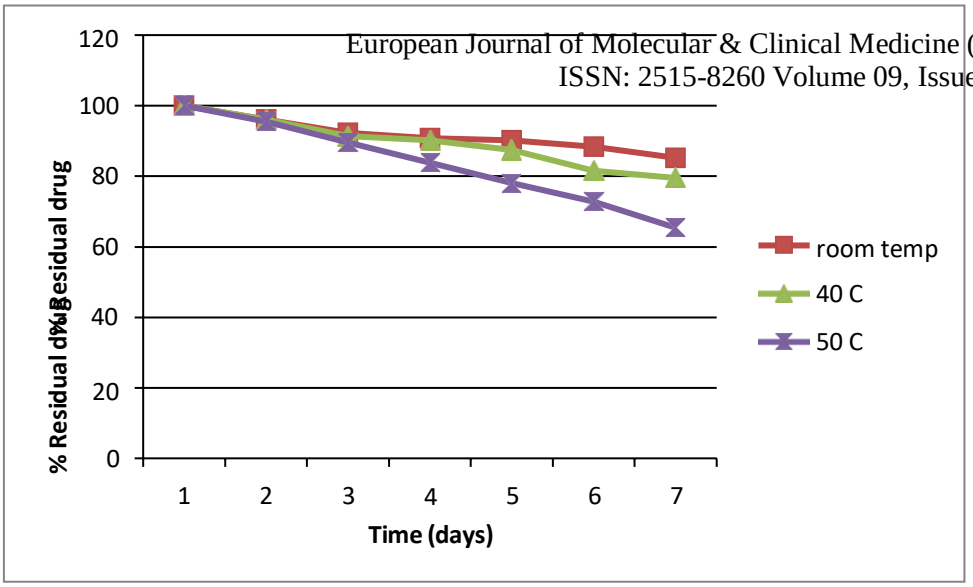

Fig 8.1: Degradation curve of cefixime in DSB-6

Table 8.7: Chemical stability testing data for syrup formulationsRSB6

Conditions	Time (days)	Percent residualdrug
		RSB-6
Room temperature	1	100
Room temperature	7	96.15
Room temperature	14	92.35
40±2°C/75% RH	1	100
40±2°C/75% RH	7	96.87
40±2°C/75% RH	14	93.49
50°C	1	100
50°C	7	95.52
50°C	14	91.23

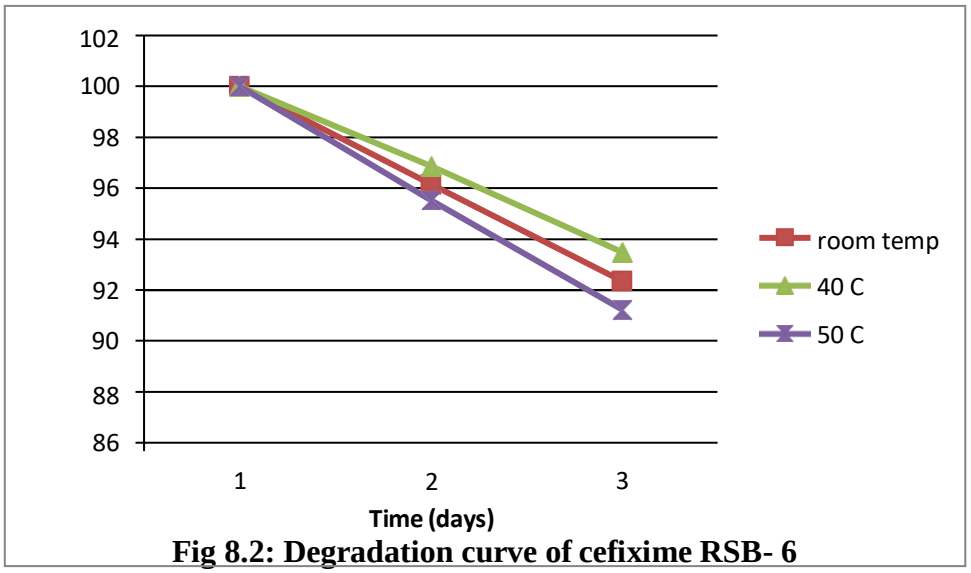

Fig 8.2: Degradation curve of cefixime RSB- 6

Result and discussion: The results of chemical stability studies showed that the residual drug content at the end of 42 days was found to be 85.21% in DSB-6. The residual drug content at 42 day time period in the formulation DSB-6 is 91.59% at 40°C and 65.39% at 50°C.

