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FORMULATION AND DEVELOPMENT OF SOLID DISPERSION OF POORLY WATER SOLUBLEDRUG, HYDROCHLOROTHIAZIDE, WITH THE HELP OF MIXED SOLVENCY CONCEPT AND THEIR EVALUATIONS

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Abstract:

The aim of the present research work is to explore the application of mixed solvency concept to formulate and develop a fast dissolving solid dispersion. In the present study, poorly soluble drug, hydrochlorothiazide (model drug) was tried to be solubilized by employing the combination of physiologically compatible water soluble additives (solubilizers) to formulate its fast dissolving solid dispersion. For poorly water soluble drug hydrochlorothiazide, combination of solubilizers such as sodium caprylate, sodium benzoate, sodium acetate, lysine hydrochloride, and poloxomer 407 as mixed solvent systems were used to decrease the overall concentration of solubilizer required to produce substantial increase in solubility of hydrochlorothiazide. The procured sample of hydrochlorothiazide was characterized by melting point, UV, and DSC studies. Mixed solvency concept has been successfully employed for enhancing drug loading of poorly water soluble drug, hydrochlorothiazide.

Keywords: Mixed Solvency Concept, Hydrotropy, Hydrochlorothiazide, Solid Dispersion, Solubility.

1. INTRODUCTION:

As per the mixed solvency concept proposed by Dr. R.k. Maheshwari[1-4], each and every substance present in the universe has got solubilizing property i.e. all the liquids, gases and solids possess solubilizing power. As per his statement, each substance is solubilizer. A concentrated aqueous solution containing various water-soluble substances may act as good solvent for poorly water-soluble drugs. Such concentrated solutions may show synergistic or additive solubilizing actions of solubilizers present in the solution for a particular solute. By combining various excipients, additive and synergistic solvent actions are expected which has advantage of reducing the toxicities. For a desired solubility enhancement, a single solubilizer may prove toxic for human being but the combination of different excipients in safe smaller concentrations solves the problem of toxicity for same desired solubility of drug. A large number of drugs have been studied for solubility enhancement using mixed solvency concept.[5-31]

Solid dispersion technique has been utilized to increase the dissolution and thereby the rate of absorption and total bioavailability of poorly water- soluble drugs. The common methods of making solid dispersion are solvent evaporation, fusion- solvent evaporation, fusion and fusion solvent methods.[32-38]The use of organic solvent is completely precluded if the solid dispersion is prepared using hydrotropy, mixed hydrotropy and mixed solvency concept. The hydrotropic agents (water soluble carriers) are hydrophilic in nature and while the drug is insoluble in water. A large amount of hydrotropic agent is used to solubilize the drug in water. Later, water (solvent) is removed to obtain dried solid dispersion. In case, hydrotropic agent is not used, the

drug is insoluble in water, hence, this method is different from common solvent method which makes mixed solvency techniques of highest utilization.

2. MATERIAL

Hydrochlorothiazide was obtained as gift sample from Schon Pharmaceuticals Limited, Indore.

3. DRUG CHARACTERIZATION

3.1 UV SPECTROPHOTOMETRIC ANALYSIS OF DRUG HYDROCHLOROTHIAZIDE

About 50 mg of hydrochlorothiazide was weighed accurately and dissolved in 400 ml D.M. water in a 500 ml volumetric flask. Then the flask was shaken so that the drug dissolves completely. After that, volume was made up to 500 ml with D.M. water to obtain a 100 mcg/ml concentration stock solution. Ten ml stock solution was taken and diluted up to 50 ml with D.M. water to obtain a 20 mcg/ml concentration. The resulting solution was scanned between 200-400 nm on a (Shimadzu-1700) UV spectrophotometer against demineralized water. The spectrum is depicted in figure 1.

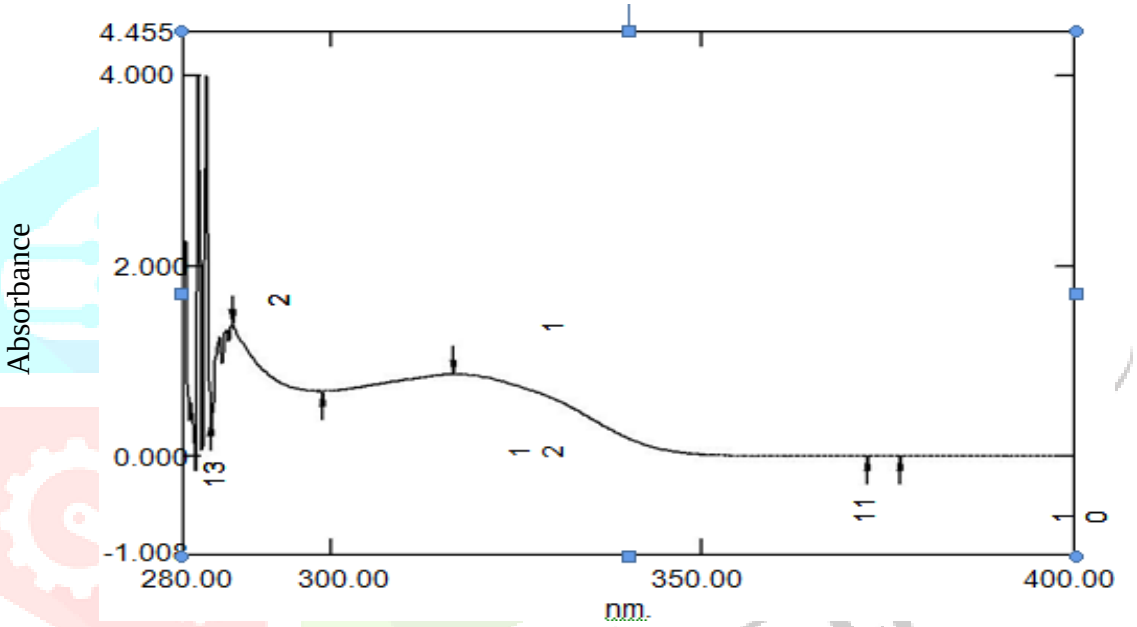

Figure 1: The UV spectrum of hydrochlorothiazide

Result and discussion- The UV spectrum of the sample displayed a peak at 317 nm for hydrochlorothiazide which is concordant to that reported in the literature.

3.2 DETERMINATION OF MELTING RANGE OF DRUG HYDROCHLOROTHIAZIDE

The open capillary method was used to examine the melting range of hydrochlorothiazide. The drug powder sample (hydrochlorothiazide) was filled into a capillary tube with one end closed and connected to a thermometer mounted in a liquid paraffin-filled Thiele's tube. The tube was heated, and the drug melting range was calculated.

Result and discussion- The melting point range of the sample of hydrochlorothiazide drug was hound to be 269-278 ℃, which is comparable to the value reported in the literature.

