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Formulation Development of Dry Injection for Reconstitution of a Poorly Water Soluble Drug, Candesartan Cilexetil, Using Mixed Solvency Concept and their 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 possess 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 pharmaceutical 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 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, candesartan cilexetil, was selected as a drug and its dry injection for reconstitution was formulated. Candesartan cilexetil is an anti-hypertensive drug belonging to the category of angiotensin II type 1 (AT1) receptor antagonist (AII-RA). However, it has low aqueous solubility and undergoes extensive hepatic first pass metabolism, leading to poor drug bioavailability (15%) and therefore, higher doses are required to achieve the desired therapeutic efficacy. (BCS class II: highly permeable and low soluble). In order to get expected synergistic enhancement on solubility, various blends of solubilizers were tried thereby reducing the amount of individual solubilizer employed to achieve the desired solubility enhancement ratio. The successful completion of the research work was there for preparation of stable dry injection for reconstitution of candesartan cilexetil.***

Keywords: Mixed solvency concept, solubilization, candesartan cilexetil, solubility enhancement, dry injection for reconstitution

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[1-6] 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 eg. 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[7-28] 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. In the present investigation, the poorly water-soluble drug, candesartan cilexetil, has been selected as a drug for formulating its dry injection for reconstitution by using mixed solvency approach.

2. Materials and Methods

2.1 Materials

Candesartan cilexetil was obtained as gift sample from Cadila Healthcare Limited, Ahmedabad. All other chemicals and solvents employed were of analytical grade.

2.2 Methods

2.2.1 UV Spectrophotometric analysis of candesartan cilexetil

About 50 mg of candesartan cilexetil drug was accurately weighed and 400 ml of millipore water was taken in a volumetric flask of 500 ml capacity. Then the flask was shaken to dissolve the drug completely. After that, the volume was made with millipore water up to 500 ml to obtain the stock solution of 100 µg/ml concentration. The stock solution (10 ml) was taken and diluted up to 50 ml with millipore water to obtain dilution of 20 µg/ml concentration. The resulting solution was scanned between 200-400 nm on Shimadzu-1700 UV spectrophotometer against millipore water. The spectrum is shown in figure 1.

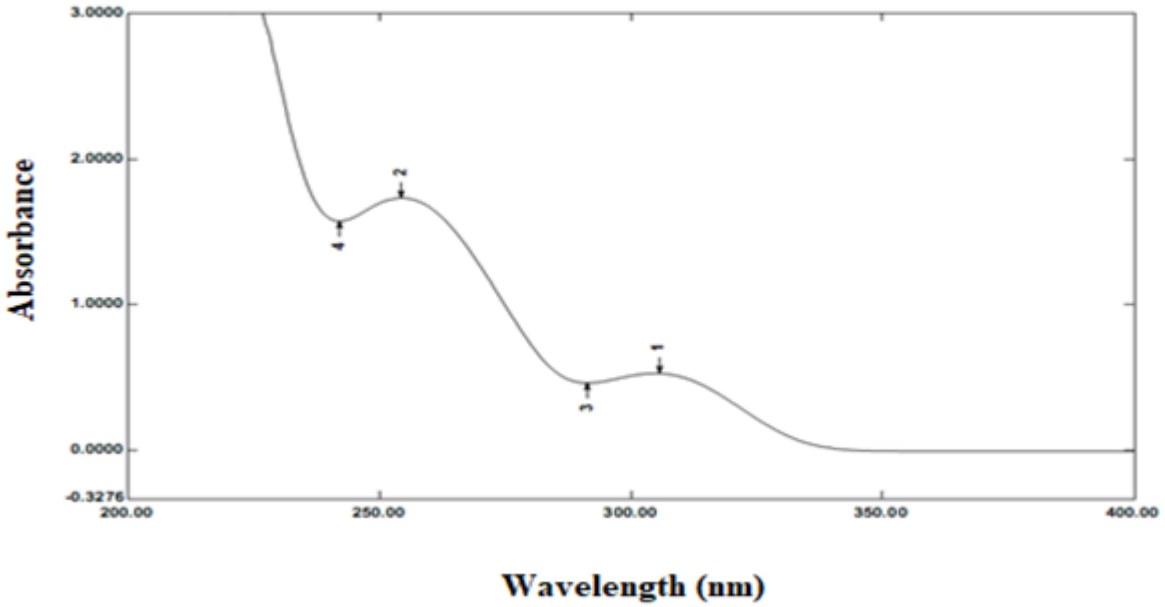

Figure 1: UV spectra of candesartan cilexetil in millipore water

2.2.2 DSC of Drug Sample

The DSC study was carried out on a Perkin Almer Differential Scanning Calorimeter with thermal analyzer. The drug sample (4.2 mg) was placed in an aluminium pan. The pan was placed on the heating cell after sealing. Heating at a rate of 20°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 50-260°C. Obtained DSC thermogram (melting isotherm) is shown in fig. 2.

