Original Article

Characterization And Identification & Development Of Physical Mixture Of Torsemide

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Abstract

Innumerable problems are encountered while formulating a drug of poor water solubility into a formulation with good bioavailability. A couple of decades ago, the reason behind failures in drug development was due to poor biopharmaceutical properties such as poor water solubility of the drugs molecules. The process of new drug development can come to a standstill if the drug candidate has poor water solubility or if it is completely insoluble in water. Due to poor solubility of drugs in water, many marketed products need to be reformulated as the formulation cannot avail the desired amount of drug to the site of action. The drugs can provide relief, but the diuretics are poorly soluble in nature. So, formulating them is a tedious and difficult task. So, before formulation their solubility should be enhanced in order to increase drug availability and bioavailability simultaneously. The present research work aims to enhancing the solubility of the drug to multiple folds. Solid dispersion particularly aims at enhancing the solubility of poorly water-soluble drugs by the use of solid solubilises. A combination of solubilises can be used to enhance the solubility of the drug leading to reduction in individual concentrations of solubilises and effective enhancement of solubility of the drug. 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 solubilizes. The solubilizes were dissolved in water and then drug was added, a clear yellow solution was formed. The excess water was evaporated from this solution and solid dispersion was obtained which was later dried completely, pulverized and packed

Keywords: Poorly water-soluble drug, Solubility, Drug, Enhancing, Torsemide.

INTRODUCTION

A system in which excess amount of drug is present more than its saturation solubility inthe medium at room temperature is referred to as solid dispersion where the excess drug separates in the form of crystals or in amorphous form in the vehicle after separating as a solid phase. Advantage of a solid dispersion as compared to a conventional capsule or tablet formulation is shown schematically in Figure 1.

Solid Dispersions Generations

First generation solid dispersions

Earlier the solid dispersions were prepared using urea and sugars which are believed to be the first carriers. The disadvantage associated with these solid dispersions is that they form crystalline solid dispersions which is highly thermodynamically stable and slows down the release of drug as compared to the amorphous forms.

Second generation solid dispersions

The second generation of solid dispersions is identified with the use of amorphous carriers. Polymeric carriers are believed to be of highest utility because they are amorphous solid dispersions. The drug particle size was reduced appreciably to molecular size in order to completely dissolve the drug in the water-soluble carrier, to achieve better wettability and distribution of the drug in the carrier material resulting into the production of amorphous system containing amorphous carriers and drug. The dissolution of carrier dominates the drug release.

Third generation solid dispersions

A third generation of solid dispersion appeared when the thought of improvement in dissolution profiles emerged. The drug release can be enhanced if the carrier has any surface activity or self-emulsifying characteristics. These contain a

surfactant carrier, or a mixture of amorphous polymers and surfactant as carriers. These not only help in reducing drug crystallization to minimum but also help achieve higher bioavailability resulting into highly stable solid dispersions.

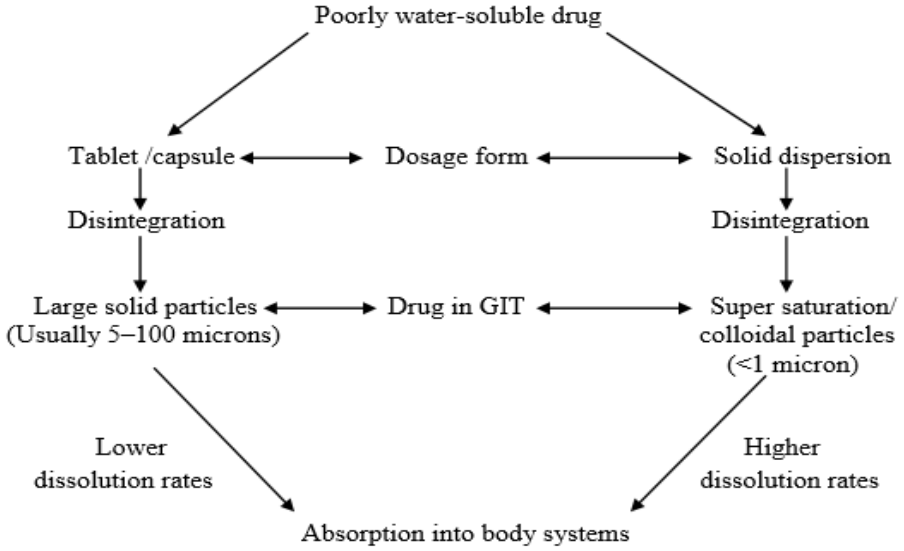

Figure 1 Advantages of a solid dispersion formulation, as compared to conventional capsule or tablet formulations.