3.3DSC STUDY OF HYDROCHLOROTHIAZIDE DRUG SAMPLE

The DSC study was accomplished on a Perkin Almer differential scanning calorimeter with thermal analyzer. The drug sample (2.9 mg) was placed in an aluminium pan. The pan was placed on the heating cell after sealing. Heating at a rate of 20^{o} 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 20-350^{o}C. Obtained DSC thermogram (melting isotherm) is depicted in figure 2.

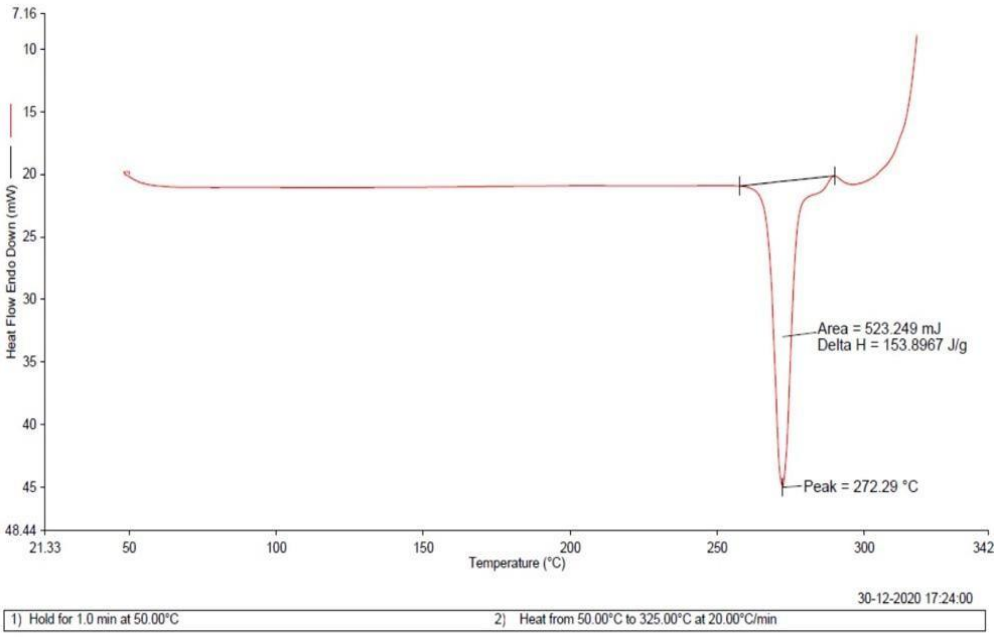

Figure 2: DSC graph of hydrochlorothiazide

Result: The range of melting point was observed from 264-280^{o}C while sharp peak appears as evident at 272.29^{o}C which is very close to the melting point recorded in literature 268-275^{o}C. Also the narrow peak area indicates the purity of drug.

4. PREFORMULATION STUDIES

4.1 PREPERATION OF CALIBRATION CURVE OF HYDROCHLOROTHIAZIDE IN D.M. WATER

About 100 mg of hydrochlorothiazide drug was weighed accurately and transferred to a 100 ml volumetric flask. After this, 20 ml of 30% (w/v) of sodium benzoate solution was added, and the flask was shaken to dissolve the drug. Then the volume was made up until 100 ml with D.M. water to prepare 1000 mcg/ml solution. Appropriate dilutions were made with D.M. water to obtain 20, 40, 60, 80 and, 100 mcg/ml solutions of the drug. Absorbance of these solutions (20, 40, 60, 80, 100 mcg/ml) were measured at 317 nm against respective reagent blanks on UV spectrophotometer (Shimadzu-1700). Table 1 shows the results of a calibration curve. The data of the calibration curve is represented in the table 1and graph in figure 3.

Table 1: Absorbance data for calibration curve of hydrochlorothiazide in D.M. water (in the presence of sodium benzoate) at 317 nm

S. no.	Concentration of drug (mcg/ml)	ean absorbances ± standard deviation (n=3)
1.	0	0.000 ± 0.0000
2.	20	0.239 ± 0.0049
3.	40	0.488 ± 0.0032
4.	60	0.736 ± 0.0028
5.	80	0.941 ± 0.0054
6.	100	1.197 ± 0.0024

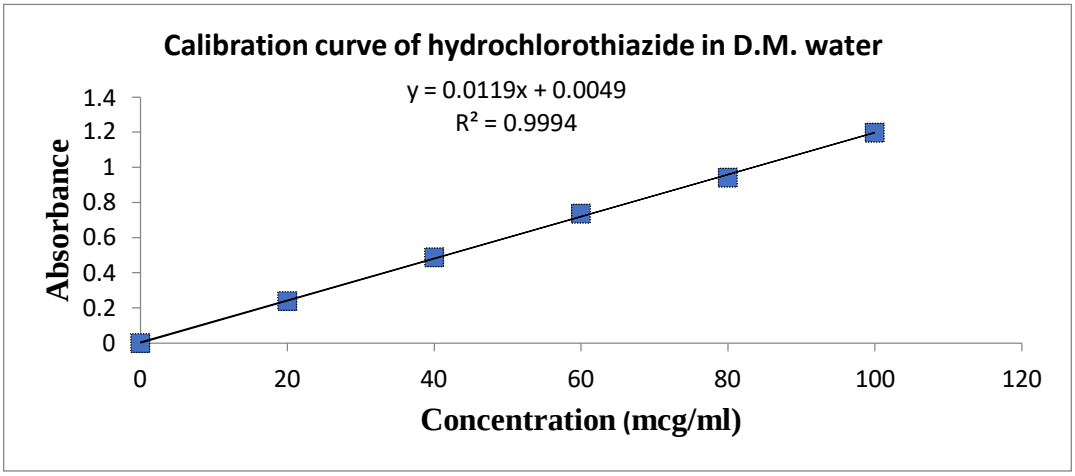

Figure 3: Calibration curve of hydrochlorothiazide in D.M. water

4.2 PREPERATION OF CALIBRATION CURVE OF HYDROCHLOROTHIAZIDE IN 0.1 N HCl

About100 mg of drug hydrochlorothiazide was accurately weighed and transferred to a 100 ml volumetric flask. After this, 20 ml of 20 % sodium caprylate solution was added, and the flask was shaken to dissolve the drug. Then, the volume was made up until 100 ml with the help of 0.1 N HCl. This 1000 mcg/ml stock solution was appropriately diluted to prepare solutions of different concentrations (20-100 mcg/ml). The absorbance of the resulting drug solutions were measured at 317 nm. Data was recorded in table 2 and graphically represented in figure 4.