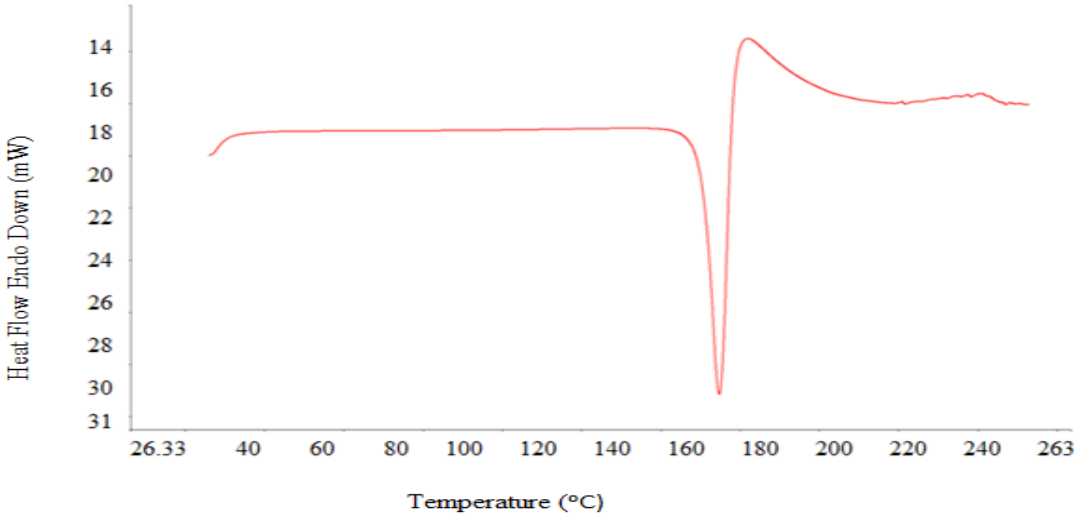

Figure 2: DSC spectrum of candesartan cilexetil drug sample

2.2.3 FT-IR Spectroscopy study

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

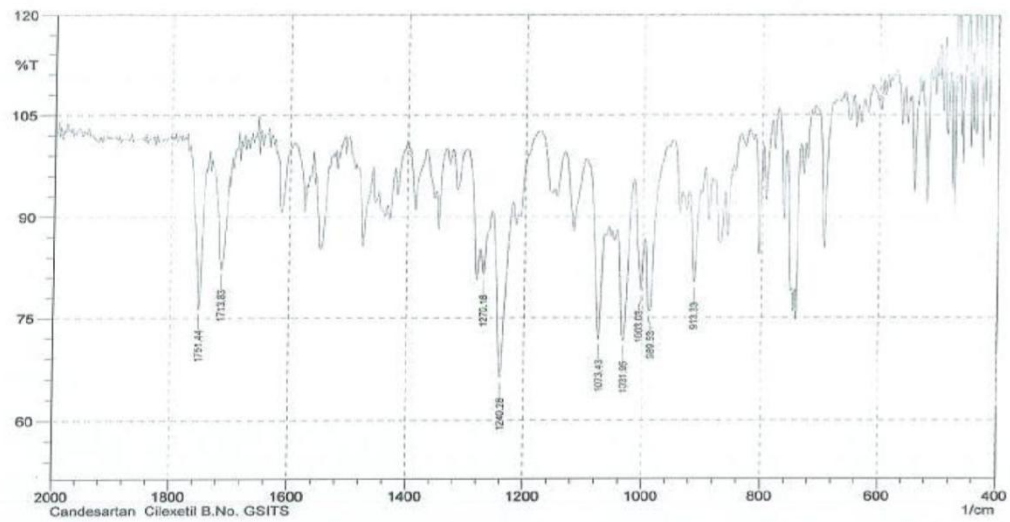

Figure 3: FTIR spectra of candesartan cilexetil

2.2.4 Preparation of calibration curve of candesartan cilexetil in millipore water

About 50mg of candesartan cilexetil drug was accurately weighed and transferred to a 50 ml volumetric flask. The drug was dissolved by addition of 20 ml of Blend-24 (sodium caprylate-30%, sodium benzoate-5%, sodium citrate-5%) and volume was made up to 50ml with millipore water, so as to obtain a solution of 1000 µg/ml. Above solution (0.5 ml) was taken and diluted up to 50 ml with millipore water to obtain the dilution of 10 µg/ml concentration. Likewise, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml solutions were taken and diluted up to 50 ml to obtain dilutions of 20, 30, 40 and 50 µg/ml concentrations, respectively. Absorbances of these solutions (10, 20, 30, 40, 50 µg /ml) were measured at 305 nm against the respective reagent blanks on Shimadzu-1700 UV spectrophotometer. The obtained data was graphically represented in figure 4.

