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FORMULATION DEVELOPMENT OF AQUEOUS INJECTION OF A POORLY WATER-SOLUBLE DRUG (HYDROCHLOROTHIAZIDE) USING MIXED SOLVENCY CONCEPT AND ITS EVALUATION

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ABSTRACT

In this current era of pharmaceutical research, maximum newly invented drugs are found to be very poorly soluble in water. It poses difficulties in various developmental, manufacturing and administrating processes, which lead to the high failure of clinical trials of the drug due to poor pharmacokinetics. Parenteral dosage form could be expected to be an effective tool for avoiding the oral side effects and also achieving maximum bioavailability. Poor solubility of drugs in water is currently the 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 aqueous 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, hydrochlorothiazide was selected and its aqueous injection was formulated. Hydrochlorothiazide is a thiazide diuretic often considered a prototype member of this class. It reduces the reabsorption of electrolytes from the renal tubules. This leads to increased excretion of water and electrolytes, including sodium, potassium, chloride, and magnesium. It is used in the treatment of several diseases including edema, hypertension, diabetes insipidus, and hypoparathyroidism. (BCS class II: highly permeable and low soluble). Due to the poor water solubility of hydrochlorothiazide, the products are available in the market in tablet form. In order to get expected synergistic enhancement on solubility, various blends of solubilizers can be tried thereby reducing the amount of individual solubilizer employed to achieve the desired solubility enhancement ratio. Thus, the successful completion of the research work will enable the preparation of stable aqueous injection of hydrochlorothiazide.

Keywords: Mixed solvency concept, Hydrochlorothiazide, Solubility Enhancement, injection.

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, dimethylformamide, acetonitrile, ethyl acetate, toluene, carbon tetrachloride, acetone, hexane etc. The main drawbacks of organic solvents include high cost, toxicity, and pollution. Organic solvents have numerous 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

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solutions for this challenge. Maheshwari [1-5] has given a nice concept, known as a 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 eco-friendly 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[1-3] provides a means to develop innumerable solvent systems employing a 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 a high concentration of a single solubilizer can be solved in this manner. The solubility of a large number of poorly soluble drugs has been enhanced by mixed solvency concept. In the present investigation, the poorly water-soluble drug, hydrochlorothiazide, which is white crystalline solid powder, has been selected for formulating its aqueous injection by using mixed solvency approach.

MATERIALS & METHOD

Hydrochlorothiazide was obtained as gift sample from Schon Pharmaceuticals Limited, Indore. All other chemicals and solvents employed were of analytical grade.

Preparation of calibration curve of hydochlorothiazide in demineralized water

About 50mg of hydrochlorothiazide drug was accurately weighed and transferred to a 50 ml volumetric flask. The drug was dissolved by addition of 20 ml of 30% sodium benzoate solution and volume was made up to 50ml with demineralised water (DM water), so as to obtain a solution of 1000 µg/ml. One ml of the above solution was taken and diluted up to 50 ml with DM water to obtain the dilution of 20 µg/ml concentration. Likewise, 2.0 ml, 3.0 ml, 4.0 ml, 5.0 ml solutions were taken and diluted up to 50 ml to obtain dilutions of 40, 60, 80 and 100 µg/ml concentrations, respectively. Absorbances of these solutions (20, 40, 60, 80, 100 µg /ml) were measured at 317 nm against the respective reagent blanks on Shimadzu-1700 UV spectrophotometer [6-16]. The data is graphically represented in figure 1&2.

FT-IR Spectroscopy study

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

DSC of Drug Sample

The DSC study was carried out on a Perkin Almer differential scanning calorimeter with a 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 20ºC/min with a continuous purge of nitrogen (45 CC/min) was done with a recording of energy changes in the sample with respect to an empty aluminium pan as a reference in the temperature range of 20-350ºC. Obtained DSC thermogram (melting isotherm) is shown in fig. 4.