Table 2: Absorbance data for calibration curve of hydrochlorothiazide in 0.1 N HCl at 317 nm

S. no.	Concentration of drug (mcg/ml)	Mean absorbances ± standard deviation (n=3)
1.	0	0.00 ± 0.0000
2.	20	0.272 ± 0.0020
3.	40	0.503 ± 0.0016
4.	60	0.765 ± 0.0017
5.	80	1.041 ± 0.0024
6.	100	1.295 ± 0.0017

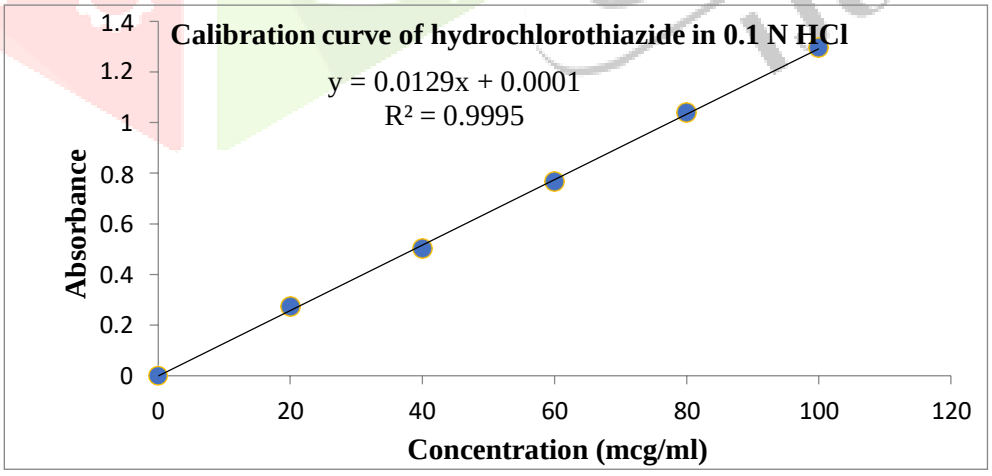

Figure 4: Calibration curve of hydrochlorothiazide in 0.1 N HCl at 317 nm

4.3 DETERMINATION OF APPROXIMATE SOLUBILITY STUDIES OF HYDROCHLOROTHIAZIDE IN DIFFERENT BLENDS

- **DETERMINATION OF APPROXIMATE SOLUBILITY IN DIFFERENT BLENDS AT ROOMTEMPERATURE**

Different blends were prepared with different solubilizers, and 2.5 mg drug was added to 1 ml of each blend. The vials were shaken for about 20 minutes to dissolve the drug altogether, again 2.5 mg of drug was added in batches with shaking for 20 minutes until a suspension was obtained similar procedure was followed for all the blends, and the approximate solubility of the drug was determined. The results are mentioned in table 3.

Table 3: Results of approximate solubility studies of hydrochlorothiazide in different blends at room temperature

S. no.	Blend	Composition	Approximate solubility (mg/ml)
1.	I	2.5 % Sodium benzoate 2.5 % Sodium citrate 2.5 % Sodium acetate 2.5 % Sodium caprylate	20
2.	II	3 % Sodium benzoate3 % Sodium caprylate 2 % Sodium citrate2% Sodium acetate	25
3.	III	3 % Sodium benzoate3 % Sodium acetate 3 % Sodium caprylate1 % Sodium citrate	40
4.	IV	2 % Sodium benzoate 5 % Sodium caprylate3 % Sodium acetate	40
5.	V	% Sodium caprylate3 % Niacinamide 2 % Sodium benzoate2 % Sodium citrate	50
6.	VI	1 % Poloxomer 4071 % Sodium citrate 0.75 % Sodium acetate2 % Sodium benzoate 0.25 % Niacinamide	20
7.	VII	1 % Glycine 2 % Sodium caprylate 0.5 % Sodium citrate 1.5 % Beta cyclodextrin	15
8.	VIII	1 % Poloxomer 407 1.5 % Beta cyclodextrin .5 % Sodium caprylate1 % Sodium citrate	10
9.	IX	1 % Poloxomer 407 Beta cyclodextrin 1.5 % Sodium benzoate 1 % Sodium citrate	20
10.	X 1.	5% Poloxomer 407 0.75% eta cyclodextrin 1% Sodium caprylate 1 % Sodium citrate 0.25 % Niacinamide	35
11.	XI	10 % Poloxomer 407 10 % Sodium benzoate	40

		10 % Sodium citrate	
12.	XII	10% Poloxomer 407 10% Sodium caprylate10 % Sodium citrate	50

- **DETERMINATION OF APPROXIMATE SOLUBILITY IN DIFFERENT BLENDS AT 80 – 90 ℃**

Various blends were prepared with different concentrations of solubilizes (table 4) and 2.5 mg drug was added to a 1 ml blend. Using water bath the temperature was maintained at 80 – 90 ℃. Again, the 2.5 mg drug was added, and the temperature was maintained at 80 – 90 ℃. Shaking was done until the drug was dissolved. The same procedure was repeated until the suspension was obtained. A similar procedure was followed for all the blends, and the approximate solubility of the drug was determined in each blend. Table 4 shows the results of approximate solubility.

Table 4: Results of approximate solubility in different blends at 80 – 90 ℃

S.no.	Blend	Blend composition	Approximate solubility (mg/ml)
1.	A	1.5 % Sodium caprylate 1.5 % Niacinamide 1 % Sodium citrate 1 % Sodium citrate 1 % Sodium benzoate	45
2.	B	2.5 % Sodium caprylate1 % Sodium benzoate 0.75 % Beta cyclodextrin 0.5 % Sodium citrate 0.25 % Niacinamide	50
3.	C	1.5 % Sodium caprylate .5 % Sodium benzoate1 % Poloxomer 407 1 % Sodium citrate	110
4.	D	1.5 % Sodium caprylate 0.25 % Niacinamide 1.75 % Poloxomer 407	30
5.	E	1.5% Sodium caprylate 1.5% Sodium benzoate 1% Poloxomer 407 0.75 % Beta cyclodextrin 0.25 % Sodium citrate	70
6.	F	1.5 % Poloxomer 407 0.5% Beta cyclodextrin2% Sodium caprylate 0.75 % Sodium acetate 0.25 % Niacinamide	60
7.	**G**	**5 % Poloxomer 407 5 % Lysine hydrochloride5 % Sodium caprylate 5 % Sodium benzoate**	**210**
8.	**H**	**2.5 % Poloxomer 407**	
		2.5 % Sodium acetate 2.5 % Sodium benzoate 2.5 % Sodium caprylate	**190**

4.4 DETERMINATION OF EQUILIBRIUM SOLUBILITY

The solubility determination of hydrochlorothiazide was carried out in D.M. water and 0.1 N HCl. The excess amount of drug (hydrochlorothiazide) was added in 5 ml of respective mediums in clean glass vials and sealed and kept on a mechanical shaker (Scientech) at room temperature for 12 hours, then the vials were kept undisturbed for 12 hours. Then solutions were filtered with the help of Whatman Grade 41 filter paper. The aliquot of the filtrate was suitably diluted with D.M. water, and absorbances of these solutions were measured at 317 nm on a double beam UV spectrophotometer (Shimadzu - 1700). The results are recorded in table 5.