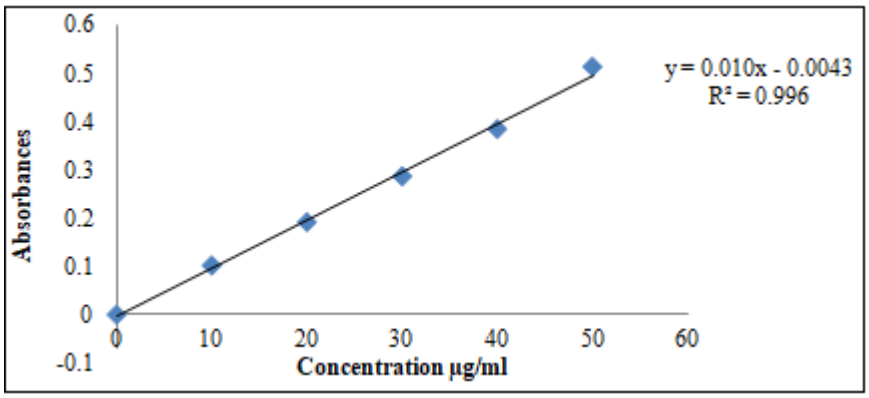

Figure 4: Calibration curve of candesartan cilexetil in millipore water

2.2.5 Approximate Solubility Determination of Candesartan Cilexetil in various Aqueous Solutions of Solid Solubilizers (Mixed Blends)

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

Table 1: Results of approximate solubility studies of candesartan cilexetil in various aqueous solutions of solubilizers.

S. No.	Blends	The composition of blends (w/v)	Approximate solubility (per ml)
1.	**B-1**	Sodium Caprylate 10 % Sodium Benzoate 5 % Sodium Citrate 5 %	10 mg/ml
2.	**B-2**	Sodium Caprylate 10 % Sodium Benzoate 5 % Sodium Acetate 5 %	10 mg/ml
3.	**B-3**	Sodium Caprylate 15 % Sodium Benzoate 2.5 % Sodium Citrate 2.5 %	20 mg/ml
4.	**B-4**	Sodium Caprylate 12.5 % Sodium Benzoate 2.5 % Sodium Acetate 2.5 % β-Cyclodextrin 2.5 %	10 mg/ml
5.	**B-5**	Sodium Caprylate 10 % Sodium Benzoate 5 % Sodium Acetate 2.5 %	10 mg/ml