TYPES OF SOLID DISPERSIONS

Table 1 Classification of solid dispersions

S. No.	Solid dispersion type	Matrix	Drug	Remarks	No. of phase
I	Eutectics	Crystalline	Crystalline	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	Crystalline	Amorphous	Rarely encountered	2
III	Solid solutions				
A	Continuous solid solutions	Crystalline	Molecularly dispersed	Miscible at all composition, never prepared	
B	Discontinuous solid solutions	Crystalline	Molecularly dispersed	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
C	Substitutional solid solutions	Crystalline	Molecularly dispersed	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous.	1 or 2
D	Interstitial solid solutions	Crystalline	Molecularly dispersed	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
IV	Glass suspension	Amorphous	Crystalline	Particle size ofdispersed phase dependent on cooling/evaporationrate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	Amorphous	Amorphous	Particle size of dispersed phase dependent on cooling/ evaporation rate. Many solid dispersions are of this type	2
VI	Glass solution	Amorphous	Molecularly dispersed	Requires miscibility or solid solubility, complex formation or upon fast cooling or evaporation during	1

				preparation, many (recent) examples especially with PVP	

Table 2 Carriers used in solid dispersions

Polymers	Polyvinylpyrrolidone, PEG, HPMC, HEC, Cyclodextrin, HPC, Pectin.
Insoluble/enteric polymer	HPMC phthalate, Eudragit L 100, Eudragit S-100, Eudragit RL, Eudragit RS
Surfactant	Polyoxyethylene stearate, Renex, Poloxamer 188, Texafor AIP, Deoxycholic acid, Tween 80
Acids	Citric acid, Succinic acid
Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol
Miscellaneous	Urea, Urethane, Hydroxy alkylamine, Pentaerythritol, sodium benzoate

DRUG CHARACTERIZATION

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 Figure 2.

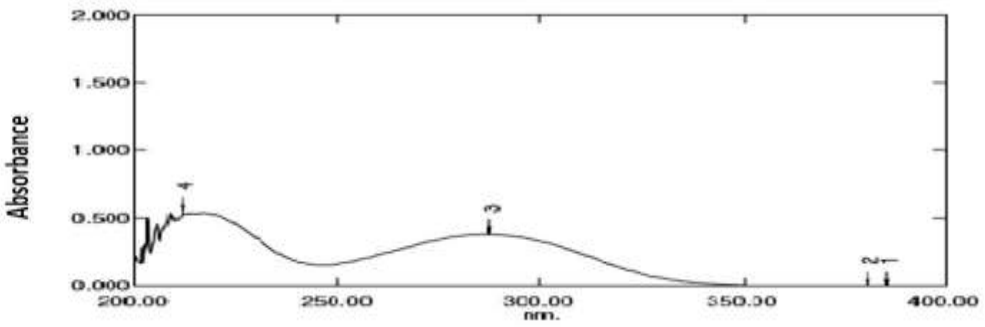

Figure 2 UV spectra of torsemide in DM water

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. 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 aluminium pan. The pan was sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10ºC/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 40-300ºC. Various DSC thermograms (melting isotherms) are shown in Figure 3.