Table 5: Solubility of hydrochlorothiazide in D.M. water and 0.1 N HCl

S. No.	Solvent	Solubility (mg/ml)	Description
1	Demineralisedwater	0.624	very slightly soluble
2	0.0.1 N HCl	0.245	very slightly soluble

4.5 DETERMINATION OF EQUILIBRIUM SOLUBILITY OF HYDROCHLOROTHIAZIDE IN SELECTED BLENDS

Equilibrium solubility of hydrochlorothiazide was determined in D.M. water and selected blends. An excess amount of drug was added to vials containing a 5ml solvent system, covered with rubber closures, and sealed with aluminum seals. The vials were shaken for 12 hours on a mechanical bath shaker (Scientech) and kept undisturbed for another 12 hours to let the drug equilibrate. The undissolved drug was filtered using Whatman filter paper no. 41 and suitable dilutions of the filtrate were made for analysis on UV spectrophotometer (Shimadzu 1700). The results of equilibrium solubility are mentioned in table 6.

Table 6: Results of equilibrium solubility of hydrochlorothiazide in selected blends

S. no.	Blend	Blends composition	olubility (mg/ml)
1	G	5 % Poloxomer 407 5 % Lysine hydrochloride5 % Sodium benzoate 5 % Sodium caprylate	218.57
2	H	2.5 % Poloxomer 407 2.5 % Sodium caprylate 2.5 % Sodium acetate 2.5 % Sodium benzoate	197.50

4.6 DRUG SOLUBILIZERS INTERFERENCE STUDIES IN UV SPECTROPHOTOMETER ANALYSIS

It was important to study that the solubilizers to be used must not interfere with the absorbance of the drug at 317 nm to make accurate estimations. Drug excipients such as sodium caprylate, sodium acetate, sodium benzoate, Poloxomer 407, lysine HCl were used for the interference study. To determine UV spectrophotometric interference, the standard solution of the drug was prepared in D.M. water alone and with excipients. Accurately 50 mg of drug was weighed and dissolved in 450 ml DM water taken in 500 ml volumetric flask and heated at 50- 60°C with brisk shaking until a clear solution was formed and after cooling, the volume was made up to 500 ml with D.M. water to make the stock solution (100 mcg/ml). Then, 10 ml of the above solution was taken and diluted 50 ml with D.M. water. This gives a 20 mcg/ml solution.Then, solutions of excipients were prepared by dissolving 1000 mg of each solubilizer in 80 ml D.M. water and, volume was made up to 100 ml with D.M. water to obtain 1000 mcg/ml stock solution. From the above solution, 20 ml of stock solution of the drug (100 mcg/ml) and 10 ml of stock solution of excipient (1000 mcg/ml) were taken and the volume was made up to 100 ml with D.M. water. The absorbances were analyzed against water at 317 nm, and the results were illustrated in table 7.

Table 7: Drug solubilizers interference studies in the spectrophotometric estimation of hydrochlorothiazide

Drug	Solubilizers	Drug conc. (mcg/ml)	olubilizer conc. (mcg/ml)	velength Ab (nm)	sorbanc e gainst water
HCTZ	-	20	-	317	0.217
HCTZ	Sodium acetate	20	100	317	0.219
HCTZ	Sodium benzoate	20	100	317	0.218
HCTZ	Sodium caprylate	20	100	317	0.219
HCTZ	Lysine HCl	20	100	317	0.218
HCTZ	Poloxomer 407	20	100	317	0.219

Result – The values of absorbances in the presence of solubilizers and absorbances of drug solutions were approximately the same. Therefore it was concluded that the solubilizers were not interfering in UV spectrophotometric analysis of the drug at 317 nm.

4.7 DRUG EXCIPIENT INTERACTION STUDIES

Interaction studies between drug and excipients were carried out. The drugs and excipients were mixed in a separate clean glass vial in a 1:1 ratio, which was then properly sealed and kept undisturbed under different temperature conditions for a month at room temperature and in the refrigerator. After every week (for one month), the vials were checked, and the material was noticed for any change in their physical appearance. The observations were presented in table 8.

Table 8: Observations of drug solubilizers incompatibility studies

no.	Drug solubilizer 1:1 blend)	Initial	Refrigerated condition				Room temperature			
			Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
1	HCTZ	WP	-	-	-	-	-	-	-	-
2	TZ+ SB	WP	-	-	-	-	-	-	-	-
3	CTZ + SC	WP	-	-	-	-	-	-	-	-
4	CTZ + SA	WP	-	-	-	-	-	-	-	-
5	TZ + L-HCl	WP	-	-	-	-	-	-	-	-
6	HCTZ + P 407	WP	-	-	-	-	-	-	-	-

HCTZ- Hydrochlorothiazide, SB- Sodium benzoate, SC- Sodium caprylate, SA-Sodium acetate, L-HCl- Lysine hydrochloride, P 407- Poloxomer 407, (-) No change,(+) Change, WP- White powder,

5. FORMULATION OF SOLID DISPERSIONS OF HYDROCHLOROTHIAZIDE BY APPLICATION OF MIXED SOLVENCY CONCEPT

According to the results of solubility studies of the drug in mixed solvent blends, the formula for solid dispersion was finalized. The drug having the desired solubility in selected blends (blend G and blend H) at 80-90 ℃ were employed to prepare the solid dispersion.

5.1 PROCEDURE FOR FORMULATION OF SOLID DISPERSION

To prepare the solid dispersion using blend G (SDG) in 1:10 ratios, accurately weighed 6.25 gm of each solubilizer (poloxomer 407, lysine hydrochloride, sodium acetate, sodium benzoate, sodium caprylate) were taken in a 100 ml beaker and were appropriately mixed. Then 25 ml of D.M. water was added and mixture was heated to about 70- 80 ℃. A solution containing solubilizers was prepared on a magnetic stirrer using Teflon coated magnetic bead. Weighed quantity of hydrochlorothiazide drug was dissolved in the above solution, and the temperature was maintained in the range of 70- 80℃ so as to facilitate the evaporation of water. As evaporation proceeded, the speed of the bead automatically decreased, and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet).

The wet solid dispersion thus obtained was spread on the watch glass, and the watch glasses were kept in a hot air oven maintained at 50 ± 2 ℃ so that remaining moisture could also be evaporated out and a constant weight with no further weight loss due to evaporation could be obtained. After this, 104 gm of MCC (Avicel PH200) was added to make the powder free flowing. Table 10 illustrates the amount of MCC consumed. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve no. 100 and were finally stored in an airtight container.