		β-Cyclodextrin 2.5 %	
6.	**B-6**	Sodium Caprylate 12.5 % Sodium Benzoate 2.5 % Sodium Citrate 5 %	20 mg/ml
7.	**B-7**	Sodium Caprylate 12.5 % Sodium Benzoate 5 % Sodium Citrate 2.5 %	15 mg/ml
8.	**B-8**	Sodium Caprylate 12.5 % Sodium Benzoate 2.5 % Sodium Acetate 5 %	**20 mg/ml**
9.	**B-9**	Sodium Caprylate 12.5 % Sodium Benzoate 5 % Sodium Acetate 2.5 %	15 mg/ml
10.	**B-10**	Sodium Caprylate 17.5 % Sodium Benzoate 5 % Sodium Citrate 2.5 %	25 mg/ml
11.	**B-11**	Sodium Caprylate 17.5 % Sodium Benzoate 2.5 % Sodium Citrate 5 %	25 mg/ml
12.	**B-12**	Sodium Caprylate 17.5 % Sodium Benzoate 2.5 % Sodium Citrate 2.5 % β-Cyclodextrin 2.5 %	**25 mg/ml**
13.	**B-13**	Sodium Caprylate 15 % Sodium Benzoate 5 % Sodium Citrate 5 %	**20 mg/ml**
14.	**B-14**	Sodium Caprylate 17.5 % Sodium Benzoate 5 % Sodium Acetate 2.5 %	25 mg/ml
15.	**B-15**	Sodium Caprylate 17.5 % Sodium Benzoate 2.5 % Sodium Acetate 5 %	25 mg/ml
16.	**B-16**	Sodium Caprylate 17.5 % Sodium Benzoate 2.5 % Sodium Acetate 2.5 % β-Cyclodextrin 2.5 %	20 mg/ml
17.	**B-17**	Sodium Caprylate 15 % Sodium Benzoate 2.5 % Sodium Citrate 2.5 % β-Cyclodextrin 5 %	15 mg/ml
18.	**B-18**	Sodium Caprylate 15 % Sodium Benzoate 2.5 % Sodium Acetate 2.5 % β-Cyclodextrin 5 %	15 mg/ml
19.	**B-19**	Sodium Caprylate 20 % Sodium Benzoate 5 % Sodium Citrate 5 %	30 mg/ml
20.	**B-20**	Sodium Caprylate 25 % Sodium Benzoate 2.5 % Sodium Citrate 2.5 %	35 mg/ml
21.	**B-21**	Sodium Caprylate 25 % Sodium Benzoate 2.5 % Sodium Acetate 2.5 %	25 mg/ml
22.	**B-22**	Sodium Caprylate 20 % Sodium Benzoate 5 % Sodium Acetate 5 %	25 mg/ml
23.	**B-23**	Sodium Caprylate 30 % Sodium Benzoate 5 % Sodium Acetate 5 %	45 mg/ml
824.	**B-24**	Sodium Caprylate 30 % Sodium Benzoate 5 % Sodium Citrate 5 %	60 mg/ml

2.2.6 Determination of Equilibrium Solubility of Drug Candesartan Cilexetil in Millipore Water

The equilibrium solubility determination of drug candesartan cilexetil was carried out in millipore water. The excess amount of drug was added to 10 ml of water contained in a 20 ml glass vial and vial was sealed with closure. The vial was shaken for 12 hrs on mechanical bath shaker (Khera Instrument Pvt. Ltd., Delhi India) and then allowed to equilibrate for 24 hrs undisturbed. The solution containing drug was filtered through Whatmann filter no. 41. Aliquot of the filtrate was suitably diluted with millipore water and the dilution was analyzed on UV-Visible spectrophotometer (Shimadzu 1700). The result is presented in table 2.

Table 2: Equilibrium solubility of drug candesartan cilexetil in millipore water

S.No.	Solvent	Solubility (% w/v)
1.	Millipore water	0.00203

2.2.7 Equilibrium Solubility Determination of Candesartan Cilexetil in Selected Blends (B-8, B-12, B-13)

In order to carry out the equilibrium solubility study of candesartan cilexetil in various selected blends (table 3), 4ml of each blend 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 Whatmann filter paper no. 41, the filtrates were suitably diluted with millipore water and absorbances were measured at 305nm against reagent blank. 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 (0.0203 mg/ml). Results are shown in table 3.

Table 3: Results of equilibrium solubility studies of candesartan cilexetil in selected blends

S. No.	Blends	The composition of blends (w/v)	Equilibrium solubility (%)
1.	**B-1**	Sodium Caprylate 10 % Sodium Benzoate 5 % Sodium Citrate 5 %	1.90 %
2.	**B-2**	Sodium Caprylate 10 % Sodium Benzoate 5 % Sodium Acetate 5 %	2.69 %
3.	**B-3**	Sodium Caprylate 15 % Sodium Benzoate 2.5 % Sodium Citrate 2.5 %	2.37 %

2.2.8 Optimization of blend for preparation of dry powder for injection

On the basis of results obtained from solubility studies, the mixed blends (three) in which solubility of candesartan cilexetil was more than 15 mg/ml were selected. Further selection of blend was done on the basis of solubility enhancement ratio (keeping in mind to employ less amounts of solubilizers). Such selected mixed blends were B-8, B-12, and B-13. To develop 1 ml of candesartan cilexetil 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 candesartan cilexetil in blends. The proposed formulations are shown in table 4, 5 and 6.

