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Formulation & Evaluation of Solid Dispersion of Torsemide

Mohd. Faarooq Khan*[1], Dishant Gupta[2], Sudha Vengurlekar[3], Sachin Kumar Jain[4]

[1]Research Scholar, Faculty of Pharmacy, Oriental University, Indore (M.P.), India

[2, 3, 4]Faculty of Pharmacy, Oriental University, Indore (M.P.), India

***Corresponding Author :**

Email ID: mohd.faarooqkhan@yahoo.com

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ABSTRACT

By using solid solubilizers, solid dispersion specifically seeks to increase the solubility of medications that are not very soluble in water. A mixture of solubilizers may be employed to increase the drug's solubility, which will lower the concentrations of each solubilizer alone and effectively increase the drug's solubility. The goal of this study is to make the medication torsemide more soluble in water. Three distinct batches of solid dispersions (SDA, SDB, and SDC) with varying ratios (1:4, 1:5, and 1:6) are made using precisely weighed sodium caprylate, beta cyclodextrin, sodium citrate, sodium acetate, water, and torsemide, and the temperature is kept between 70 and 80 degrees Celsius. Micromeritic Properties of Solid Dispersions, Powder X-Ray Diffraction Studies, Scanning Electron Microscopy, and Dissolution Rate Studies were used to assess the solid dispersion, and the SDA batch produced good results.

Keywords: *Solid Dispersion, Poorly Water Soluble, Torsemide, Solubility.*

1. INTRODUCTION

Solid dispersion is a system where the surplus medication separates as crystals or in an amorphous form in the vehicle after first separating as a solid phase. This occurs when the excess drug is present in the medium in excess of its saturation solubility at room temperature. Figure roughly illustrates the benefits of a solid dispersion over a traditional capsule or tablet format [1-3].

Solid Dispersions Generations

First generation solid dispersions

Previously, urea and sugars which are thought to be the original carriers—were used to create the solid dispersions. The drawback of these solid dispersions is that, in contrast to their amorphous counterparts, they slow down the release of the medication by forming crystalline solid dispersions, which are very thermodynamically stable [4].

Solid dispersions of the second generation

Amorphous carriers are used to identify the second generation of solid dispersions. Since polymeric carriers are amorphous solid dispersions, they are thought to be the most useful. In order to achieve better wet ability and distribution of the drug in the carrier material, the drug particle size was significantly reduced to molecular size. This resulted in the creation of an amorphous system that contained both the drug and amorphous carriers. The drug release is dominated by the carrier's breakdown [5].

Solid dispersions of the third generation when the idea of improved dissolving profiles surfaced, a third generation of solid dispersion evolved. If the carrier exhibits any surface activity or self-emulsifying properties, the drug release may be improved. These include a surfactant carrier or a combination of surfactant and amorphous polymers. In addition to minimizing medication crystallization, they also contribute to increased bioavailability, which produces very stable solid dispersions.