The same procedure was utilized to prepare solid dispersions in the ratio of SDH (1:5) and SDH (1:6), using an appropriate quantity of solubilizers. Table 9 illustrates the composition of solid dispersions of hydrochlorothiazide.

Table 9: Composition of solid dispersion of hydrochlorothiazide

S. no.	Drug: solubilizers	Quantity taken (gm)					
		P- 407	L-HCl	SA	SB	SC	D
1	SDG (1:10)	6.250	6.250	-	6.250	6.250	2.5
2	SDH (1:5)	3.125	-	3.175	3.125	3.125	2.5
3	SDH (1:6)	3.750	-	3.750	3.750	3.750	2.5

407 =poloxomer 407, L-HCl = lysine hydrochloride, SA =sodium acetate, SB = sodium benzoate, SC = sodium caprylate, D = drug (hydrochlorothiazide)

Table 10: Amount of MCC taken

S. no.	Solid dispersion	Adsorbent	ntity taken(gm)
1	SDG 1:10	Avicel PH200	104.0
2	SDH 1:5	Avicel PH200	22.20
3	SDH 1:6	Avicel PH200	25.80

5.2 PROCEDURE FOR FORMULATION OF PHYSICAL MIXTURE

To prepare a physical mixture using blend G (PMG) in 1:10 ratio, accurately weighed 6.25 gms of all the solubilizers (poloxamer 407, lysine hydrochloride, sodium acetate, sodium benzoate, sodium caprylate) of blend G and drug (hydrochlorothiazide) were used. This mixture was mixed using the geometric dilution technique and was triturated using glass pestle mortar for about 10 minutes. After complete mixing, the powder mass was passed through sieve no.100 and was finally stored in an airtight glass bottle.

The same procedure was used to prepare a physical mixture in the ratio of PMH (1:5) and PMH (1:6), using appropriate quantities of solubilizers. Table 11 illustrates the composition of physical mixtures of hydrochlorothiazide.

Table 11: Composition of physical mixtures of hydrochlorothiazide

S. no.	Drug: solubilizers	Quantity taken (gm)					
		P- 407	- HCl	SA	SB	SC	D
1	PMG (1:10)	6.250	6.250	-	6.250	6.250	2.5
2	PMH (1:5)	3.125	-	3.125	3.125	3.125	2.5
3	PMH (1:6)	3.750	-	3.750	3.750	3.750	2.5
407 =poloxomer 407, L-HCl = lysine hydrochloride, SA =sodium acetate, SB = sodium benzoate, SC = sodium caprylate, D = drug (hydrochlorothiazide)							

6. EVALUATION OF SOLID DISPERSION AND PHYSICAL MIXTURE

DETERMINATION OF DRUG CONTENT OF SOLID DISPERSION AND PHYSICAL MIXTURE

To determine the drug content of powdered solid dispersion or physical mixture, powder equivalent to 25 mg drug was taken in a 500 ml volumetric flask. About 350 ml of 0.1 N HCl was added to the volumetric flask, and the flask was shaken continuously for 30 minutes to get a clear solution. Then the volume was made up to 500 ml with 0.1 N HCl. The absorbances of filtered solutions were recorded at 317 nm in a UV spectrophotometer (Shimadzu-1700) against 0.1 N HCl as blank. Results of drug content are mentioned in table 12.

Table 12: Drug content of solid dispersion and physical mixture

S. no.	solubilizersratio	mount analyzed (mg)		g content(%)	
		SD	PM	SD	PM
1	(1:10)	24.80	24.53	99.20	98.12
2	(1:5)	24.49	24.22	97.96	96.88
3	(1:6)	24.60	24.34	98.40	97.36

SD- Solid dispersion, PM- Physical mixture

6.1 DISSOLUTION PROFILE

Dissolution profile of each batch was analyzed to determine which batch was best for scaling up. For dissolution studies, 0.1 N HCl was taken as dissolution media, and the paddle rotation speed was kept at 100 rpm at 37 ± 0.5°C in 900 ml of media. After 2 minutes, 20 ml sample was withdrawn from dissolution media for analysis, and an equal quantity of 0.1 N HCl was replaced in dissolution medium. A similar procedure was performed again after different time intervals. Table 13 and 14 show the quantity of solid dispersion and physical mixture in each batch used for dissolution studies in 0.1 N HCl.

Table 13: Quantity of solid dispersion in each batch used for dissolutionstudies

S. no.	Solid dispersion	nt of powder(mg)	mount of drug (mg)
1	SDG (1:10)	1325.6	25
2	SDH (1:5)	380.0	25
3	SDH (1:6)	439.0	25

cal mixture in each batch used for dissolutionstudies

S. no.	Physical mixture	nt of powder(mg)	Amount of drug (mg)
1.	PMG (1:10)	280.0	25
2.	PMH (1:5)	155.0	25
3.	PMH (1:6)	180.0	25

6.2 DISSOLUTION PROFILE OF PURE DRUG HYDROCHLOROTHIAZIDE IN 0.1 N HCL

Table 15 illustrates the data for the dissolution study of pure drug hydrochlorothiazide in 0.1 N HCl.

Table 15: Data for dissolution study of the pure drug (hydrochlorothiazide) in 0.1 N HCl

Time (min)	(%) Cumulative drug release
02	3.9
05	5.7
10	8.8
15	14.2
30	25.8
45	31.1
60	39.0

6.3 DISSOLUTION PROFILE OF SOLID DISPERSION AND PHYSICAL MIXTURE

Table 16, 17 and 18 illustrates the comparative data of dissolution studies of each respective batches of solid dispersion, physical mixture and pure drug in 0.1 N HCl. Figures 5, 6, and 7 illustrate the comparative dissolution study of solid dispersion, physical mixture, and pure drug.

Table 16: Data for dissolution study of solid dispersion, physical mixture and pure drug in 0.1 N HCl

Time (min)	(%) Cumulative drug release		
	SDG (1:10)	PMG (1:10)	Pure drug
02	83.0	75.3	3.9
05	91.7	82.6	5.7
10	96.9	88.4	8.8
15	99.2	92.3	14.2
30	99.9	95.3	25.8
45	99.9	96.5	31.1
60	99.9	97.5	39.0

Dissolution study of powder of solid dispersion (SDG 1:10) showed that in 2 minutes 83.0% drug wasreleased, in 5 minutes 91.7% drug was released and in 15 minutes 99.2% of drug was released.
Dissolution study of physical mixture (PMG 1:10) showed that 75.3% drug was released in 2 minutes, 82.6% drug was released in 5 minutes and 92.3% drug was released in 15 minutes.