Table 4: Formulation DPF_1

S. No.	Ingredients	Formula for 8 mg / 1 ml	Formula for 100 ml batch
1	Candesartan Cilexetil	8 mg	800 mg
2	Sodium Caprylate	125 mg	12.5 g
3	Sodium Benzoate	25 mg	2.5 g
4	Sodium Acetate	50 mg	5 g

Table 5: Formulation DPF_2

S. No.	Ingredients	Formula for 8 mg / 1 ml	Formula for 100 ml batch
1	Candesartan Cilexetil	8 mg	800 mg
2	Sodium Caprylate	150 mg	15 g
3	Sodium Benzoate	50 mg	5 g
4	Sodium Citrate	50 mg	5 g

Table 6: Formulation DPF_3

S. No.	Ingredients	Formula for 8 mg / 1 ml	Formula for 100 ml batch
1	Candesartan Cilexetil	8 mg	800 mg
2	Sodium Caprylate	175 mg	17.5 g
3	Sodium Benzoate	25 mg	2.5 g
4	Sodium Citrate	25 mg	2.5 g
5	β- Cyclo dextrin	25 mg	2.5 g

2.2.9 Formulation of dry powder injection for reconstitution

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

2.2.10 Evaluation of dry powder injection for reconstitution

The prepared formulations were subjected for various evaluation parameters

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a) Determination of pH of reconstituted injection

The developed formulations were reconstituted by use of millipore water and 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.

Table 7: pH values of reconstituted injection formulations

Formulation code	pH
DPF_1	8.94
DPF_2	8.35
DPF_3	8.27

b) Determination of reconstitution time

To determine the reconstitution time, millipore water (1 ml) was used to dissolve the dry injection formulation (by manual shaking) for all the batches and time were noted to obtain a clear solution. The reconstitution times obtained were recorded in table 8.

Table 8: Reconstitution times of various formulations

Formulation code	Reconstitution Time
DPF_1	1 min 5 sec
DPF_2	1 min 15 sec
DPF_3	55 sec

c) 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 9.

Table 9: Clarity of various reconstituted injections

Formulation code	Clarity
DPF_1	Clear
DPF_2	Clear
DPF_3	Clear

2.2.11 Stability study of candesartan cilexetil in dry powder injection

In order to investigate the stability of this drug in dry powder injection, the stability studies were performed. All the three above formulated batches of candesartan cilexetil dry powder injection samples were kept at two different temperatures (room temperature and 2-8^{o} C) for 3 months.

At time intervals of 1 week, samples were analyzed spectrophotometrically. The initial drug content in the formulation was taken as 100%. The % residual drug at definite time intervals was calculated and shown in fig. 5 to 7.

