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NOVEL APPLICATION OF MIXED SOLVENCY CONCEPT IN THE DEVELOPMENT OF FAST DISSOLVING SOLID DISPERSION OF POORLY WATER-SOLUBLE DRUG, TORSEMIDE AND ITS 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, torsemide (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. **Material and Methods:** For poorly water soluble drug torsemide, combination of solubilizers such as sodium caprylate, sodium citrate, sodium acetate and beta cyclodextrin as mixed solvent systems were used to decrease the overall concentration of solubilizer required to produce substantial increase in solubility of torsemide. The procured sample of torsemide was characterized by melting point, IR, UV, and DSC studies. Stability studies of solid dispersion of torsemide were performed for two months at room temperature and cool temperature. All the formulation were physically, chemically and microbiologically stable. **Conclusion:** Mixed solvency concept has been successfully employed for enhancing drug loading of poorly water soluble drug, torsemide.

KEYWORDS: Mixed solvency, hydrotropy, torsemide, solid dispersion, solubility.

INTRODUCTION

As per the mixed solvency concept[1-10] proposed by Maheshwari R.K., 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. Mixed solvency concept[11-29] can also be employed in titrimetric, UV spectrophotometric and HPLC analysis of poorly water-soluble drugs avoiding the use of harmful organic solvents.

Solid dispersion technique[30-37] 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. 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

MATERIALS AND METHODS

Materials: Torsemide was obtained as a gift sample from Zydus Cadila pharmaceutical limited, Ahmedabad.

Methods

UV Spectrophotometric Analysis in DM Water

Ten mg of torsemide was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in an adequate amount of DM water and the volume was made up to 100 ml with DM water so as to obtain a stock solution of 100 µg/ml. A dilution of 10 µg/ml concentration was made from the above stock solution with demineralized water and the resulting solution was scanned on a double-beam UV-visible spectrophotometer (Shimadzu® 1700) between wavelength ranges of 200 nm to 400 nm. The UV spectra so recorded is shown in fig. 1.

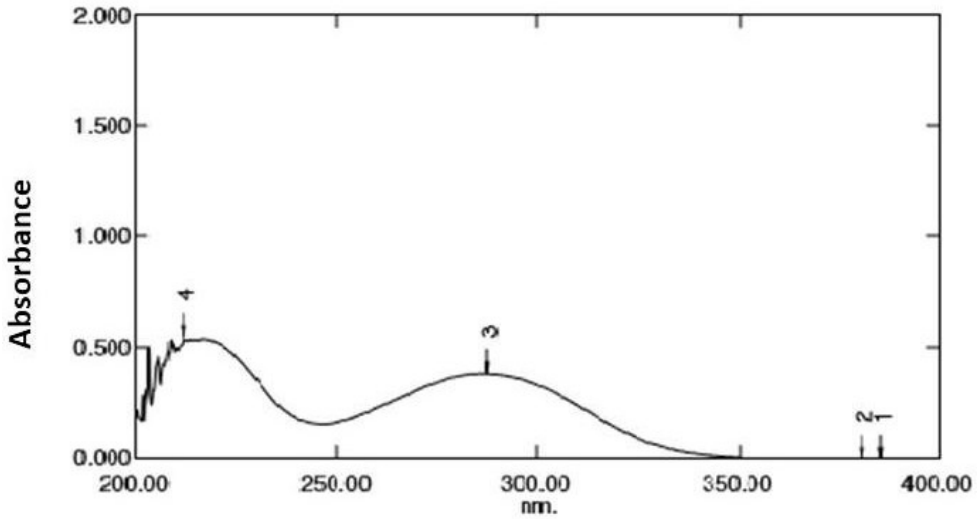

Fig. 1: U. V. spectra of torsemide in DM water.

Result and discussion: The torsemide drug sample exhibited a peak at 287 nm which was comparable to the value reported in the literature.

Melting Point

The melting point of drug sample was determined using the open capillary tube method. The drug sample was filled into a capillary tube one end closed and was attached to the thermometer placed in a Thiele's tube filled with liquid paraffin. The tube was heated and the temperature at which the drug melted was noted.

RESULT AND DISCUSSION

Melting point of drug sample was found to be 165°C and was comparable to the value reported in the literature. (163-164°C).

Differential Scanning Calorimetric Studies

Differential scanning calorimetry (DSC) measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. In order to obtain the DSC thermograms, 4 mg of sample was weighed accurately and placed in aluminum pan. The pan was sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10^{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 the reference in the temperature range of 40- 300^{o}C. Various DSC thermograms (melting isotherms) are shown in fig. 2.