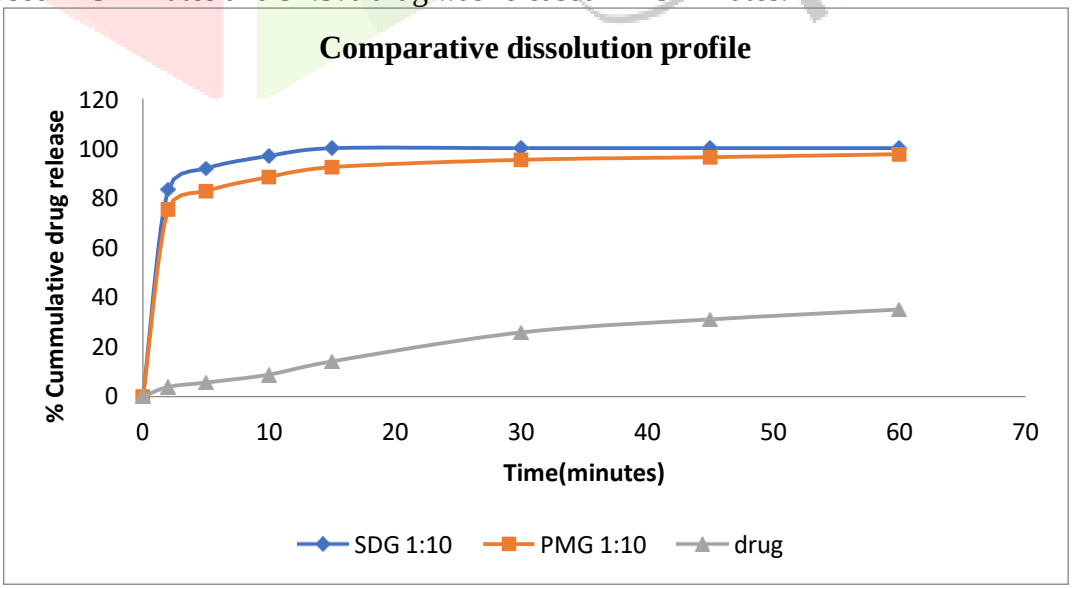

Figure 5: Comparative dissolution profile in 0.1 N HCl of SDG 1: 10, PMG 1:10, and pure drug

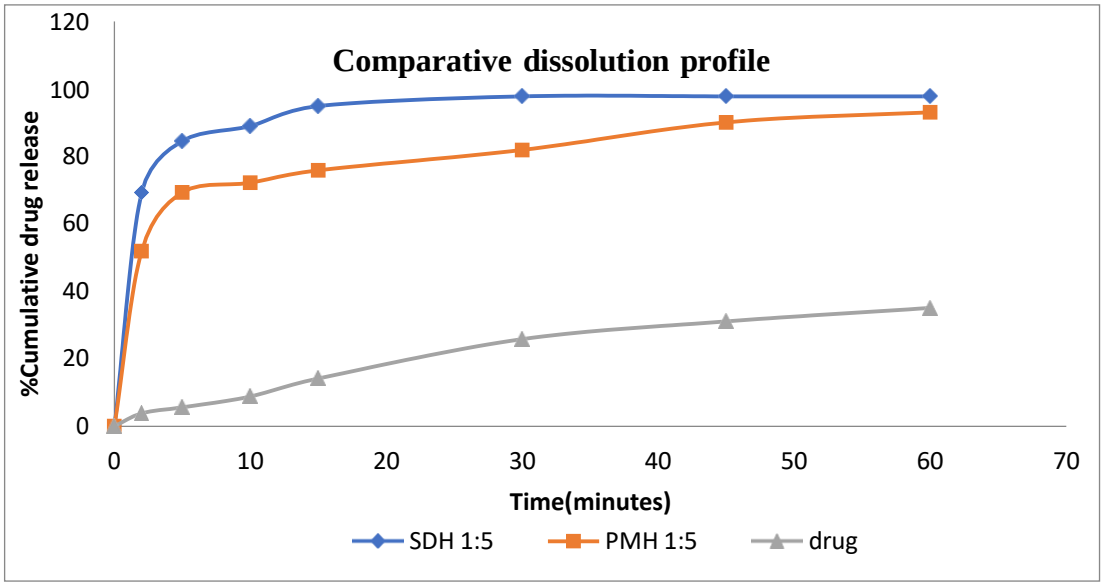

Figure 6: Comparative dissolution profile in 0.1 N HCl of SDH 1:5, PMH 1:5, and pure drug

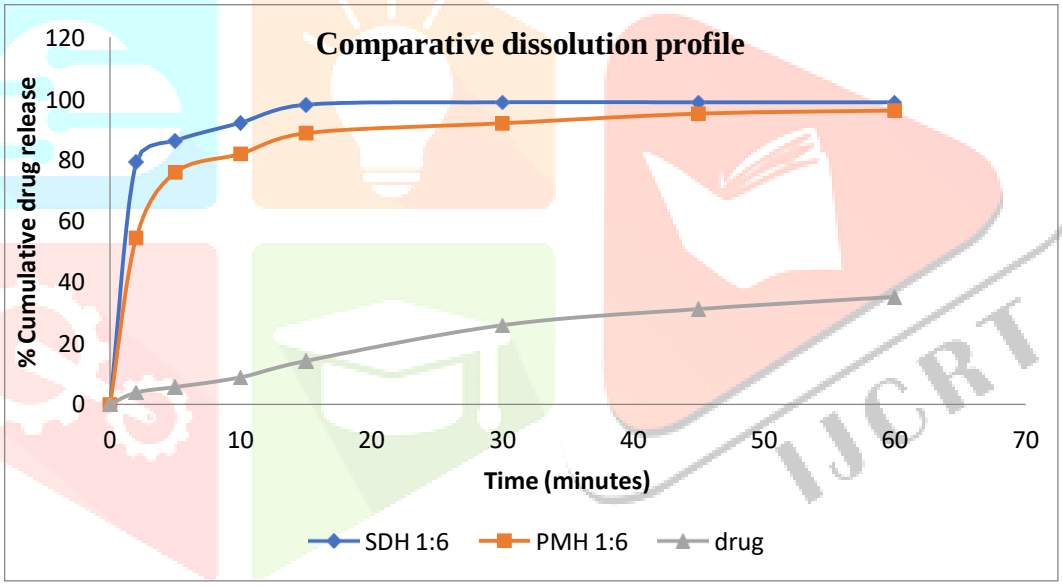

Figure 7: Comparative dissolution profile in 0.1N HCl of SDH 1:6, PMH 1:6, and pure drug

dy of the solid dispersion (SDH 1:5), physical mixture (PMH 1:5) and puredrug in 0.1 N HCl

Time (min)	(%) Cumulative drug release		
	SDH (1:5)	PMH (1:5)	Pure drug
02	69.2	51.8	3.9
05	84.5	69.2	5.7
10	87.8	72.1	8.8
15	94.9	75.8	14.2
30	97.8	81.8	25.8
45	97.8	90.0	31.1
60	97.8	92.9	39.0

SD- solid dispersion,PM – physical mixture

Dissolution study of powder of solid dispersion (1:5) showed that in 2 minutes 69.2%, in 5 minutes 84.5% drug was released and in 15 minutes 94.9% drug was released.