Solubility determination of drug in various aqueous solutions of solubilizers (Mixed Blends)

i) Approximate solubility determination 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 25 mg of hydrochlorothiazide drug was transferred to this flask and vigorous shaking was done for 15-20 minutes to dissolve the drug. If a drug does not dissolve completely to give a clear solution then another 0.5 ml of the blend was added to the flask. Again, vigorous shaking was done. The same process was repeated until drug got solubilize completely to give a clear solution. The same procedure was repeated for all blends to get approximate solubility of hydrochlorothiazide. Amount dissolved per ml of a solvent system was determined. Table 1 gives the results of the solubility studies.

Result and Discussion: The desired solubility was observed in the three blends i.e. **B-9, B-13, B-15.** These blends were selected for the equilibrium solubility study.

ii) Equilibrium solubility determination of hydrochlorothiazide in selected blends (AB-5, AB-6, AB-7)

In order to carry out the equilibrium solubility of hydrochlorothiazide in various selected blends (table 2), 4ml of each blend was taken in the appropriate vials and then some excess amount of drug was added into each vial. The vials were found to contain an excess drug. Then vials were subjected to continuous shaking in water bath incubator shaker for 24 hrs. Then, vials were kept undisturbed for 12 hrs. After filtration through Whatmann filter paper no. 41, the filtrates were suitably diluted with DM water and absorbances were measured at 317 nm. 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 (0.812mg/ml). Results are shown in table 2.

Chromatographic study of solubilized drug product

In order to examine the possibility of interaction between drug and solubilizers, 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 solution of hydrochlorothiazide in acetone alone and the aqueous solution of solubilizers containing hydrochlorothiazide in AF_1, AF_2, AF_3 were spotted with the aid of microdropper on the baseline. Then, the plate was left in air for sufficient time to dry and transferred to a solvent jar saturated with the solvent system ethyl acetate. The solvent system was allowed to run for about 4 cm. Finally, the plate was allowed to air dry for 5 min and was observed for visualization of spots under iodine chamber. The respective RF values were determined and recorded in table 3.

Physical stability of the drug in the presence of solubilizers

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

Optimization of a blend for preparation of aqueous injection

On the basis of results obtained from solubility studies, the mixed blends in which solubility of hydrochlorothiazide was more than 10 mg/ml were selected. Such selected mixed blends were AB-5, AB-6, and AB-7. To develop 2 ml of hydrochlorothiazide 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 hydrochlorothiazide in individual blends. The proposed formulations are shown in table 3, 4 and 5.

Formulation of aqueous injection for reconstitution

Initially, the appropriate weighed amounts (required for 100 ml) of solubilizers were transferred to the volumetric flask of 100 ml capacity containing 70 ml of DM water. The flask was shaken to dissolve the solubilizers. The volume was made up to the mark with the same DM water. To prepare the aqueous injection of a drug, the calculated quantity of hydrochlorothiazide was transferred to another volumetric flask (100 ml) and prepared blend solution was added to dissolve the drug and shaken vigorously to assure complete dissolution of the drug. After complete dissolution, volume was made up to the mark with the same prepared blend and shaken to get a homogenous solution. This solution was kept in pre-washed and dried airtight glass bottle and drug content was determined on the same day. As soon as the injection is formulated, it is subjected to studies like physical stability studies, the freeze-thaw cycle, and chemical stability studies. For this, required numbers (30 vials for each batch) of pre-washed and oven dried (at 160°C for 2 hours in an inverted position) glass vials along with rubber closures and aluminium seals were taken and in each vial 2ml of formulation was filled and was properly sealed. These prepared formulations were used for further studies [17-24].

Evaluation of dry injection for reconstitution

The prepared formulations were subjected for various evaluation parameters

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- **Freeze-thaw cycling (FTC)**

This method was designed to simulate storage and temperature conditions and to induce any anticipated precipitation and check it in a much shorter time. The vials were kept alternately at 25±1°C and 4±1°C for 24 hours each and shaken every day for 5 minutes on a touch type vortex mixer. Two vials of each formulation were taken, one of which was kept at 25±1°C and the other at 4±1°C for the first day, followed by subsequent temperature cycling and shaking as described. After 7-7 such cycles at 4±1°C and 25±1°C (alternately), the vials were visually observed in good light to check turbidity and precipitation, if any.