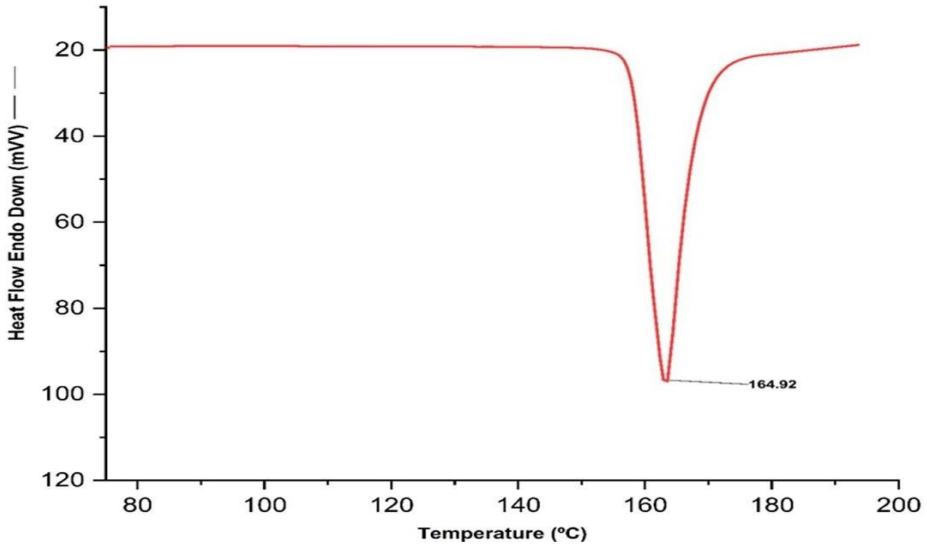

Fig. 2: DSC curve of torsemide.

RESULT: The DSC curve of the crystalline form of torsemide showed a sharp endothermic peak at **164.92°C** attributable to melting.

Infrared Spectroscopic Analysis

The infrared spectroscopic analysis of torsemide sample was performed on IR spectrophotometer (Shimadzu IRAffinity-1) and the spectra so obtained is shown in fig 3.

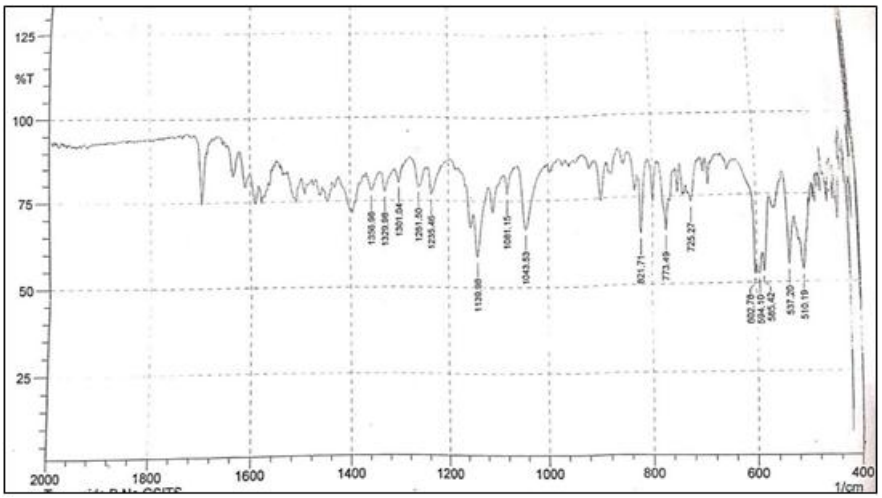

Fig. 3: FT-IR spectra of torsemide drug sample Table 1: FT-IR peaks of torsemide drug sample.

Peak (cm^{-1})	Interpretation
1139.98	S=O symmetric stretch
1329.98	S=O symmetric stretch
1565.92	N-H Bending
1695.31	C=N bending

Preparation of Calibration Curve of Torsemide in DM Water

Fifty milligram of drug torsemide was accurately weighed and transferred to a 100 ml volumetric flask. To this 5ml of 30 % (w/v) sodium caprylate solution was added to dissolve the drug and the volume was made up to 100 ml with DM water to prepare a 500 µg /ml solution. Appropriate dilutions were made with DM water to obtain 10, 15, 20, 25, and 30 µg/ml solution of drug. The absorbances of resulting drug solutions were measured spectrophotometrically at 287 nm against the corresponding reagent blank. Data was recorded in graphically represented in figure 4.

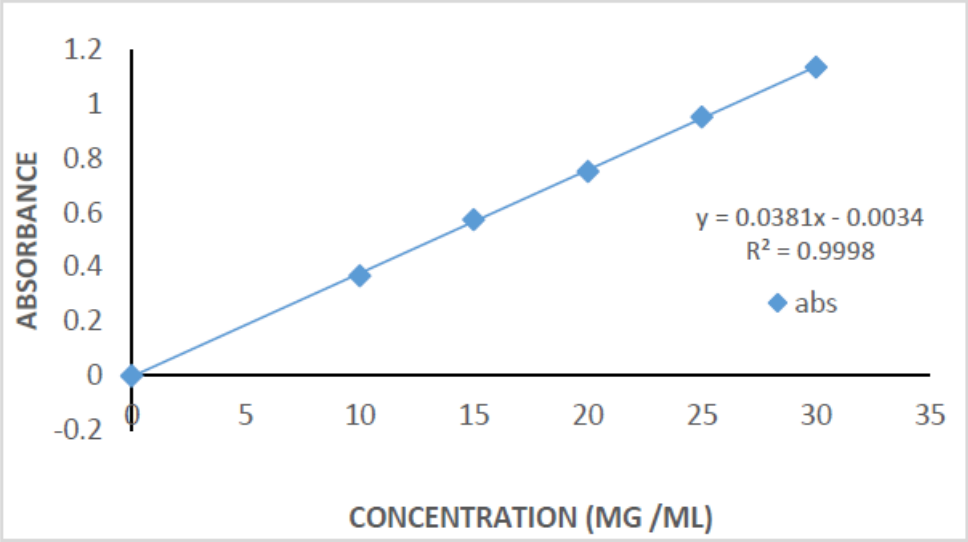

Fig 4: Calibration curve of torsemide in DM water.