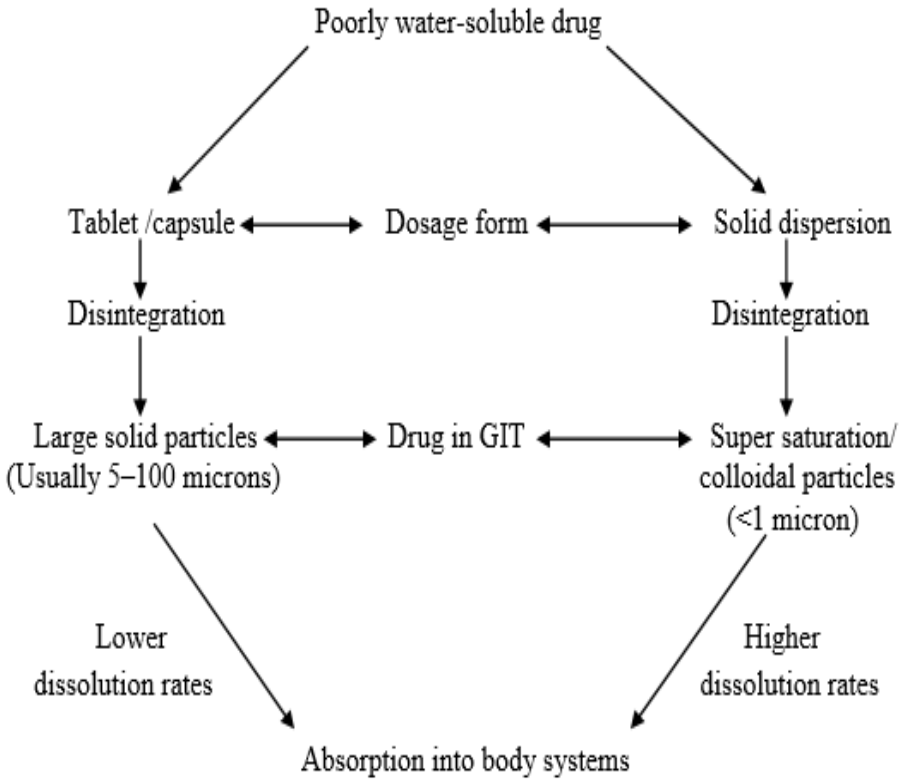

Fig. 1: Advantages of a solid dispersion formulation, as compared to conventional capsule or tablet formulations.

Methods for Preparation of Solid Dispersions

Hot melt method

The carrier and the drug are mixed together and heated till the highest melting point of the constituent is achieved which is indicated by formation of a clear liquid. Then this liquid mixture is allowed to cool and solidify only to pulverize later and passed through sieve of size 125-250 µm. This method applies only to those drugs that are thermo-resistant [6].

Hot melt extrusion

Melt extrusion method is same as the fusion method except that intense mixing of the components is induced by the extruder. The melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. By the help of this technique there is possibility of continuous production, as compared to the traditional fusion method, which makes it suitable for large scale production [7].

Solvent method

The carrier is dissolved in a solvent and then the drug is incorporated into it later the solvent is evaporated under the vacuum. The most important point here is that the solvent used here should be a good solvent for the drug and the carrier. The solvent can be removed later once the carrier and the drug completely solubilise [8].

Solid Dispersion Prepared by Using Hydrotropy, Mixed Hydrotropy and Mixed Solvency Concept

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 concept of highest utilization. Nowadays, maximum drugs have poor aqueous solubility and the drugs under development pose the same problem as well indicating an urge to develop techniques to enhance the solubility and bioavailability of drugs. Solid dispersion not only enhances the drug dissolution but absorption too [9].

Eutectic solid dispersion

The crystalline drugs lead to formation of more physically stable solid dispersions when compared to amorphous solid dispersions.A eutectic mixture forms crystalline type of solid dispersion comprising crystalline drug and a water-soluble

crystalline polymer. The polymer and the drug are first melted and form a molten mixture (above melting point) indicating complete miscibility of the two components. One example of this type of eutectic mixture is reported in the literature containing feno fibrate and PEG 8000 in the ratio of 35:65 (w/w) and a drug release of 90% was observed within 30 minutes of exposure to media followed by maintaining the sink condition. A phase diagram is provided to understand the mechanism of formation of eutectic mixture (figure 3). A crystalline drug that contains a molten composition (A) Following the drug's crystallization, a water-soluble polymer (B) is chilled to create a eutectic combination. The soluble carrier quickly dissolves and separates from the crystalline drug when drug dissolution is studied. The Noyes-Whitney equation explains how a reduction in particle size results in an increase in the rate of dissolution [10].

dW/ dt = DA (Cs-C) /L

Where dW/dt is the dissolution rate, A is the surface area, C is the concentration of the drug in the bulk media, C is the solubility of the drug in the media and L is the diffusion layer. The eutectic compositions dominate the possibility of formation of eutectic solid dispersions. Before preparing a eutectic composition, a phase diagram needs to be generated to figure out the possibility of formation of eutectic mixture which is slightly time consuming.Clinical use of the eutectic composition is limited because a specific composition of the ingredients is required to form a eutectic mixture. Hence, in spite of the fact that thermodynamically stable formulation has been prepared but still this cannot be used widely in the pharmaceutical industry.