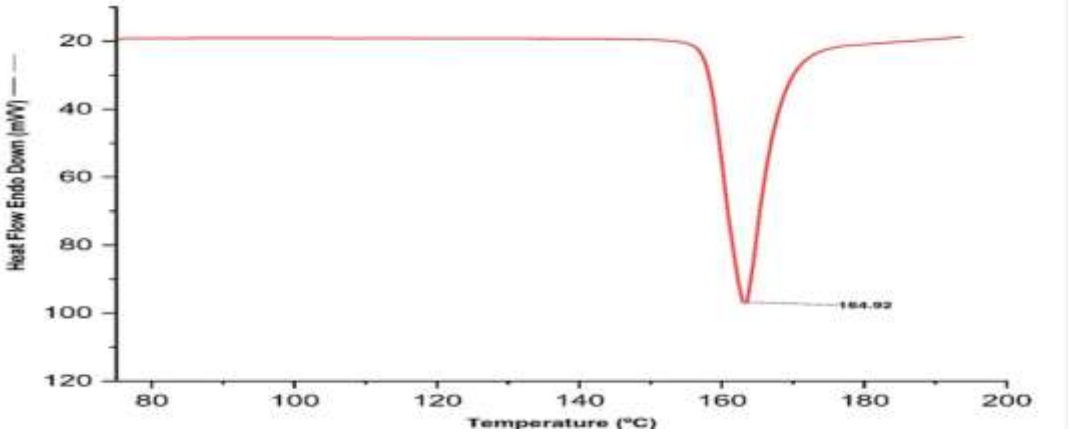

Figure 3 DSC curve of torsemide

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 are shown in Figure 4.

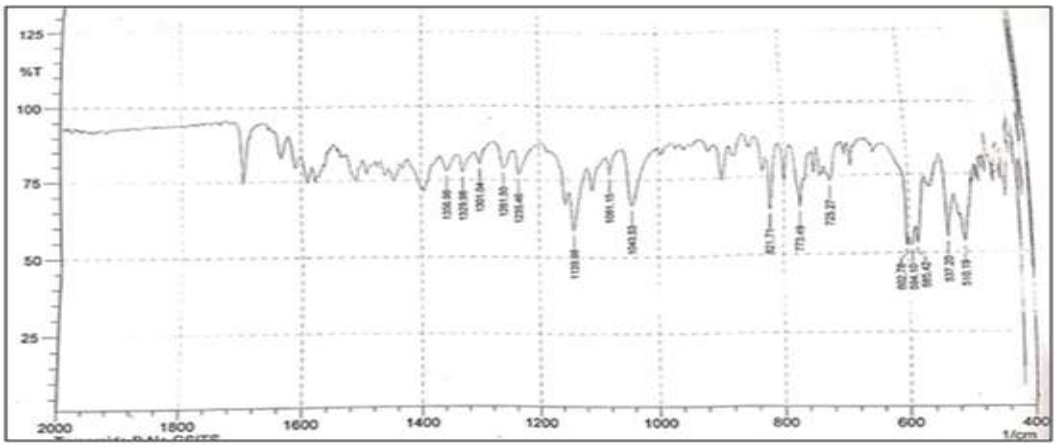

Figure 4 FT-IR spectra of torsemide drug sample

Table 3 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

The procured sample of torsemide was characterized by UV/visible spectrophotometry, melting point determination, DSC analysis and FTIR spectroscopy studies. The results from the above analysis were found matching with the values reported in the literatures for torsemide. Hence it was inferred that the procured drug sample was of pure torsemide and hence used for further studies.

Formulation of Physical Mixtures

For preparation of physical mixture in PMA (1:4) ratio, accurately weighed sodium caprylate, beta cyclodextrin, sodium citrate, sodium acetate and 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 (1:2), PMB (1:4) and PMC (1:6), using appropriate quantity of solubilizers.

S. No.	Batch	Blend composition	Drug: solubilizers1:2	Drug: solubilizers1:4	Drug: solubilizers :6
1	A	30% CP	1gm: 2gm	1gm:4gm	1gm:6gm
2	B	20% CP + 10% SC	1gm: 2gm	1gm:4gm	1gm:6gm
3	C	20% CP + 10% SA	1gm: 2gm	1gm:4gm	1gm:6gm
4	D	20% CP + 10% βCD	1gm: 2gm	1gm:4gm	1gm:6gm
5	E	10% SA + 10 % SC	1gm: 2gm	1gm:4gm	1gm:6gm
6	F	30% CP + 5% SC + 5% SA	1gm: 2gm	1gm:4gm	1gm:6gm
7	G	30% CP + 5% SA + 5% βCD	1gm: 2gm	1gm:4gm	1gm:6gm
8	H	30% CP + 5% SC + 5% βCD	1gm: 2gm	1gm:4gm	1gm:6gm
9	I	20% CP + 5% SC + 5% SA	1gm: 2gm	1gm:4gm	1gm:6gm
10	J	10% CP + 5% SA + 5% SC	1gm: 2gm	1gm:4gm	1gm:6gm
11	K	5% CP + 5% SC + 5% SA	1gm: 2gm	1gm:4gm	1gm:6gm
12	L	5% CP + 5% βCD + 5% SC + 5% SA	1gm: 2gm	1gm:4gm	1gm:6gm
13	M	7.5% CP + 2.5% βCD + 2.5% SA + 2.5% SC	1gm: 2gm	1gm:4gm	1gm:6gm
14	N	10% CP + 2.5% βCD + 2.5 SA + 2.5% SC	1gm: 2gm	1gm:4gm	1gm:6gm
15	O	10% CP + 10% βCD +10% SC	1gm: 2gm	1gm:4gm	1gm:6gm
16	P	10% CP + 10% βCD + 10% SA	1gm: 2gm	1gm:4gm	1gm:6gm
17	Q	10% CP + 5% βCD + 2.5% SA + 2.5% SC	1gm: 2gm	1gm:4gm	1gm:6gm
18	R	15% CP + 2.5% SC + 2.5% SA	1gm: 2gm	1gm:4gm	1gm:6gm