Preparation of Calibration Curve of Torsemide in 0.1 N HCl

Fifty milligram of drug torsemide was accurately weighed and transferred to a 100 ml volumetric flask. Eighty ml of 0.1N HCl solution was added to dissolve the drug and the volume was made up to 100 ml with 0.1N HCl to prepare a 500 µg /ml solution. Appropriate dilutions were made with 0.1N HCl to obtain 10, 15, 20, 25 and 30 µg/ml solutions of drug. The absorbances of resulting drug solution were measured spectrophotometrically at 287 nm. Data was recorded in table 2 and graphically represented in figure 5.

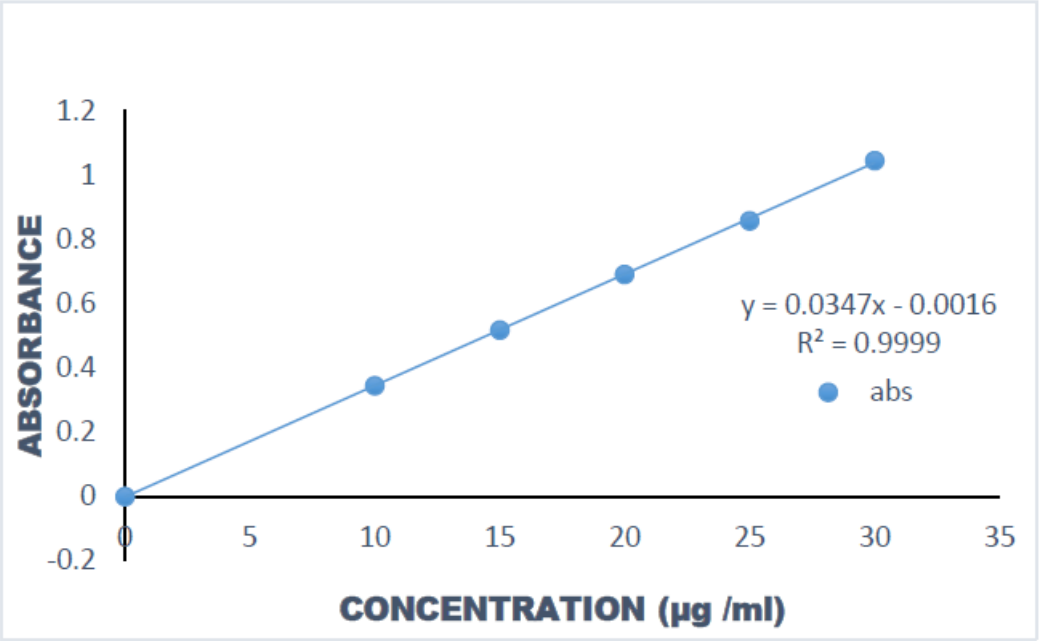

Fig. 5: Calibration curve of torsemide in 0.1N HCl.

Determination of Interference of Solubilizers in the Spectrophotometric Estimation of Torsemide

Different excipients such as sodium caprylate, sodium citrate, sodium acetate and beta cyclodextrin were used for the interference study. To determine UV spectrophotometric interference, standard solution of drug was prepared in DM water alone and also with the excipients. Accurately, 50 mg drug was weighed and dissolved in 450 ml DM water taken in 500 ml volumetric flask and heated at 50-60ºC with brisk shaking until a clear solution was formed and after cooling, the volume was made up to 500ml with DM water to make stock solution of drug (100µg/ml). Then, 10ml of the above solution was taken and diluted up to 50ml with DM water. This gives a solution of 20µg/ml. Likewise, solutions of excipients were prepared by dissolving 100mg of each solubilizer in 50ml DM water and volume were made up to 100 ml with DM water to obtain 1000µg/ml stock solution. From the above solution, 20ml of stock solution of drug (100 µg/ml) and 10 ml of stock solution of excipient (1000 µg/ml) were taken in a 100ml volumetric flask and volume was made up to 100ml with DM water. The absorbances were recorded against water at 287 nm and results are shown below in table 2.

Table 2: Drug solubilizers interference studies in the spectrophotometric estimation of torsemide.

Drug	Solubilizer	Drug conc. (µg/ml)	Solubilizer conc. (mg/ml)	Wavelength (nm)	Absorbance against water
Torsemide	-	20	-	287	0.380
Torsemide	Sodium acetate	20	100	287	0.378
Torsemide	Sodium citrate	20	100	287	0.384
Torsemide	Sodium caprylate	20	100	287	0.385
Torsemide	Beta cyclodextrin	20	100	287	0.383

DISCUSSION

Observing the results of drug-solubilizers interference study, it was concluded that there was no interference in UV spectrophotometric analysis of torsemide due to excipients.

Determination of solubility

The solubility determination of torsemide were carried out in DM water and 0.1N HCl. The excess drug was added to 30 ml of water contained in a 50 ml glass bottle and bottle was sealed with closure. The bottle was shaken for 12 hrs on mechanical bath shaker (Khera Instrument Pvt. Ltd., Delhi, India) and allowed to equilibrate for 24 hrs undisturbed. The solution containing drug were filtered through Whatman filter paper grade no.41. Aliquot of the filtrate were suitably diluted with DM water and the dilution was analysed on UV-Visible spectrophotometer (Shimadzu 1700). The result is presented in table 3.

