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Formulation Development of a Model Dry Powder Injection for Reconstitution of Poorly Water-Soluble Drug, Diazepam Using Mixed Solvency Concept and its Evaluations

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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 poorly water 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, diazepam was selected as a model drug and its dry injection for reconstitution was formulated. Diazepam is a type of medicine called a benzodiazepine. Benzodiazepines are used for their anxiety-relieving, sedative and muscle-relaxing effects. Due to poor solubility of diazepam, the products are available in tablet, gel & emulsion form. Various blends of solubilizers were tried thereby reducing the amount of individual solubilizer employed to achieve the desired solubility enhancement ratio. Thus, the successful completion of the research work enabled the preparation of stable dry injection for reconstitution ofdiazepam.

Keywords: Mixed solvency concept, diazepam, solubility enhancement, dry powder injection for reconstitution.

I. 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 safe solvent systems can be developed. Maheshwari is of the opinion that each substance possesses solubilizing power. He has given several eco - friendly 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, glycerine, 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 solubledrugs.

Mixed solvency concept, proposed by Maheshwari[6-30]provides a means to develop innumerable solvent systems employing

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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 solubilizing agent can be solved in this manner. The solubility of a large number of poorly soluble drugs have been enhanced by mixed solvency concept. In the present investigation, the poorly water-soluble drug, diazepam, which is crystalline powder has been selected as a model drug for formulating its model dry powder injection for reconstitution by using mixed solvency approach.

II. MATERIALS &METHOD

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

2.1 Preparation of calibration curve

45mg diazepam drug was accurately weighed and transferred to a 50 ml volumetric flask. The drug was dissolved by addition of 10 ml of a blend containing 10% sodium benzoate & 10% phenol and volume was made up to 50 ml with the same blend, so as to obtain a solution of 900 µg/ml. The above solution (0.5 ml) was taken and diluted with 89.5 ml Millipore water to obtain the dilution of 5 µg/ml concentration. Likewise, 1.0 ml, 1.5 ml, 2 ml and 2.5 ml solutions were taken and diluted with 89 ml, 88.5 ml, 88 ml and 87.5ml respectively to obtain dilutions of 10, 15, 20 and 25 µg/ml concentrations, respectively. Absorbances of these solutions were measured at 312 nm against the respective reagent blanks on Shimadzu-1700 UV spectrophotometer. The obtained data is graphically represented in figure 1.

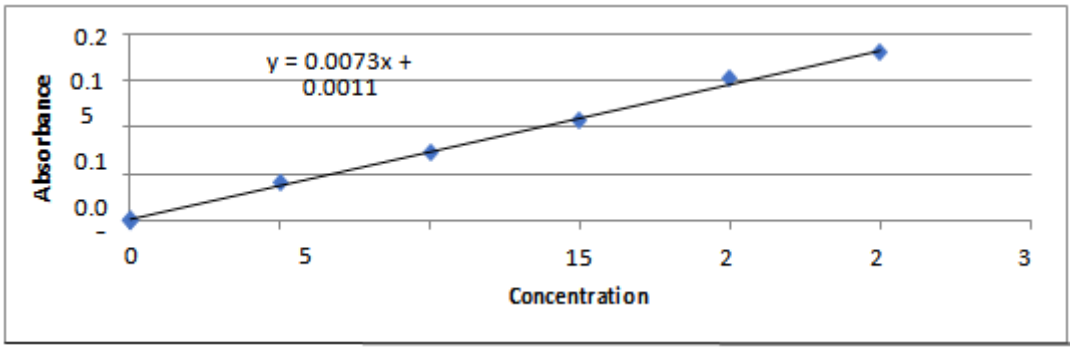

Figure 1: Calibration curve of diazepam in Millipore water

2.2 Approximate Solubility Determinatioin Of Diazepam In Various Aqueous Solutions Of Solid Solubilizers (Mixedblends).

One ml of the blend was taken in a 10 ml volumetric flask and accurately weighed about 5 mg of diazepam drug was transferred to this flask and the flask was vigorously shaken for 15-20 minutes. If the drug dissolves completely & gives clear solution then another 5 mg of the drug was added to the flask. Again, vigorous shaking was done. The same process was repeated until a turbid suspension is obtained even after shaking for 30 minutes. The same procedure was repeated for all blends to get approximate solubility of diazepam in remaining blends. Amount dissolved per ml of a solvent system was determined. Table 1 gives the results of the solubility studies.