Determination of drug content of aqueous injection formulation

In order to determine the drug content of AF_1 formulation, quantity sufficient ingredients for 2ml formula was transferred to a 500 ml volumetric flask and about 400 ml DM water was added and the flask was shaken to solubilize it. After complete dissolution, the volume was made up to 500 ml with DM water and the absorbance of this solution was noted at 317 nm. Using the calibration curve, drug content was determined. The same procedure was repeated with AF_2 & AF_3.

Determination of pH of the developed aqueous injection

The pH of prepared formulations was determined using a digital pH meter (Cyber Scan 510, Eutech Instruments, Singapore). The pH so obtained were recorded in table 9.

Chemical stability study and degradation kinetics of hydrochlorothiazide in aqueous injection

In order to investigate the degradation kinetics of this drug in aqueous injection, the stability studies of hydrochlorothiazide were performed. Degradation study was performed by keeping all the three above formulated batches of hydrochlorothiazide aqueous injection samples

at two different temperatures (room temperature and 2-8° C) for 3 months.

At time intervals of 1 week, samples were dissolved with sufficient DM water and diluted with DM water up to 1000 ml and analyzed by UV/Visible spectrophotometer (Shimadzu 1700) against respective reagent blanks at 317 nm to determine the amount of drug remaining in the formulation [25-32]. The initial drug content in the formulation was taken as 100%. The % residual drug at definite time intervals were calculated and shown in table 10 to 12 and fig. 1 to 3.

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

S.no.	Blend	Composition of blends (% w/v or % v/v)	Approximate solubility (mg/ml)
1.	**AB-1**	5% Ethanol+5% Tween 80+6%PEG 400+5% Sodium benzoate+5% PVP K25+4% Benzyl alcohol	8.3mg/ml
2.	**AB-2**	5% Ethanol+5% Propylene glycol+5% Sodium benzoate+5% PVP K25+5% PEG 400	5.0mg/ml
3.	**AB-3**	2.5% PEG4000+5% Tween 80+7.5% PEG 400+5% Sodium benzoate+6% PVP K25 +4% Benzyl alcohol	10.0mg/ml
4.	**AB-4**	2% Benzyl alcohol+10% PEG400+3% Tween 80+5% PVPK25+5% Sodium benzoate	12.5mg/ml
5.	**AB-5**	5% Ethanol+5% Tween 80+5% PEG 400 +5% Sodium benzoate+3% PVP K25+2% PEG4000	**13.3mg/ml**
6.	**AB-6**	3% Ethanol+5% Tween 80+10% PEG 400+5% Sodium benzoate+2% PEG4000	**13.3mg/ml**
7.	**AB-7**	2% Propylene glycol+5% Tween 80+5% PEG 400+5% Sodium benzoate+3% PVP K25	**13.3mg/ml**
8.	**AB-8**	5% Ethanol+5% Tween 80+2% PEG 400+5% Sodium benzoate+5% PVP K25+4% Benzyl alcohol	8.3mg/ml
9.	**AB-9**	5% Ethanol+5% Propylene glycol+5% Sodium benzoate+5% PVP K25+5% PEG 400	12.5mg/ml
10.	**AB-10**	2.5% PEG4000+5% Tween 80+2.5% PEG 400+5% Sodium benzoate+6% PVP K25+4% Benzyl alcohol	5.0mg/ml

Table 2: Results of equilibrium solubility studies of hydrochlorothiazide in selected blends

S. No.	Blends	The composition of blends (w/v)	Equilibrium solubility (mg/ml)	Equilibrium solubility (%w/v)	Solubility enhancement ratio
1.	**AB-5**	5% Ethanol+5% Tween 80+5% PEG 400+5% Sodium benzoate+3% PVP K25+2% PEG4000	13.54mg/ml	1.35%	16.71
2.	**AB-6**	3% Ethanol+5% Tween 80+10% PEG 400+5% Sodium benzoate+2% PEG4000	24.15mg/ml	2.41%	29.81
3.	**AB-7**	2% Propylene glycol+5% Tween 80+5% PEG 400+5% Sodium benzoate+3% PVP K25	18.20mg/ml	1.82%	22.46