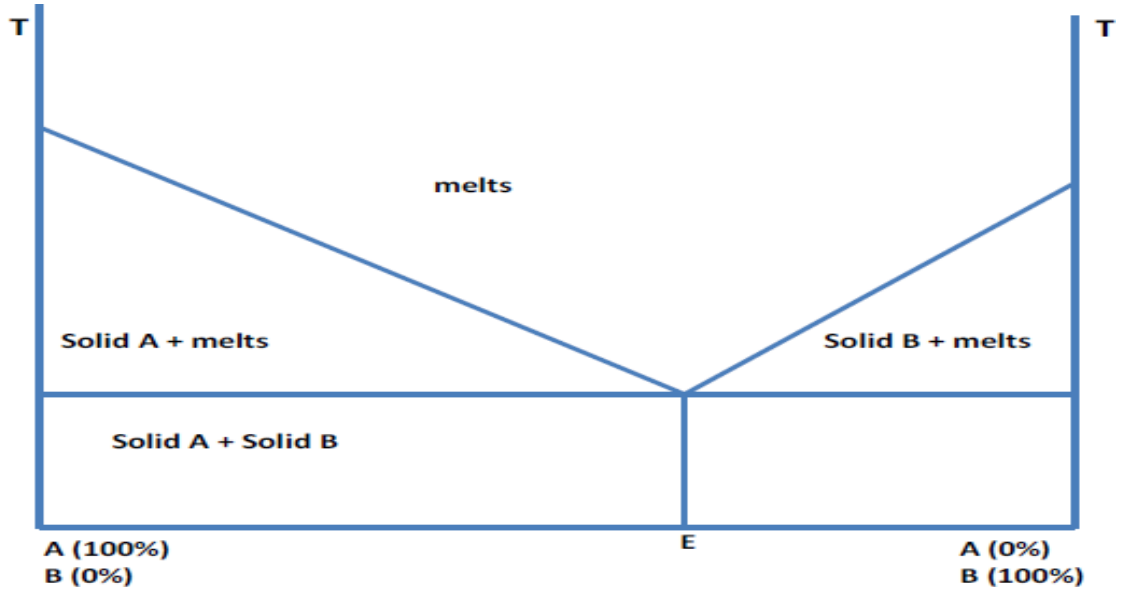

Fig. 2: Phase diagram of the formation of eutectic mixture of a drug (A) and a polymer (B) with the composition of E.

Characterization of solid dispersions

- Dissolution
- Thermal analysis Cooling curve method
    - Thaw meltmethod
    - Thermo-microscopicmethod
    - Differential thermalanalysis
    - Differential scanning calorimetry
- X-ray diffractionmethod
- Spectroscopicmethod

Microscopic method

Method 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)

Table 1: 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						

2. MICROMERITIC PROPERTIES OF SOLID DISPERSIONS

Any method of measuring the powder flow must be practical, useful, reproducible and sensitive must yield meaningful results, but actually no simple powder flow method is adequate or complete to characterize the wide range of flow properties experienced in the pharmaceutical industries. Therefore, an appropriate strategy is the use of multiple standardized test methods to characterize various aspects of powder flow as needed by the pharmaceutical scientist.

Following micromeritic properties of the solid dispersion of torsemide were studied and recorded in table

- Bulk density
- Tapped density
- Compressibility index
- Hausners ratio
- Angle of repose

Table 2: Results of micromeritic properties of solid dispersions

S. No.	Parameter	Result
1	Bulk density (gm/cm^3)	0.543
2	Tapped density (gm/cm^3)	0.669
3	Compressibility index	19.01
4	Hausner ratio	1.221
5	Angle of repose	28.79°

Conclusion

The closeness of values of bulk densities and tapped densities indicates the free flowing property of solid dispersions. The values of compressibility index, Hausner ratio and angle of repose indicate that the flow character of solid dispersion is fair and no aid is needed to increase the flow properties.