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

S.No.	Blends	Composition of blends (% w/v)	Approximate solubility (mg/ml)
1.	B-1	5 % Sodium citrate 5 % Sodium acetate 5% Sodium caprylate 5 % Sodium benzoate	Less than 5
2.	B-2	5 % Sodium citrate 5 % Beta Cyclodextrin 10% Sodium caprylate 5 % Sodium benzoate	10

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3.	B-3	4.5 % Sodium acetate 15% Sodium caprylate 5 % Sodium benzoate	15
4.	B-4	2.5 % Sodium benzoate 2.5 % Sodium acetate 5% Beta cyclodextrin	5
5.	B-5	5 % Sodium benzoate 5 % Sodium acetate 5% Beta cyclodextrin	5
6.	B-6	5 % Sodium citrate 5 % Sodium acetate 5% Beta cyclodextrin	Less than 5
7.	B-7	2.5 % Sodium acetate 2.5 % Beta Cyclodextrin 15% Sodium caprylate 4.5% Sodium benzoate	15
8.	B-8	5 % Sodium benzoate 5 % Sodium acetate 20 % Sodium caprylate	20
9.	B-9	5 % Sodium benzoate 3.5 % Sodium acetate 25 % Sodium caprylate	25
10.	B-10	5 % Sodium benzoate 5 % Sodium citrate 20 % Sodium caprylate	20
11.	B-11	5 % Sodium benzoate 4.5 % Sodium acetate 15 % Sodium caprylate	15
12.	B-12	5 % Sodium acetate 3.5 % Beta Cyclodextrin 25% Sodium caprylate 5% Sodium benzoate	25
13.	B-13	5 % Sodium benzoate 5 % Sodium acetate 30 % Sodium caprylate	35
14.	B-14	4 % Sodium benzoate 4 % Sodium acetate 10 % Sodium caprylate	10
15.	B-15	5 % Sodium benzoate 5 % Sodium acetate 10 % Sodium caprylate	10
16.	B-16	5 % Sodium benzoate 4.5 % Sodium acetate 5 % Beta cyclodextrin	5
17.	B-17	5 % Sodium benzoate 3.5 % Sodium citrate 20 % Sodium caprylate 2.5 % Beta cyclodextrin	20

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2.3 Equilibrium Solubility Determination Of Diazepam In Selected Blends (B-8, B-9 & B-10)

In order to carry out the equilibrium solubility study of diazepam in Millipore water & various selected blends (table 1), 10ml of each solvent system was taken in the appropriate vials and then some excess amount of drug was added into each vial. Then, vials were subjected to continuous shaking in water bath incubator shaker for 24 hrs. Vials were found to contain suspensions. Then, vials were kept undisturbed for 12 hrs. After filtration through Whatman filter paper no. 41, the filtrates were suitably diluted with Millipore water and absorbances were measured at 312 nm against respective reagent blanks. Then equilibrium solubility of a drug in each blend was calculated by using the calibration curve. Solubility enhancement ratio is calculated as the ratio of solubility of a drug in the solution of blends and solubility of a drug in water (0.0483 mg/ml). Results are shown in table2.

Table 2: Results of equilibrium solubility studies of Diazepam in selected blends.