Table 3: Solubility of torsemide.

S. No.	Solvent	Solubility % (w/v)
1.	Demineralized water	0.0169
2.	0.1N HCl	0.5225

Determination of Partition Coefficient

Partition coefficient is a measurement of drug's lipophilicity and its ability to cross cell membrane. Partition co-efficient was determined as ratio of concentration of drug in octanol to the concentration of drug in DM water and its log value was taken for log P.Partition coefficient of torsemide was determined at 37 ±0.5ºC by taking 20 ml of octanol which was saturated with 20 ml of DM water by moderate stirring with externally driven magnetic stirrer for 6 hours. After stirring the system remained undisturbed for half an hour. Accurately weighed 20 mg of drug was added to this solution and was moderately shaken on wrist action mechanical stirrer for about 3 hours. It turns observed that no suspended particles were present undissolved. Two layers were

separated through separating funnel and the amount of torsemide dissolved in each phase was determined by measuring the absorbance of water at 287 nm against reagent blank on a double beam UV visible spectrophotometer (Shimadzu-1700). After determining the concentration of drug in water phase, the concentration of drug in octanol phase was calculated by subtracting the amount of drug present in aqueous phase from 20 mg.

RESULT

Partition coefficient of toremide was found to be **2.4 (octanol water)**, which showed that torsemide is lipophilic in nature.

pH Dependent Solubility Profile of Torsemide

For determination of pH dependent solubility, buffer solutions of pH 1.2 to pH 10 were prepared. Solubility studies in different pH medias were carried out by adding an excess amount of drug in 10 ml of respective medium contained in 20 ml glass vials and keeping the sealed vials containing this solution on a bath shaker (Khera Instrument Pvt. Ltd., Delhi, India) at room temperature for 24 hrs, so that equilibrium solubility can be achieved and solution were equilibrated for 12 hrs (undisturbed). The solutions were filtered through Whatman filter paper grade no.41. Filtrates were suitably diluted with respective buffer solutions and absorbance of the solutions were measured at 287 nm against reagent blank on a double beam UV-visible spectrophotometer (Shimadzu 1700). The solubilities at different pH are shown in table 4.

Table 4: pH solubility profile of torsemide.

S. No.	Buffer pH	Solubility (%w/v)	Inference
1	1.2	0.246	Slightly soluble
2	2	0.106	Slightly soluble
3	2.8	0.100	Slightly soluble
4	4	0.032	Very slightly soluble
5	5	0.017	Very slightly soluble
6	7	0.042	Very slightly soluble
7	8	0.119	Slightly soluble
8	9	0.328	Slightly soluble
9	10	0.366	Slightly soluble

Drug Solubilizers Incompatibility Studies

The different formulation components involved in the development of the proposed formulations were physically mixed with drug in 1:1 ratio and properly filled in glass vials, capped and sealed. The vials of each sample were kept either at room temperature, or in

refrigerator for one-month period. After every week (for one month), the vials were withdrawn and the changes in physical appearance (if any) and colour of the contents were observed. The observations were recorded in table 5.

Results and discussion: Observing the results of drug-solubilizers compatibility study, it was concluded that there was no physical incompatibility between drug and selected formulation solubilizers.

Table 5: Observations of drug solubilizers incompatibility studies.

S. No.	Drug solubilizer (1:1 blend)	Initial	Refrigerated condition (2-8 ° C)				Room temperature (25°)			
			1wk	2wk	3wk	4wk	1wk	2wk	3wk	4wk
1.	Torsemide	WP	NC	NC	NC	NC	NC	NC	NC	NC
2.	Torsemide + Sodium acetate	WP	NC	NC	NC	NC	NC	NC	NC	NC
3.	Torsemide + Sodium citrate	WP	NC	NC	NC	NC	NC	NC	NC	NC
4.	Torsemide + Sodium caprylate	WP	NC	NC	NC	NC	NC	NC	NC	NC
5.	Torsemide + beta cyclodextrin	WP	NC	NC	NC	NC	NC	NC	NC	NC

WP- White Powder, NC-No Change

Formulation Development of Solid Dispersion of Torsemide

Solubility Studies

The equilibrium solubility of torsemide was determined in DM water and several other mixed solvent blends. Excess amount of drug was added to vials containing 5 ml solvent system & covered with rubber closures and sealed with aluminium seals. The vials were shaken for 12 hours on mechanical bath shaker (Khera Instrument Pvt. Ltd., Delhi, India) 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 were made for analysis on UV-spectrophotometer (Shimadzu 1700).

Determination of Equilibrium Solubility of Torsemide in Various Aqueous Solutions of Solubilizers (Blends)

Table 6 shows solubility of torsemide in mixed blends of solubilizers sodium caprylate, sodium citrate, sodium acetate, and beta cyclodextrin. Solubility enhancement ratio is calculated as the ratio of solubility of drug in solution of solubilizers and solubility of drug in water (0.169mg/ml).

Table 7: Results of equilibrium solubility studies of torsemide in various aqueous solutions of solubilizers.