Dissolution study of physical mixture (PMH 1:5) showed that 51.8% drug was released in 2 minutes, 69.2%

drug was released in 5 minutes, and 75.8% drug was released in 15 minutes.

Table 18: Comparative data for dissolution study of solid dispersion (SDH 1:6), physical mixture PMH (1:6), and pure drug.

Time (minutes)	% Cumulative drug release		
	SDH (1:6)	PMH (1:6)	Pure drug
2	79.2	54.3	3.9
5	86.1	75.8	5.7
10	90.0	81.9	8.8
15	97.8	88.6	14.2
30	98.6	91.8	25.8
45	98.6	94.9	31.1
60	98.6	95.9	39.0

Dissolution study of solid dispersion (1:6) showed that in 2 minutes 79.2% drug was released, in 5 minutes 86.1 % drug was released and in 15 minutes 97.8% drug was released

Dissolution study of physical mixture (PMH 1:6) showed that 54.3 % drug was released in 2 minutes, 75.8 % drug was released in 5 minutes, and 88.6 % drug was released in 15 minutes

6.4 THIN LAYER CHROMATOGRAPHY

To analyze the possibility of interaction between drug and solubilizer, thin layer chromatographic studies were performed. A plate of silica gel GF 120 was activated at 110℃ for 1hour and then used. The baseline was spotted with the hydrochlorothiazide solution (1 %) in acetone alone and SDG 1:10 and PMG 1:10 dissolves in 20 % sodium caprylate solution. The plate was dried in the air for a sufficient period before being placed in a beaker containing 20 % sodium acetate solution (mobile phase). After drying the plate for a suitable time, it was analyzed for spot visibility in a UV chamber. The results of the TLC study revealed that there was no significant difference in Rf values of hydrochlorothiazide solubilized in acetone and solid dispersion and physical mixture solubilized in sodium caprylate (1%). From the results of TLC, it can be concluded that there is no reaction of the drug with solubilizer molecules. It can also be concluded that safe hydrotropic solutions can safely replace toxic organic solvents. TLC was carried out in a 20 % sodium acetate solution as the mobile phase proved that the solids possess the solubilizing power. The result of TLC is recorded in table 19.

Table 19: Results of TLC studies

Solven system	Adsorbent	Rf value		
		Pure drug	SDG 1:10	PMG 1:10
20% sodium acetate (aqueous)	Silica gel GF 120	0.88	0.89	0.89

SD- solid dispersion, PM- physical mixture

7. FORMULATION AND DEVELOPMENT OF HYDROCHLOROTHIAZIDE TABLETS FINALBATCH SELECTION

SDG (1:10) was selected for the final batch preparation based on the dissolution profile from the trial batches. This batch was scaled up.

The tablets of hydrochlorothiazide were prepared by direct compression method. In this method, the solid dispersion was weighed accurately and compressed into tablets with the help of a tablet compression machine. The formed tablets were collected and evaluated.

8. EVALUATIONS

The evaluation tests performed on SDG (1:10) are:-

- Weight variation
- Determination of drug content of solid dispersion
- Disintegration time of tablets of solid dispersion
- Comparative dissolution study
- Friability

- Hardness

8.1 WEIGHT VARIATION

As per IP, twenty tablets from SDG (1:10) were taken and weighed individually. The average weight of all the tablets was calculated. Individual tablet weight was compared with the average weight.
None of the tablets of the batch went beyond the accepted range of ± 5 %. Hence, the test was passed.

8.2 DRUG CONTENT DETERMINATION

Five tablets of SDG (1:10) were taken. All the tablets were weighed, and the average weight was calculated. The tablets were triturated to get a fine powder, and powder containing equivalent to 25 mg of drug was placed in a 500 ml volumetric flask to determine drug content. The volumetric flask was filled with 300 ml 0.1 N HCl, shaken for 30 minutes constantly, and the volume was made up to 500 ml with 0.1 N HCl. Filtration was done. Then the absorbance was measured at 317 nm against a blank of D.M. water. The amount of drug analyzed was found to be 24.34 mg, and the drug content in the scale-up batch was found to be 97.44 %.

8.3 DISINTEGRATION TIME STUDIES

Six tablets of SDG (1:10) were individually put into disintegration tubes. In the disintegration beaker, 900 ml of 0.1 N HCl was filled, and the disintegration test was performed at 37 ± 2℃, at 28–32 cycles per minute frequency. The disintegration period of tablets was found to be ranging from 2 minutes 58 seconds to 4 minutes 52 seconds.

8.4 COMPARATIVE DISSOLUTION PROFILE

The dissolution profile of tablets of SDG (1:10) and marketed tablet Aquazide 25 mg was studied and compared. One tablet of SDG (1:10) was taken and compared with one tablet of Aquazide 25 mg. For dissolution, 900 ml of 0.1 N HCl was taken as dissolution media, and the paddle rotation speed was kept at 100 rpm at 37 ± 0.5℃. After 2 minutes, a 20 ml sample was withdrawn from dissolution media for analysis, and an equal quantity of media was added. The comparative dissolution profile in 0.1 N HCl of tablets and the pure drug is illustrated in table 20 and depicted in figure 8.

HCl of the final batch of solid dispersion tablets, marketed formulation,pure drug.

S. no.	Time (min)	(%) cumulative drug release		
		Tablet ofSDG (1:10)	Aquazide(25 mg)	Pure drug
1.	02	54.1	6.5	3.9
2.	05	75.8	15.4	5.7
3.	10	85.2	27.7	8.8
4.	15	94.9	55.0	14.2
5.	30	98.7	74.4	25.8
6.	45	98.7	85.2	31.1
7.	60	98.7	88.2	39.0