Table 3: Results of TLC studies

Solvent System	Adsorbent	R_f Value			
		HCTZ/acetone	AF_1	AF_2	AF_3
Ethyl acetate	Silica Gel GF 254	0.44	0.41	0.47	0.51

Table 4: Formulation AF_1

S. No.	Ingredients	Formula for 25 mg/2 ml	Formula for100 ml batch
1	Hydrochlorothiazide	25.0 mg	1.25g
2	Ethanol	0.10 ml	5.0 ml

3	Tween 80	0.10 ml	5.0 ml
4	PEG 400	0.10 ml	5.0 ml
5	Sodium benzoate	100.0 mg	5.0 gm
6	PVP K25	60.0 mg	3.0 gm
7	PEG 4000	40.0 mg	2.0 gm
8	DM water	q. s. to 2 ml	q. s. to 100 ml

Table 5: Formulation AF_2

S. No.	Ingredients	Formula for 25mg/2 ml	Formula for100 ml batch
1	Hydrochlorothiazide	25.0 mg	1.25g
2	Ethanol	0.06 ml	3.0 ml
3	Tween 80	0.10 ml	5.0 ml
4	PEG 400	0.20 ml	10.0 ml
5	Sodium benzoate	100.0 mg	5.0 gm
6	PEG 4000	40.0 mg	2.0 gm
7	DM water	q. s. to 2 ml	q. s. to 100 ml

Table 6: Formulation AF_3

S. No.	Ingredients	Formula for 25mg/2 ml	Formula for100 ml batch
1	Hydrochlorothiazide	25.0 mg	1.25 g
2	Tween 80	0.10 ml	5.0 ml
3	PEG 400	0.10 ml	5.0 ml
4	Sodium benzoate	100.0 mg	5.0 gm
5	PVP K25	60.0 mg	3.0 gm
6	Propylene glycol	0.04 ml	2.0 ml
7	DM water	q. s. to 2 ml	q. s. to 100 ml

Table 7: Observations of freeze-thaw cycling

Formulation code	Precipitate or turbidity
AF_1	Not observed
AF_2	Not observed
AF_3	Not observed

Table 8: Drug content of aqueous injection formulations

Formulation code	Drug content (in mg)
AF_1	23.91
AF_2	24.75
AF_3	23.63

Table 9: pH values of developed injection formulations

Formulation code	pH
AF_1	6.81
AF_2	6.93
AF_3	6.77

Table 10: Chemical stability data of hydrochlorothiazide in formulation AF_1

Weeks	% Residual drug	
	Room temperature	2-8 ºC
0	100.00	100.00
1	99.82	99.87

2	99.64	99.73
3	99.15	99.46
4	98.98	99.01
5	98.30	98.92
6	98.11	98.32
7	97.96	98.06
8	97.61	97.36
9	96.00	96.24
10	95.52	95.88
11	95.15	95.39
12	94.03	94.67

Table 11: Chemical stability data of hydrochlorothiazide in formulation AF_2

Weeks	**% Residual drug**	
	Room temperature	**2-8 ºC**
0	100.00	100.00
1	99.80	99.56
2	99.44	99.28
3	99.04	98.80
4	98.78	98.55
5	98.43	98.19
6	98.07	97.95
7	97.71	97.35
8	97.47	97.23
9	96.81	96.87
10	96.23	96.39
11	95.51	95.76
12	94.99	95.08

Table 12: Chemical stability data of hydrochlorothiazide in formulation AF_3

Weeks	**% Residual drug**	
	Room temperature	**2-8 ºC**
0	100.00	100.00
1	99.76	99.64
2	99.39	99.27
3	98.99	98.91
4	98.54	98.42
5	97.88	97.93
6	97.18	97.33
7	96.32	96.45
8	95.84	95.94
9	95.35	95.63
10	94.86	95.07
11	94.26	94.83
12	93.77	94.16