S. No.	Blend	Blends composition (w/v)	Solubility (mg/ml)	Solubility enhancement ratio
1	A	30% CP	49.12	290.65
2	B	20% CP + 10% SC	40.07	237.1
3	C	20% CP + 10% SA	42.82	253.37
4	D	20% CP + 10% βCD	37.38	211.18
5	E	10% SA + 10 % SC	4.49	26.56
6	F	30% CP + 5% SC + 5% SA	56.12	332.07
7	G	30% CP + 5% SA + 5% βCD	52.191	308.82
8	H	30% CP + 5% SC + 5% βCD	49.82	294.79
9	I	20% CP + 5% SC + 5% SA	44.59	263.84
10	J	10% CP + 5% SA + 5% SC	32.42	191.83
11	K	5% CP + 5% SC + 5% SA	9.572	56.63
12	L	5% CP + 5% βCD + 5% SC + 5% SA	10.07	59.58
13	M	7.5% CP + 2.5% βCD + 2.5% SA + 2.5% SC	10.12	59.88
14	N	10% CP + 2.5% βCD + 2.5 SA + 2.5% SC	28.35	167.75
15	O	10% CP + 10% βCD +10% SC	26.75	158.28
16	P	10% CP + 10% βCD + 10% SA	29.77	176.15
17	Q	10% CP + 5% βCD + 2.5% SA + 2.5% SC	34.1	201.77
18	R	15% CP + 2.5% SC + 2.5% SA	36.791	217.69

CP = Sodium caprylate, SC = Sodium citrate, SA = Sodium acetate, βCD = Beta cyclodextrin

Discussion: Maximum increase in solubility of torsemide was observed in blend F (30%CP+5%SC+5%SA) but this blend has higher concentration of sodium caprylate. **Blend Q (10%CP+5%βCD+2.5%SA+2.5%SC)** having a pH of 7.8 has shown higher increase in solubility of torsemide, therefore blend Q was selected to be used in solid dispersion formation of torsemide.

Formulation of Solid Dispersions of Torsemide by Application of Mixed Solvency Concept

Depending upon the solubility of drug in mixed solvent blends, the formula for solid dispersion was finalized. The drug having desired solubility in respective blends was selected to formulate solid dispersion.

Procedure for Formulation of Solid Dispersion

For preparation of solid dispersion in SDA (1:4) ratios, accurately weighed sodium caprylate (5 gm), beta cyclodextrin (2.5 gm) sodium citrate (1.25 gm) and sodium acetate (1.25gm) were taken in a 100 ml beaker and were mixed properly. Then, 25 ml DM water was added. A

solution containing solubilizers was prepared on magnetic stirrer using teflon coated magnetic bead. Weighed quantity of torsemide drug (2.5 gm) was dissolved in the above solution and temperature was maintained in the range of 70- 80ºC so as to facilitate the evaporation of water. As evaporation proceeded, speed of 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 several watch glasses and the watch glasses were kept in hot air-dry oven maintained at 50 ± 2ºC so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve # 100 and were finally stored in an air tight glass bottle.

Same procedure was utilized to prepare solid dispersions in the ratio of SDB (1.5) and SDC (1.6), using appropriate quantity of solubilizers (table 7).

Table 7: Composition of solid dispersions of torsemide.

S. no.	Drug: solubilizers	Quantity taken (gm)				
		TR	**CP**	**SA**	SC	βCD
1	SDA (1:4)	2.5	5.00	1.25	1.25	2.5
2	SDB (1:5)	2	5.00	1.25	1.25	2.5
3	SDC (1:6)	1.67	5.00	1.25	1.25	2.5
TR= Torsemide; CP= Sodium caprylate; SA= Sodium acetate; SC= Sodium citrate; βCD= Beta cyclodextrin						

Formulation of Physical Mixtures

For preparation of physical mixture in PMA (1:4) ratio, accurately weighed sodium caprylate (5 gm), beta cyclodextrin (2.5 gm) sodium citrate (1.25 gm), sodium acetate (1.25gm) and (2.5 gm) of drug were used. This mixture was mixed using geometric dilution technique and was intensely triturated using glass pestle mortar for 10 min. After complete mixing, the powder mass was passed through sieve # 100 and was finally stored in an air tight glass bottle.

Same procedure was utilized to prepare physical mixture in the ratio of PMB (1:5) and PMC (1:6), using appropriate quantity of solubilizers. (table 8).

Table 8: Composition of physical mixtures of torsemide.

S. No.	Drug: solubilizers	Quantity taken (gm)				
		TR	CP	SA	SC	βCD
1	PMA (1:4)	2.5	5.00	1.25	1.25	2.5
2	PMB (1:5)	2	5.00	1.25	1.25	2.5
3	PMC (1:6)	1.67	5.00	1.25	1.25	2.5
TR= Torsemide; CP= Sodium caprylate; SA= Sodium acetate; SCI= Sodium citrate; βCD= Beta cyclodextrin, PMA= physical mixture A, PMB= physical mixture B, PMC= physical mixture C						

Determination of Drug Contents of Solid Dispersions and Physical Mixtures

Powdered solid dispersion or physical mixture equivalent to 20 mg of drug was accurately weighed and transferred to a 1000 ml volumetric flask. Then about 800 ml DM water was added the volumetric flask were shaken to get a clear solution, then volume was made up to 1000 ml with DM water. Absorbance of this solution was measured at 287 nm against corresponding reagent blank. Results of the analysis are shown in the table 9.