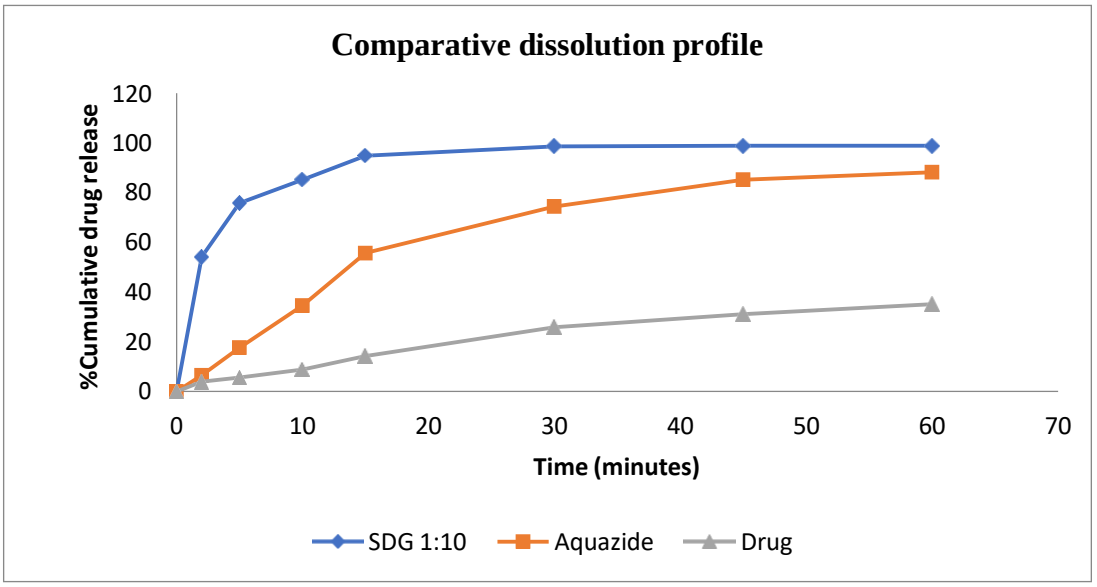

Figure8: Comparative dissolution profile in 0.1 N HCl of final batch (tablets of SDG (1:10), marketed tablet and pure drug

Dissolution study of tablets of solid dispersion (SDG 1:10) showed that in 2 minutes, 54.1 % of the drug was released, in 5 minutes 75.8 % of the drug was released, in 15 minutes 94.9 % of the drug was released.

8.5 FRIABILITY

Roche friabilator was used for testing. Then tablets of SDG (1:10) were taken. The tablets were weighed before testing. They were tumbled for 100 revolutions. After that, the tablets were reweighed. The weight loss was in the accepted range, and hence the test was passed.

8.6 HARDNESS

Three tablets of SDG (1:10) were taken. A hardness test was performed at Monsanto hardness tester. The results were recorded in kg/cm^2. The test performed on three tablets. The results hardness test are shown in table 21.

Table 21: Results of hardness test

S. no.	Tablet batch	Hardness (kg/cm^2)	
		lness of tablets (kg/cm^2)	erage hardnes of three tablets
1	SDG (1:10)	2	2
		2	
		2	

8.7 DRUG CONTENT UNIFORMITY

Since the drug present in each tablet is less than 10 % of the tablets' average weight, a content uniformity test was performed.

Ten tablets of SDG (1:10) were taken. Each 25 mg tablet was transferred in a 1000 ml volumetric flask. The volumetric flask was filled with 700 ml of D.M. water, shaken for 30 minutes constantly, and volume was made up to 1000 ml with D.M. water. The above solution was filtered. The absorbance was measured at 317 nm against a blank of D.M. water. The content of all the tablets is between 85 and 115 %. As a result, tablets of SDG (1:10) passed the test.

9. SUMMARY AND CONCLUSION

The main objective of any dosage form is to deliver the desired concentration of drug at the site of action. The absorption of drug molecules is dependent upon two processing parameters such as drug dissolution and drug permeation.

The ultimate objective of the present research work was to explore the mixed solvency technique that can be used to enhance the solubility of the poorly water-soluble drug. The main aim of this study was to showcase that solid can serve the purpose of solvent. In the future, the solids can be employed as solvents resulting in ecofriendly methods precluding the use of organic solvents.

In the present research, the poorly water-soluble drug, hydrochlorothiazide was the drug of choice. It was incorporated into solid dispersion using random combination of several solid solubilizers. The solid solubilizers were dissolved in water and then the drug was added, a clear solution was formed. The excess water was evaporated from this solution and solid dispersion was obtained which was later dried completely and stored in airtight container.

This concept of mixed solvency is expected to improve the bioavailability of drug and there will be decrease in the release time. Conventional dosage form such as capsules and tablets can be prepared from this solid dispersion by selecting suitable excipients. Solid dispersion formulation prepared from the mixed solvency concept is a promising tool for the enhancement of bioavailability of drug.

Hydrochlorothiazide, is considered a prototype member of thiazide class diuretics. It decreases electrolyte reabsorption from the renal tubules. This leads to increased excretion of water and electrolytes, including sodium, potassium, and magnesium. It is used in the treatment of many diseases such as edema, hypertension, and hypoparathyroidism.

The characterization and identification of hydrochlorothiazide was done by UV spectrophotometric analysis, determination of melting range and differential scanning calorimetry of the drug sample were carried out. The observed values were in accordance with the reported values in the literatures.

In preformulation studies solubility studies in various blends was performed. Also, preparation of calibration curves in water and 0.1 N HCl with aid of sodium benzoate and sodium caprylate was done. Solubility of hydrochlorothiazide drug sample was reported in different blends. Interaction studies of drug-excipients have shown no interaction and incompatibility between drugs and excipients. UV spectrophotometric study of drugs and solubilizers indicated no drug solubilizer interference at 317 nm.

Different blends of solubilizers were prepared by varying their concentration. Out of these prepared blends, Blend G and blend H was selected on the basis of desired solubility at 80-90 ℃.

Different solid dispersions were prepared with different drug and solubilizers ratios. Microcrystalline cellulose (Avicel PH 200) was used to adsorb the extra moisture from solid dispersions

Thin layer chromatography was also performed which concluded that there is no reaction of drug with solubilizer molecules. It was also concluded that toxic organic solvents can be safely replaced by safe hydrotropic solutions. TLC was carried out in a solution of 20 % sodium acetate solution as mobile phase proved that the solids possess the solubilizing power.

One of three trail batches of solid dispersions were selected for compression into tablets. The tablets formulated were compared with marketed tablet Aquazide 25 mg. Dissolution study of tablets of solid dispersion that in 2 minutes approximately 54.10% of the drug was released, in 5 minutes approximately 75.84% of the drug was released, in 10 minutes more than 85.26% of the drug was released and in 15 minutes more that 94.96% of the drug was released. The drug content, disintegration time, weight variation, friability, hardness, content uniformity studies and drug release studies were all assessed.

Based on the above findings, it may be concluded that the solubility and release of a poorly water-soluble drug can be enhanced using various solid solubilizers by the application of mixed solvency concept.

The principle of mixed solvency was successfully employed in formulating the fast release solid dispersion formulation of poorly water-soluble drug hydrochlorothiazide. In this study, there was no involvement of organic solvents to prepare formulation.

Higher costs and toxicity due to residual solvents are the major disadvantages of organic-solvents. The present study demonstrates the application of the principle of mixed solvency to solve the problems of the above mentioned organic solvent-related disadvantages and also to increase the solubility of the drug with increased drug release.

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