3. POWDER X-RAY DIFFRACTION STUDIES

The powder X-ray diffraction spectra were obtained using RU-H_3R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo). The graticule containing powder was placed in sample holder and exposed to C_uK_α-radiation (40 KV, 50 MA), $2\theta = 5^o$ to 40^o at a scanning speed 4°/min and step size 0.02^o 2θ. The X-ray diffractograms of torsemide, 1:4 solid dispersion and 1:4 physical mixture so obtained are presented in fig.7.5 - 7.7 respectively.

Results: The crystalline nature of the drug, torsemide was clearly demonstrated by the characteristic XRD pattern with peak appearing at 5.6°, 10.66°, 15.58°, 16.78°, 21.9° and 26.1° values. Also the XRD diffraction patterns of solid dispersion and physical mixture have same peaks and are thus easily comparable with that of torsemide. The decrease in intensity of peaks in the curve of solid dispersion shows amorphous state of solid dispersion.

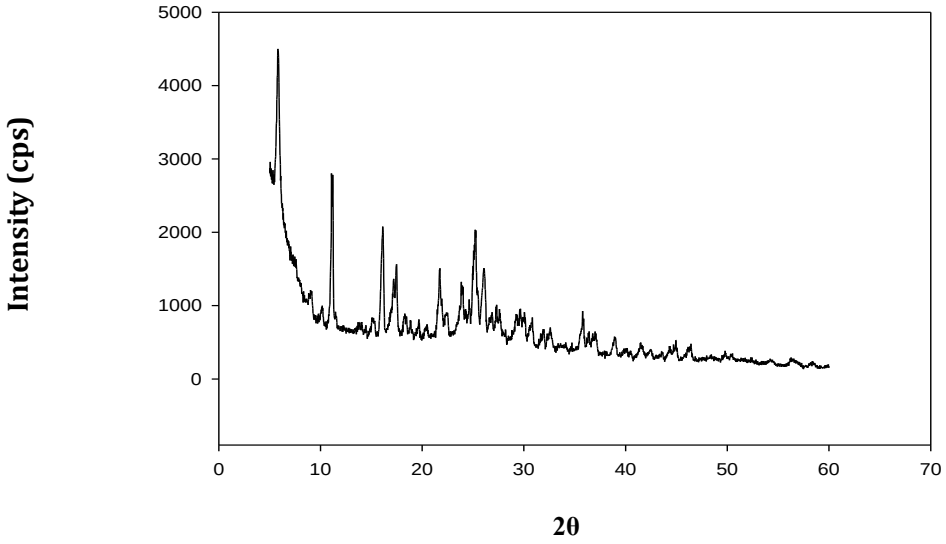

Fig 3: X.R.D. spectra of 1:4 solid dispersion of torsemide

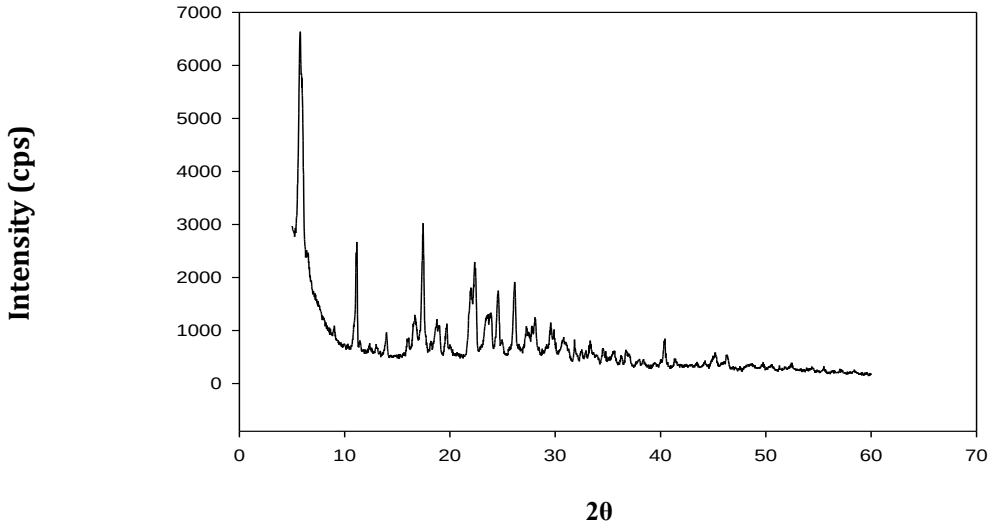