S. N0.	Blends	The composition of blends(w/v)	Equilibrium solubility (mg/ml)	Equilibrium solubility (%w/v)	Solubility enhancement ratio
1.	B-8	5% Sodium acetate 5% Sodium benzoate 20% Sodium caprylate	21.108 mg/ml	2.111%w/v	**43.706**
2.	B-9	5% Sodium benzoate 3. 5% Sodium acetate 25% Sodium caprylate	24.917mg/ml	2.492%w/v	**51.573**
3.	B-10	5% Sodium benzoate 5% Sodium citrate 20% Sodium caprylate	20.67mg/ml	2.067%w/v	**42.795**

2.4 PHYSICAL STABILITY OF DRUG IN THE PRESENCE OFSOLUBILIZERS

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 1:1 ratio and was filled in separate glass vials properly capped and sealed with teflon tape and kept undisturbed at different temperature conditions, at room temperature and in a refrigerator 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. The results observed were recorded in table 3.

Table 3. – Results of Physical stabilitytest

S.No	Drug-excipients mixture	Initial appearance	Storage conditions	
			Refrigerator (2-8°C)	Room temperature

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			Weeks				Weeks			
			1	2	3	4	1	2	3	4
1	DIAZEPAM	White powder	N	N	N	N	N	N	N	N
2	DIAZEPAM + SB	White powder	N	N	N	N	N	N	N	N
3	DIAZEPAM + SC	White powder	N	N	N	N	N	N	N	N
4	DIAZEPAM + SA	White powder	N	N	N	N	N	N	N	N
5	DIAZEPAM+βCD	White powder	N	N	N	N	N	N	N	N
6	DIAZEPAM + SCP	White powder	N	N	N	N	N	N	N	N

2.5 Selection Of Solubilizers Blends For Injection Formulation (Dry Powder Injection For Reconstitution)

On the basis of results obtained from solubility studies, three mixed blends in which solubility of diazepam was more than 15 mg/ml achieved were selected. Further selection was done on the basis of solubility enhancement ratio, desired solubility was achieved in presence of less amount of solubilizers such selected mixed blends were B-8, B-9, and B-10. To develop 1 ml of diazepam 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 diazepam in blends. The proposed formulations are shown in table 4, 5 and 6.

Table 4: Formulation DPF1

S.No	Ingredients	Formula for 5 mg /1 ml	Formula for 100 ml
1.	Diazepam	5.0 mg	500 mg
2.	Sodium benzoate	50. 0mg	5.0 g
3.	Sodium caprylate	200.0 mg	20.0 g
4.	Sodium acetate	50.0 mg	5.0 g

Table 5: FormulationDPF2

S.No	Ingredients	Formula for 5 mg /1 ml	Formula for 100 ml batch
1.	Diazepam	5 mg	500 mg
2.	Sodiumbenzoate	50 mg	5.0 g
3.	Sodium citrate	50 mg	5.0 g

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4.	Sodium caprylate	200 mg	20.0 g

Table 6: FormulationDPF3

S. No.	Ingredients	Formula for 5 mg /1 ml	Formula for 100 ml batch
1.	Diazepam	5 mg	500 mg
2.	Sodium benzoate	25 mg	2.5 g
3.	β cyclodextrin	25 mg	2.5 g
4.	Sodium citrate	25 mg	2.5 g
5.	Sodium caprylate	175 mg	17.5 g

2.6 FORMULATIONOF DRY POWDER INJECTION FORRECONSTITUTION.

The dry powder injections for reconstitution were formulated according to the formulation detail given in above tables, following the procedure 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. [Formulation DPF_1- 305 mg per vial, formulation DPF_2-305 mg per vial and formulation DPF_3-255 mg per vial.]

2.7 EVALUATION OF DRY POWDER INJECTION FORRECONSTITUTION

The prepared formulations were subjected for various evaluation parameters.

2.7.1 Determination Of Drug Content Of Dry Injection Formulation

In order to determine the drug content of DPF_1 formulation 305 mg powder was transferred to a 500 ml volumetric flask and about 400 ml Millipore water was added and the flask was shaken to solubilize it. After complete dissolution, the volume was made up to 500 ml with Millipore water and the absorbance of this solution was noted at 312 nm against reagent blank. Using the calibration curve, drug content was determined. The same procedure was repeated with DPF_2 &DPF_3.