Figure 1: UV spectra of hydrochlorothiazide

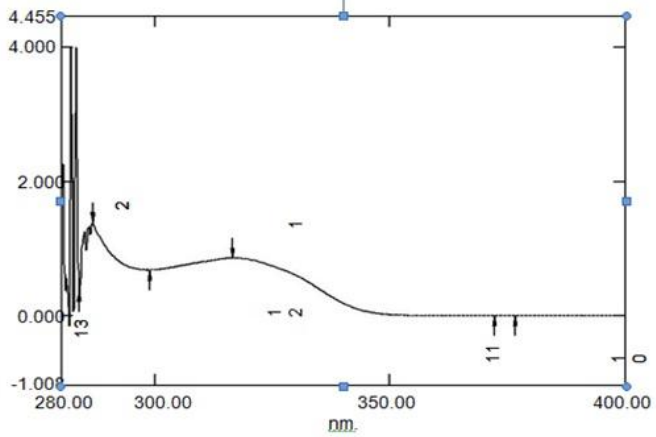


Figure 2: Calibration curve of hydrochlorothiazide in demineralized water

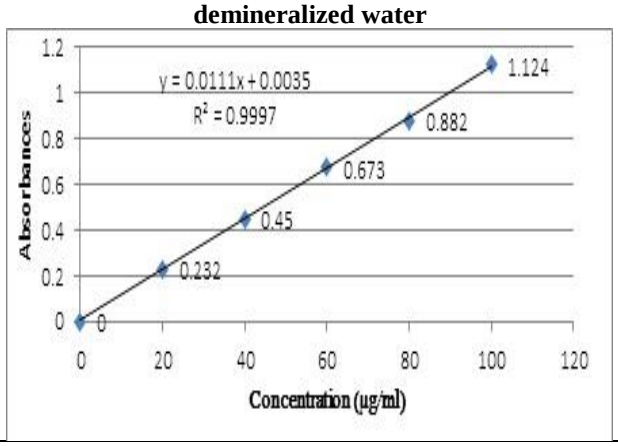


Figure 3: FTIR spectra of hydrochlorothiazide

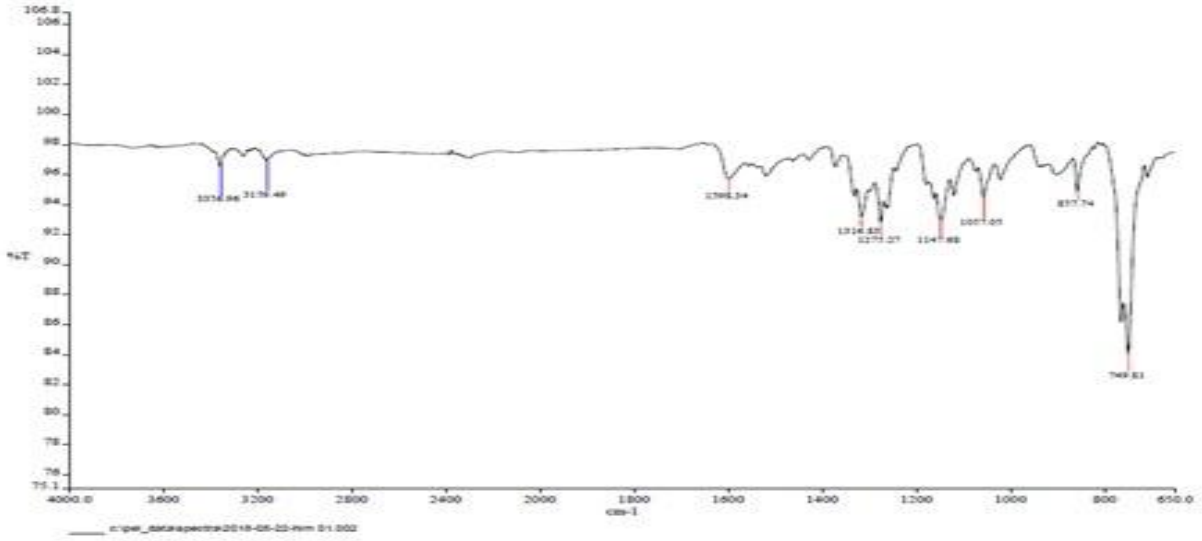


Figure 4: DSC spectrum of hydrochlorothiazide drug sample

Fig. 5: Degradation curve of HCTZ in aqueous injection formulation AF_1

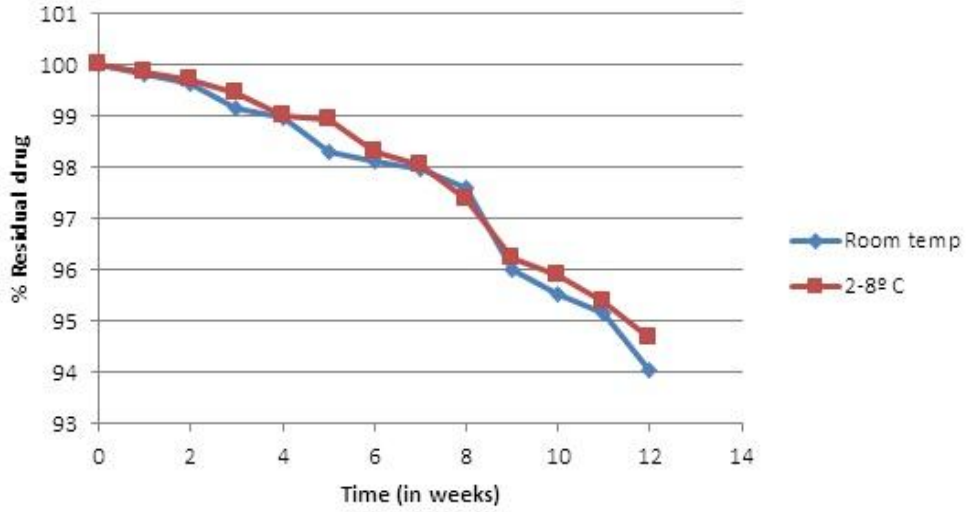


Fig. 6: Degradation curve of HCTZ in aqueous injection formulation AF_2

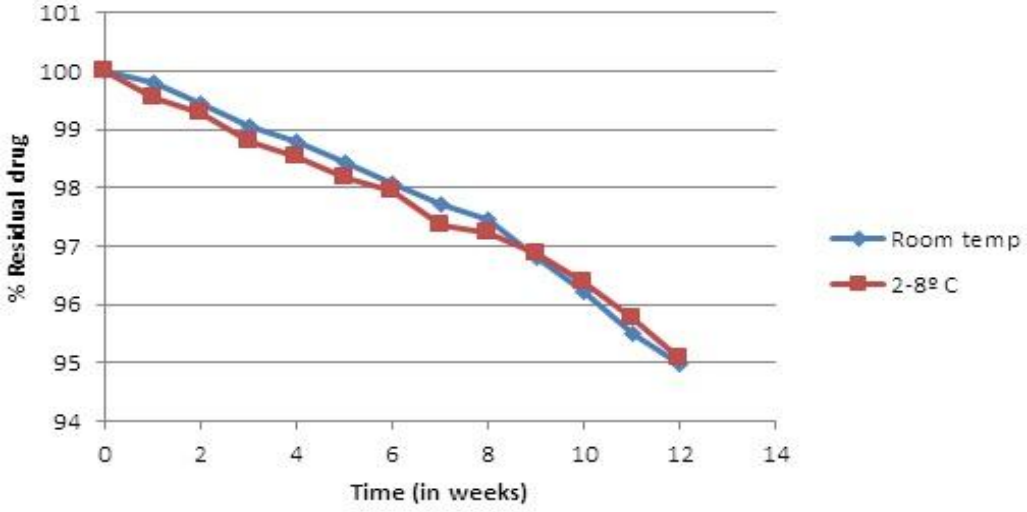
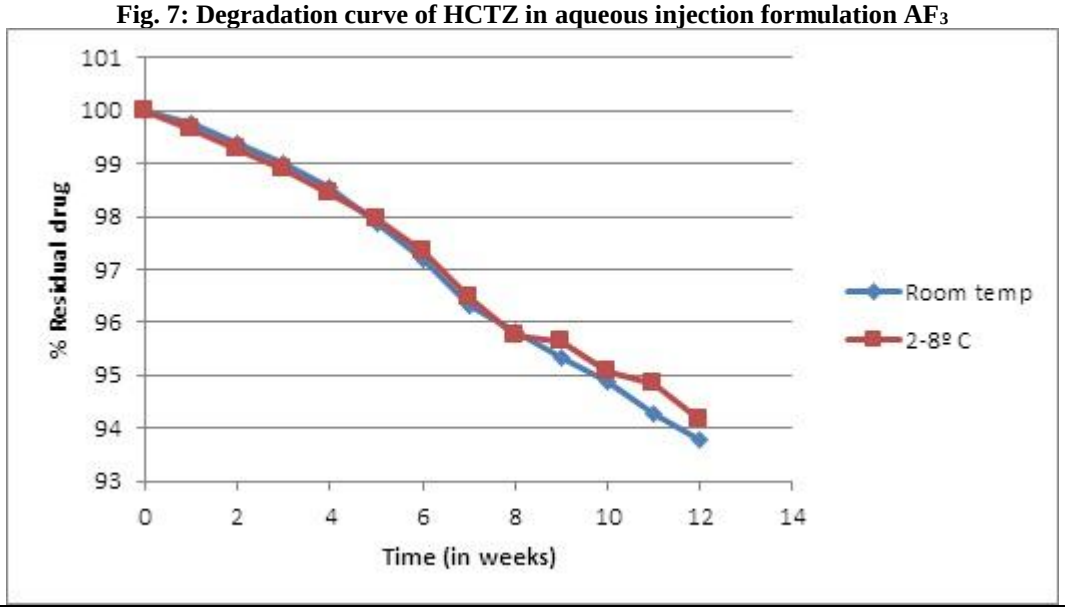


Fig. 7: Degradation curve of HCTZ in aqueous injection formulation AF_3



RESULTS AND DISCUSSION

The UV visible spectroscopy of hydrochlorothiazide showed a peak at 317 nm, which is same as reported in the literature (fig. 01). Calibration curve equation was found to be