Fig. 4: X.R.D. spectra of 1:4 Physical mixture of torsemide

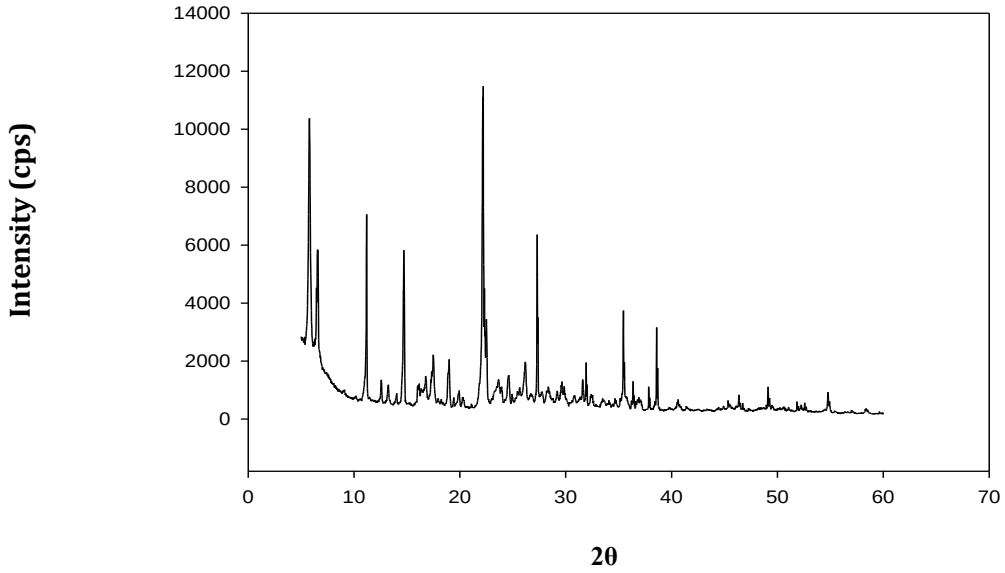

Fig. 5: X.R.D. spectra of pure torsemide

4. SCANNING ELECTRON MICROSCOPY

S.E.M. was used to investigate solid state physical structure of the prepared solid dispersions. S.E.M. photographs of torsemide, its physical mixture with solubilizers and its solid dispersions were obtained using a scanning electron microscope model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV. Results are shown in fig. 7.11-7.13.

Result: The drug crystals seemed to be irregular in shape and size. The physical mixture of the drug and solubilizers showed the presence of drug in the crystalline form. It was easy to recognize the solubilizer particles from that of drug despite the reduction in size of particles of solubilizers during mixing and its presence in high amount (1:4 ratio). In case of SDs, it was difficult to distinguish the presence of torsemide crystals. Torsemide crystals appeared to be incorporated into the solubilizer particles. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the solubilizers.