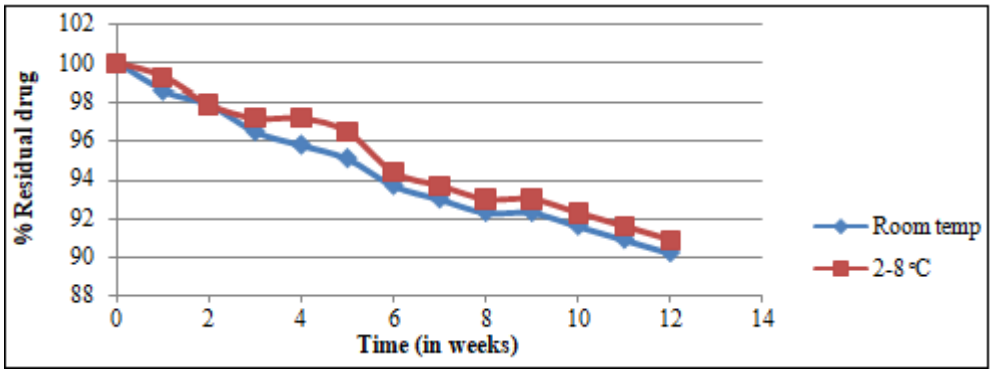

Figure 5: Degradation curve for the formulation DPF_1

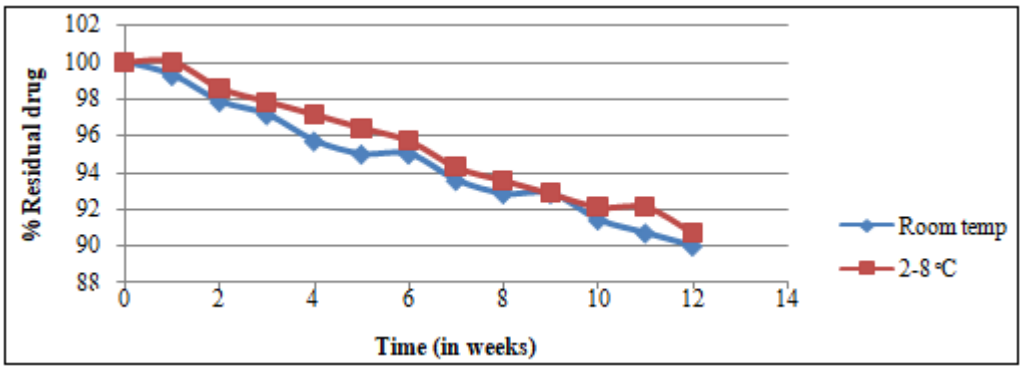

Figure 6: Degradation curve for the formulation DPF_2

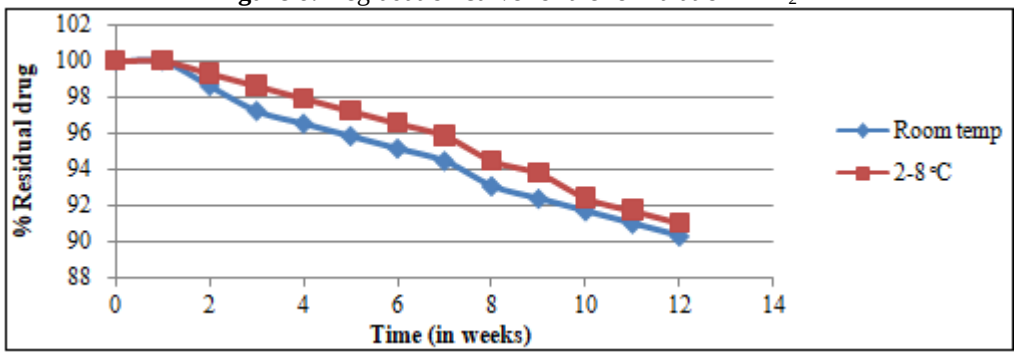

Figure 7: Degradation curve for the formulation DPF_3

2.2.12 Dilution study of reconstituted injection

Series of dilutions were done by diluting reconstituted injection of candesartan cilexetil (formulation DPF_1, DPF_2, and DPF_3) 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 10, 11 and 12.

Table 10: Dilution profile of reconstituted solution of formulation DPF_1

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 DPF_2

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 12: Dilution profile of reconstituted solution of formulation DPF_3

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

4. Results and Discussion

The UV visible spectroscopy of candesartan cilexetil showed peak at 305 nm, which is same as reported in literature (fig. 01). The DSC spectrum of candesartan cilexetil was same as reported in literature and principal peak was obtained at 162.92 °C. DSC curve was shown in figure 2. The infrared spectrum of candesartan cilexetil was concordant with the reference spectrum of candesartan cilexetil and the major peaks are shown in fig 3. From the calibration curve, equation is given as y = 0.010x - 0.0043. The value of R^2 is 0.996. On the basis of obtained result it was concluded that candesartan cilexetil, obeyed Beers Lamberts law in the range of 10 mcg/ml to 50 mcg/ml. Hence, it was inferred that the procured drug sample was pure candesartan cilexetil and hence used for further studies. Desired solubility was observed in three blends which are **Blend-8, Blend-12, Blend-13.** These blends were selected for the batch formation and were examined for

stability and other parameters. Solubilities were recorded in table 1. The results of chemical stability studies showed that the residual drug content at the end of 3 months was found to be 90.20% at room temperature and 90.90% at 2-8°C in DPF_1 formulation, for DPF_2 formulation it was found to be 90.00% at room temperature and 90.71% at 2-8°C and for DPF_3 it was found to be 90.34% at room temperature and 91.03% at 2-8°C. This indicates that the formulation DPF_3 will have longer-term stability at room temperature as compared to that of DPF_1 and DPF_2 formulations. 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_2, and DPF_3, no precipitation were found in any dilution ratio and results are shown in table 10,11 and 12.

5. Conclusion

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

6. Acknowledgement

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