Table 7: Drug content of reconstituted injection formulations

Formulation code	Drug content (in mg)
DPF_1	4.859
DPF_2	4.722
DPF_3	4.928

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2.7.2 Determination Of Ph Of Reconstituted injection

The developed formulations were reconstituted by Millipore water and approximately 10 ml volume was taken to determine the pH by using a digital pH meter (Cyber Scan 510, Eutech Instruments, Singapore). The results are shown in table8.

Table 8: pH values of reconstituted injection formulations

Formulation code	pH
DPF_1	6.479
DPF_2	6.946
DPF_3	6.792

2.7.3 THIN LAYER CHROMATOGRAPHIC STUDIES

To examine the possibility of interaction between drug and solubilizers, thin layer chromatographic studies were performed. Two plates of silica gel GF 254 were activated at 110°C for 1 hour and then used. The solution of diazepam in acetone alone and the aqueous solution containing diazepam in B-8, B-9, B-10,and B-12 were spotted with the aid of micro dropper on the baseline. Then, the plates were left in air for sufficient time to dry and transferred to the solvent jars saturated with the solvent system ethyl acetate. The solvent system was allowed to run for about 4 cm. Finally, the plates were allowed to air dry for 5 min and was observed for visualization of spots under iodine chamber. The respective Rf values were determined and recorded in the followingtable 9.

Table 9: Result of TLC studies

Adsorbent	Mobile Phases	Rf values	
Silica gel GF 254	**Chloroform: Acetone (8:3)**	Drug	DPF3
		0.72	0.73
	30 % Sodium Benzoate	0.74	0.73

2.7.4 DETERMINATION OF RECONSTITUTIONTIME

To determine the reconstitution time, Millipore 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 10.

Table 10: Reconstitution time of various formulations

Formulation code	Reconstitution time
DPF_1	1 min 50 sec
DPF_2	1 min 15 sec
DPF_3	1min 2sec

2.7.5 Clarity Testing Of Reconstituted Injection

Clarity test of the 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 table11.

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Table 11: Clarity of various reconstituted injections

Formulation code	Clarity
DPF1	Clear
DPF2	Clear
DPF3	Clear

2.7.6 Dilution Study Of Reconstituted Injection

Series of dilutions were done by diluting reconstituted injection of Diazepam (formulation DPF1, DPF2, and DPF3) 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 12,13 &14.

Table 12. Dilution profile of reconstituted solution of formulation DPF1

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

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Table13: Dilution profile of reconstituted solution of formulationDPF2

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	-	-	-	-	-	-	-	-	-	-	-	-

Table 14: Dilution profile of reconstituted solution of formulation DPF3

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	-	-	-	-	-	-	-	-	-	-	-	-

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III. RESULTS AND DISCUSSION

The UV visible spectroscopy of diazepam showed peak at 312 nm. From the calibration curve, equation is given as y = 0.0073x + 0.0011. The value of R^2 is 0.997. On the basis of obtained results, it was concluded that diazepam, obeyed Beers Lamberts law in the range of 10 mcg/ml to 50 mcg/ml. Based on solubility studies, desired solubility was observed in three blends which are **Blend-8, Blend-9, Blend-10.** These blends were selected for the batch formation. Dilution studies indicated that the formulations (DPF_1, DPF_2, and DPF_3) were stable (up to 24 hours) against precipitate formation in normal saline solution and 5% dextrose solution. In the case of batch formulation DPF_1 & DPF_3 initially there were precipitation but in DPF_2 no precipitation were found in any dilutionratio. There was no physical interaction found between drug and excipients. All the excipients were found to be stable with the drug. The result of TLC studies indicated that the Rf values of drug in both cases (pure drug and drug formulation were nearly same). This indicates that there was no chemical change in drug in the formulation.

IV. CONCLUSION

Mixed solvency concept has nicely been applied to formulate dry powder injection for reconstitution for diazepam. The problem of instability of drug in readymade injection can be solved by making dry powder injection for reconstitution using solid solubilizers (mixed solvency concept).

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