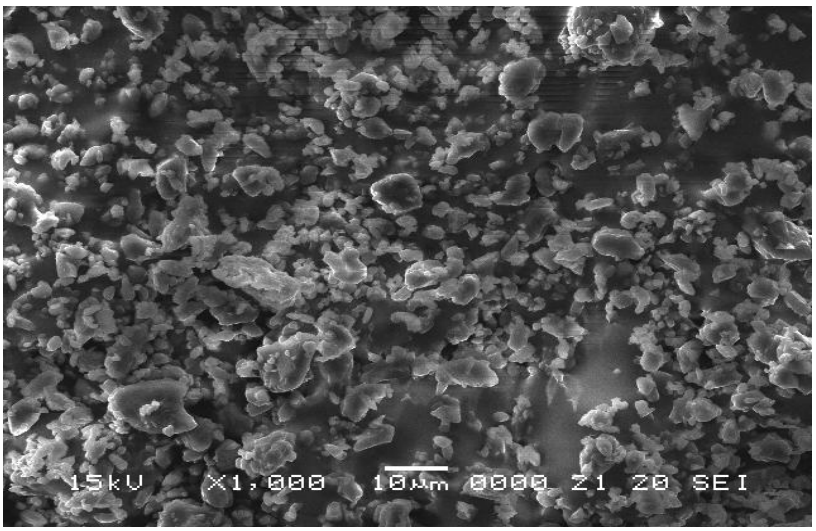

Fig. 6: SEM photograph of pure torsemide

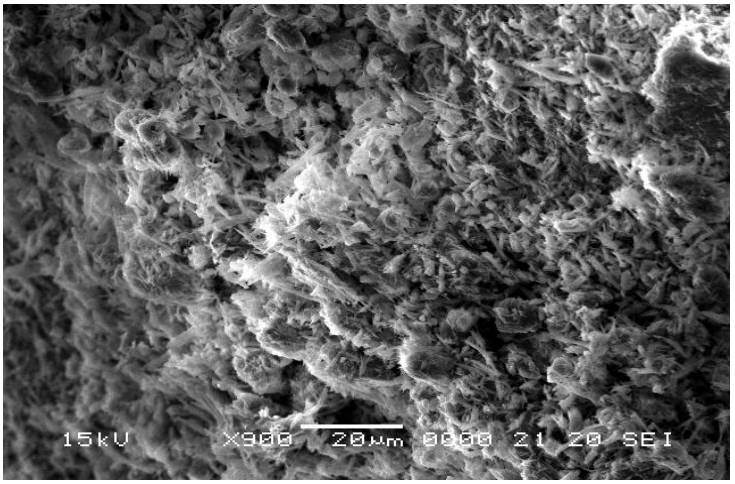

Fig 7: SEM photograph of physical mixture of torsemide

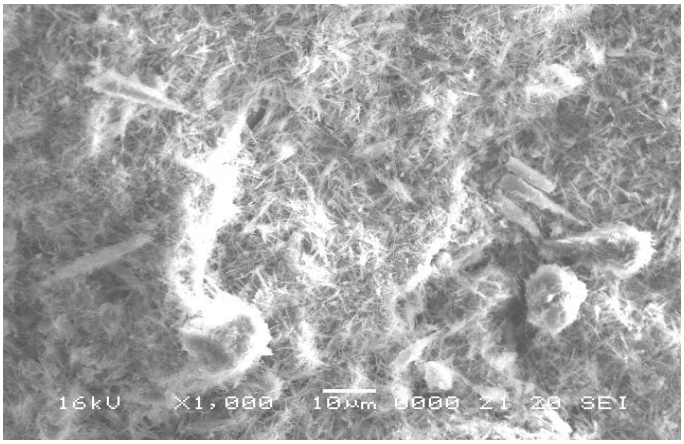

Fig 8: SEM photograph of solid dispersion of torsemide

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$\pm$ 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 tables.