Table 9: Drug contents of solid dispersions and physical mixture of torsemide.

S. No.	Drug: Solubilizers Ratio	Drug content (% w/w)	
		Solid dispersion	Physical mixture
1	1:4	20.53	19.17
2	1:5	15.97	15.45
3	1:6	14.19	13.54

Dissolution Rate Studies

Dissolution tests are one of the most widely used tests in quality control of dosage forms. Dissolution tests become especially important when dissolution is the rate limiting step as in the case of B.C.S. class II or B.C.S. class IV drugs.

- **Procedure**

Solid dispersion or physical mixture equivalent to 20 mg of torsemide was tested in dissolution rate studies using U.S.P. XXIV (type II) dissolution test apparatus (Model TDT6P, Electrolab Mumbai, India) with paddle to rotate at 50 r.p.m. Nine hundred ml of 0.1N HCl was taken as dissolution medium with temperature of 37± 0.5°C. At definite time intervals, 20 ml of the samples were withdrawn and were analysed for drug content. Withdrawn samples were also replaced with fresh dissolution medium. Calculations for the amount of drug were done using respective regression equations and the results of the dissolution studies are shown in table 10,11 and 12.

Table 10: Dissolution rate studies of solid dispersion (ratio 1:4), physical mixture (ratio 1:4) and bulk drug.

S.no.	Time (min)	SDA (1:4)		PMA (1:4)		Bulk drug	
		CAD (mg)	% CDD	CAD (mg)	% CDD	CAD (mg)	% CDD
1	1	8.6	43.132	11.79	58.95	4.295	21.47
2	2	14.1	70.54	15.45	77.27	7.969	39.84
3	3	17.86	89.3	18.3	91.53	9.859	49.29
4	5	20.37	101	19.73	98.67	11.55	57.75
5	10	20.02	100.12	20.33	101.66	15.318	76.59
6	15	20	100.04	19.73	98.69	15.604	78.02
7	30	20.02	100.12	20.05	100.29	18.965	94.82
8	45	20.34	101.7	20.24	101.23	19.873	99.36
9	60	20.64	103.29	20.5	102.53	20.015	100.07
CAD= Cumulative amount dissolved; % CDD= % cumulative drug dissolved; SDA= Solid dispersion A; PMA= Physical mixture A.							

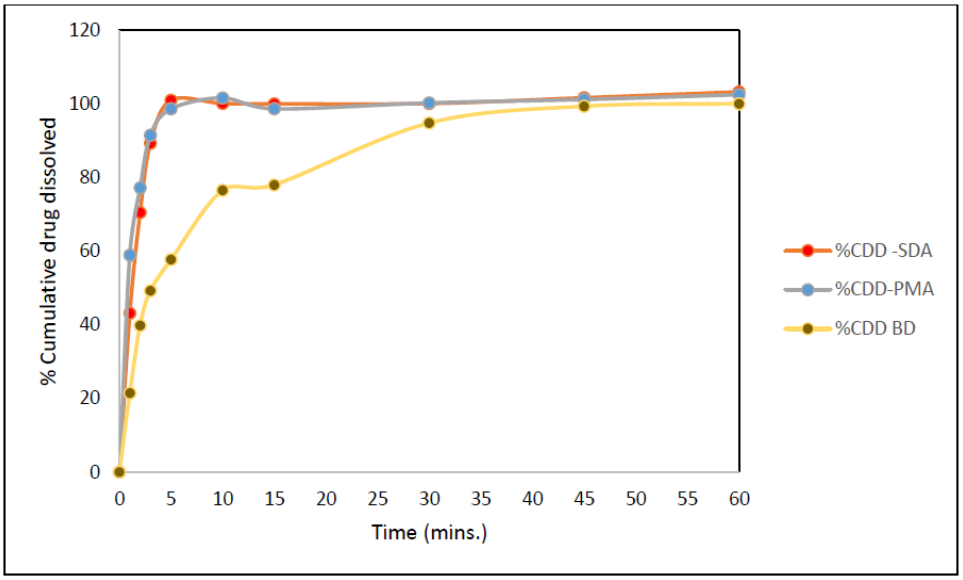

Fig. 6: Cumulative % drug dissolved v/s time plot of solid dispersion (%CDD- SDA) (ratio 1:4), physical mixture (%CDD-PMA) (ratio 1:4) and bulk drug (%CDD-BD) torsemide.

Table 11: Dissolution rate studies of solid dispersion (ratio1.5), physical mixture (ratio 1:5) and bulk drug.

S.no.	Time (min)	SDB (1:5)		PMB (1:5)		Bulk drug	
		CAD (mg)	% CDD	CAD (mg)	% CDD	CAD (mg)	% CDD
1	1	14.3	71.53	11.32	56.61	4.295	21.47
2	2	17.81	89.06	13.46	67.34	7.969	39.84
3	3	18.69	93.53	14.87	74.38	9.859	49.29

4	5	19.02	95.1	17.5	87.51	11.55	57.75
5	10	18.96	94.8	19.5	97.52	15.318	76.59
6	15	19.14	95.73	19.52	97.61	15.604	78.02
7	30	19.39	96.96	19.55	97.78	18.965	94.82
8	45	19.52	97.62	19.49	97.45	19.873	99.36
9	60	19.23	96.15	19.76	98.84	20.015	100.07
CAD= Cumulative amount dissolved; % CDD= % cumulative drug dissolved; SDB= Solid dispersion B; PMB= Physical mixture B.							