y=0.011x+0.003. The value of R^2 is 0.999. On the basis of the obtained result, it was concluded that hydrochlorothiazide, obeyed Beers Lambert's law in the range of 20 mcg/ml to 100 mcg/ml. The infrared spectrum of hydrochlorothiazide was concordant with the reference spectrum of hydrochlorothiazide and the major peaks are shown in fig 3. The DSC spectrum of hydrochlorothiazide was same as reported in the literature and the principal peak was obtained at 274.58ºC. Hence, it was inferred that the procured drug sample was pure hydrochlorothiazide and hence used for further studies. DSC curve was shown in figure 4. The desired solubility was observed in three blends which are BlendAB-5, BlendAB-6, BlendAB-7. These blends were selected for the batch formation and will be examined for stability and other parameters and solubility recorded in table 1. The results of TLC study from table 2, revealed that there is no significant change in Rf values of hydrochlorothiazide in acetone and hydrochlorothiazide in solubilizers blend solutions. From the results of TLC study, it can be concluded that there is no salt formation or complexation of the drug with solubilizer molecules. All solubilizers were found compatible with hydrochlorothiazide. The results of chemical stability studies showed that the residual drug content at the end of 3 months was found to be 94.03% at room temperature and 94.67% at 2-8°C in AF_1 formulations, for AF_2 formulation it was found to be 94.99% at room temperature and 95.08% at 2-8º C and for AF_3 it was found to be 93.77% at room temperature and 94.16% at 2-8º C. This indicates that the formulation AF_2 will have longer-term stability at 2-8º C temperature as compared to that of AF_1 and AF_3 formulations [33-39].

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