The results for the chemical stability of the readymade syrup at the end of 14 days for RSB- 6 formulation was found to be 92.35%. The residual drug content at the end of 14 days in the formulation RSB- 6 was 93.49% at 40º C and 91.23% at 50º C.

The objective of present work was to explore the novel application of mixed solvency technique 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 the present study, poorly water insoluble drug cefixime was selected. Cefixime was tried to solubilize by using solubilizers which were physiologically compatible in an attempt to prepare its parenteral formulations (dry injection for reconstitution of cefixime) as well as oral liquid formulation (dry syrup).

In the present work, the procured cefixime drug sample was characterized by various characterization tests. Open capillary method was used to determine the melting point and it was found to be 218-225º C. Spectrophotometric method was used to analyze the drug which showed its peak at 288 nm. Further characterization of drug was done by FTIR spectroscopy. The characterization report of the procured sample of drug was found to be in concordance with that reported in the literature and was thus used for further studies.

In the preformulation studies, calibration curves of drug in demineralised water was made. The UV interference studies showed no interference by the selected solubilizers in estimation of drug.

Solubility studies of cefixime was performed in demineralised water, 5% aqueous solution of mixed blend solubilizers (sodium benzoate, niacinamide, sodium citrate, lignocaine hydrochloride, PVP-K_{30}). In case of mixed blends maximum solubility was found in blend B-

4 which was 86 mg/ml and in B-6 56 mg/ml. The drug excipient interaction studies performed for one month duration showed no incompatibility between drug and selected excipients. Fromthe results of solubility studies, two mixed blends were selected namely B-4 and B-6.

For the development of dry powder injection formulation of cefixime, the mixed blends containing only solid solubilizers were selected based on solubility studies, such selected mixed blends were B-4 and B-6. Formulations were developed by geometric dilution method by help of mortar and pestle and then mixing in plastic bag manually, passed through sieve to reduce the particle size. All the developed were then subjected to various evaluations; pH of reconstituted injections were found to be physiologically compatible, reconstitution time was found to be maximum 2 min for formulation B-6, all the developed injection formulations was clear after reconstitution. The prepared dry powder injection formulations, DIB-4 and DIB-6 when subjected to accelerated stability studies showed good stability, the maximum stability

was shown by formulation DIB-4 (contained 97.25% drug as compared to initially 100% at room temperature at end of 28 days). Also the readymade injection of cefixime was also formulated and when subjected to accelerated stability studies, the maximum stability was shown by RIB-4(contained 93.05% drug as compared to initially 100% at room temperature at end of 14 days). All the prepared formulations did not showed any precipitation at the end of freeze thaw cycling.

Similarly, the dry syrup for reconstitution of cefixime was also formulated. From the solubility data obtained, the blends selected was and B-6 and both readymade and dry syrup formulation were formulated. The prepared formulation was also subjected to clarity testing physical stability studies and chemical stability studies. The prepared dry syrup formulations, DSB-6 when subjected to accelerated stability studies showed good stability. Also the readymade syrup of cefixime was also formulated and when subjected to accelerated stability studies the maximum stability shown by RSB-6 is 92.35% drug as compared to initially 100% at room temperature at end of 14 days). The prepared DSB- 6 formulation did not showed anyprecipitation whereas the RSB-6 formulation showed little opalascence at the end of freeze thaw cycling.

Thus, above findings supports that by employing novel concept of mixed solvency the required solubility can be achieved, also solubilizers can be selected in safer range and dosageforms of good stability can also be developed. Also from the syrup formulation, it can also be concluded that cefixime can also be formulated in the form of syrup instead of formulating it as a suspension and as a result better bioavailability of the drug can be obtained.

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