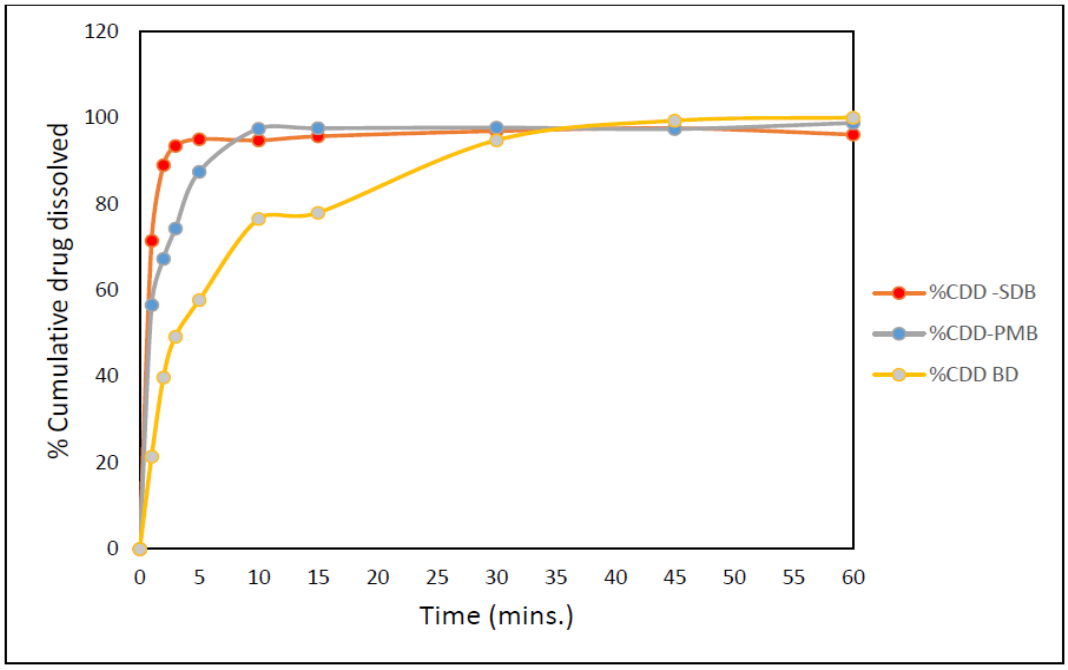

Fig. 7: Cumulative % drug dissolved v/s time plot of solid dispersion(%CDD-SDB) (ratio 1:5), physical mixture (%CDD-PMB) (ratio 1:5) and bulk drug (%CDD- BD) torsemide.

Table 12: Dissolution rate studies of solid dispersion (ratio 1:6), physical mixture (ratio 1:6) and bulk drug.

S.no.	Time (min)	SDC (1:6)		PMC (1:6)		Bulk drug	
		CAD (mg)	% CDD	CAD (mg)	% CDD	CAD (mg)	% CDD
1	1	15.24	76.2	10.62	53.11	4.295	21.47
2	2	16.43	82.17	18.61	93.07	7.969	39.84
3	3	17.99	89.97	19.04	95.24	9.859	49.29
4	5	19.35	96.75	19.74	98.7	11.55	57.75
5	10	19.27	96.39	19.56	97.8	15.318	76.59
6	15	19.26	96.33	19.7	98.51	15.604	78.02
7	30	19.22	96.12	19.68	98.42	18.965	94.82
8	45	19.5	97.51	19.65	98.28	19.873	99.36
9	60	19.74	98.7	19.98	99.9	20.015	100.07
CAD= Cumulative amount dissolved; % CDD= % cumulative drug dissolved; SDC= Solid dispersion C; PMC= Physical mixture C.							