Table 3: Dissolution rate studies of solid dispersion (ratio 1:4, 1:5,1:6)

S.no.	Time (min)	SDA (1:4)		SDB (1:5)		SDC (1:6)	
		CAD (mg)	% CDD	CAD (mg)	% CDD	CAD (mg)	% CDD
1	1	8.6	43.132	14.3	71.53	15.24	76.2
2	2	14.1	70.54	17.81	89.06	16.43	82.17

3	3	17.86	89.3	18.69	93.53	17.99	89.97
4	5	20.37	101	19.02	95.1	19.35	96.75
5	10	20.02	100.12	18.96	94.8	19.27	96.39
6	15	20	100.04	19.14	95.73	19.26	96.33
7	30	20.02	100.12	19.39	96.96	19.22	96.12
8	45	20.34	101.7	19.52	97.62	19.5	97.51
9	60	20.64	103.29	19.23	96.15	19.74	98.7
CAD= Cumulative amount dissolved; % CDD= % cumulative drug dissolved; SDA= Solid dispersion A; PMA= Physical mixture A.							

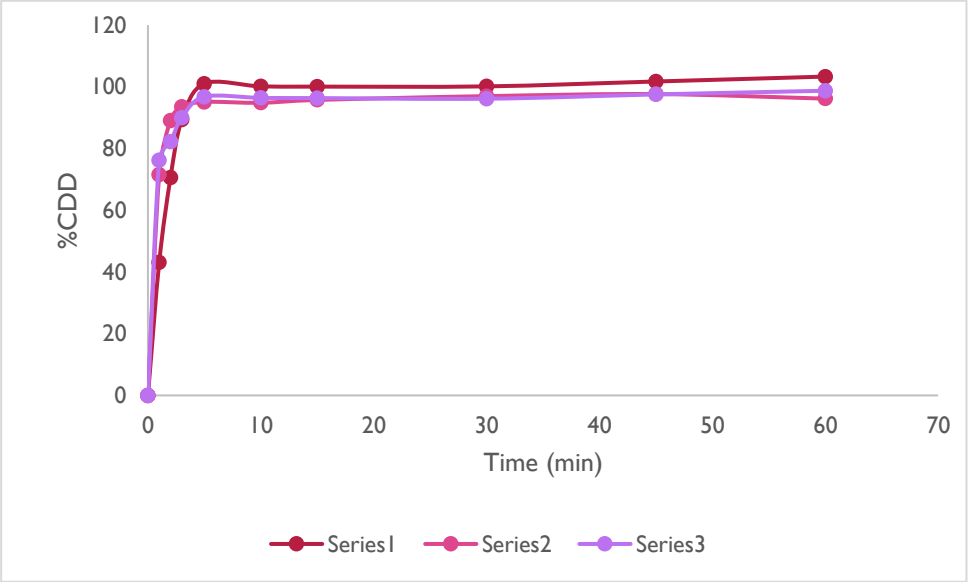

Fig. 9: Cumulative % drug dissolved v/s time plot of solid dispersion (%CDD-SDA, SDB, SDC) (ratio 1:4, 1:5, 1:6) torsemide

Conclusion: The cumulative drug dissolved in 5 min. in case of solid dispersion (1:4) was found to be 101%, 98.67%, 95.10%.

5. SUMMARY AND CONCLUSION

In the present study, poorly water-soluble drug, Torsemide, was the drug of choice. It was incorporated into solid dispersion using random combination of several solubilises, Solid dispersion is prepared by using SDA in 1:4,1:5,1:6 ratios, accurately weighed sodium caprylate, betacyclodextrin, sodium citrate, sodium acetate, water and torsemide and temperature was maintained in the range of 70- 80℃.

The Solid Dispersion is Evaluated by Solid Dispersion was evaluated by Micromeritic Properties-Bulk density (0.543), Tapped density(0.669),Compressibility index(19.01), Hausners ratio (1.221), Angle of repose (28.79°),

Powder X-Ray Diffraction Studies-The crystalline nature of the drug, torsemide was clearly demonstrated by the characteristic XRD pattern with peak appearing at 5.6˚, 10.66˚, 15.58˚, 16.78˚, 21.9˚ and 26.1° values.

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