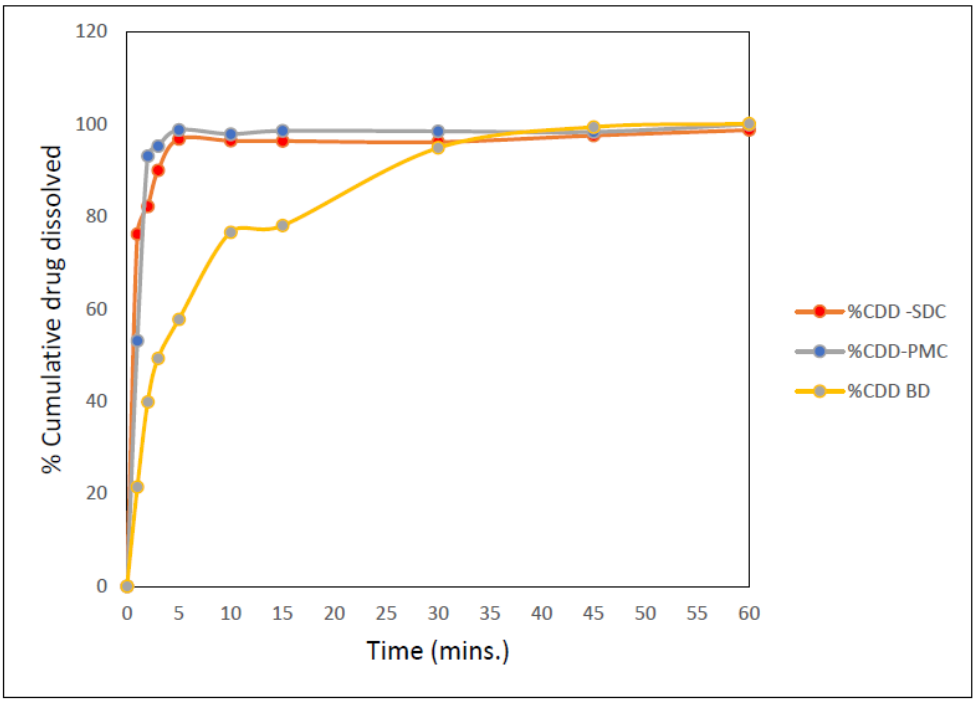

Fig. 8: Cumulative % drug dissolved v/s time plot of solid dispersion (%CDD- SDC) (ratio 1:6), physical mixture (%CDD-PMC) (ratio 1:6) and bulk drug (%CDD-BD) torsemide.

CONCLUSION

The cumulative drug dissolved in 5 min. in case of solid dispersion (1:4), physical mixture (1:4), solid dispersion (1:5), physical mixture (1:5), solid dispersion (1:6) and physical mixture (1:6), were found to be 101%, 98.67%, 95.10%, 87.51%, 96.75% and 98.70%, respectively. On the other hand, it was found to be only 57.75% in case of bulk drug.

Stability Studies

Solid dispersions of torsemide were kept at room temperature and cool temperature storage conditions. Test samples were withdrawn at different time intervals and the drug contents were determined. The results are reported in table 30.

Table 13: Chemical stability study of solid dispersion and physical mixture of torsemide.

S. No.	Time (week)	%Drug remaining			
		Solid dispersion 1:4 drug and solubilizers		Solid dispersion 1:5 drug and solubilizers	
		Room temperature	Cool temperature	Room temperature	Cool temperature
1.	0	100	100	100	100
2.	1	98.90	99.04	99.34	99.60
3.	2	98.36	98.78	99.34	99.21
4.	3	98.77	98.78	98.41	98.41
5.	4	97.40	98.08	98.15	98.41
6.	5	97.12	98.36	97.62	97.75
7.	6	96.30	97.53	96.70	97.49
8	7	95.34	96.58	95.64	96.57
9	8	94.25	95.21	95.25	95.38
10	9	93.84	94.39	94.45	94.71
11	10	93.97	94.80	93.66	93.93
12	11	93.43	93.70	93.00	93.53
13	12	92.74	93.02	92.34	92.47
14	13	91.37	92.33	91.42	91.81
15	14	90.70	91.92	90.49	90.49

Thin layer chromatography (TLC) analysis

TLC analysis was done to identify any drug solubilizer interaction (table 15). Methanol was used as a solvent for sample preparation for TLC of the drug. Solid dispersion and physical mixture were dissolved in DM water for the spot.

Table 14: TLC analysis of pure drug, solid dispersion and physical mixture.

S. No.	Mobile Phase	Rf Value			Inference
		Drug	SD	PM	
1	Hexane: Ethyl acetate (7:3)	0.43	0.45	0.41	No significant change in Rf value. Hence, no interaction between drug and solubilizer

SD= Solid dispersion, PM= Physical Mixture

CONCLUSION

The aim of the present research study was to explore the scope of mixed solvency technique that can be used to enhance the solubility of a poorly water-soluble drug. The main aim of this study was showcasing that solids can serve the purpose of solvent. In future, the solids can be employed as solvents resulting into eco-friendly methods precluding the use of organic solvents.

For identification and characterization of drug, spectrophotometric analysis, FTIR spectroscopy, differential scanning calorimetry study were carried out. The drug complied with the results reported in the literature. The calibration curve of the drug was prepared in the aqueous solution of sodium caprylate (30% w/v). The linearity of the calibration curve showed that the Beer Lambert's law was obeyed in the concentration range of 10-50µg/ml at the λ max of 287 nm in DM water. Aqueous solubility of drug was found to be 0.169 mg/ml. Drug excipient physical compatibility study was done. These studies showed no physical incompatibility between the drug and excipients. Solubilisers did not interfere in the spectrophotometric analysis of torsemide at 287 nm. Different solid dispersions were prepared with different drug and solid solubiliser ratio. Prepared solid dispersions were compared for dissolution studies with pure drug and physical mixture. Solid dispersions containing drug, polymer in various ratios showed very good drug release profile. Torsemide pure drug, physical mixture and solid dispersion were also studied for TLC that showed no interaction between drug and polymer in the ratios. Comparative study marketed tablet and formulated tablet was done.

From all the above studies, it was concluded that the approach of mixed solvency is novel, safer and user friendly. It also eliminates the problem of toxicity associated with the use of toxic organic solvents. So, it may be employed in the dosage form development of drugs where solid dispersion needs to be prepared. By the study of suitable drug: solid solubilizer ratio, the dissolution pattern may be improved.

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