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 D, Blend I, Blend N, Blend Q** having a pH of 7.8 has shown higher increase in solubility of torsemide was selected to be used in Physical Mixture formation 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

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, Electro lab 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 4-7 & Figure 5-8.

Table 4 Dissolution rate studies of batch D physical mixture

S.no.	Time (min)	PMB (1:2) % CDD	PMB (1:4) % CDD	PMB (1:6) % CDD
1	2	11.66	12.21	15.21
2	4	18.52	17.12	20.07
3	6	25.02	27.88	30.4
4	8	29.3	35.78	40.44
5	10	32.26	40.66	53.02
6	15	45.03	49.23	68.33
7	30	52.66	60.21	72.01
8	45	61.22	72.33	78.3
9	60	72.01	80.92	83.44
% CDD= % cumulative drug dissolved; PMB= Physical mixture				

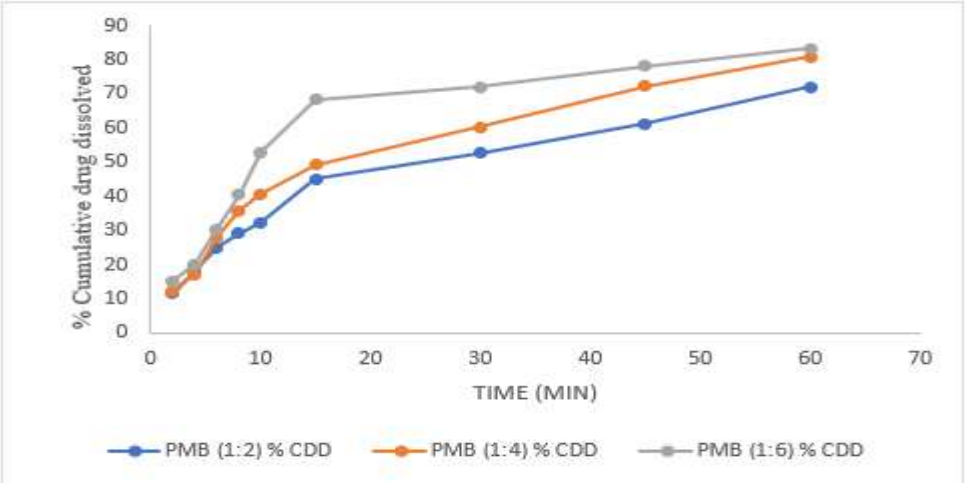

Figure 5 Cumulative % drug dissolved v/s time plot of batch D physical mixture (%CDD-PMA)

Table 5 Dissolution rate studies of batch I physical mixture

S.no.	Time (min)	PMB (1:2) % CDD	PMB (1:4) % CDD	PMB (1:6) % CDD
1	2	10	13.1	15
2	4	12.02	19.23	21.07
3	6	18.45	29.66	34.4
4	8	27.23	35.46	43.44
5	10	34.16	44.03	55.46
6	15	45.46	55.46	63.46
7	30	58.32	65.08	72.98
8	45	68.02	78.99	80.56
9	60	78.22	84.7	87.26
% CDD= % cumulative drug dissolved; PMB= Physical mixture				

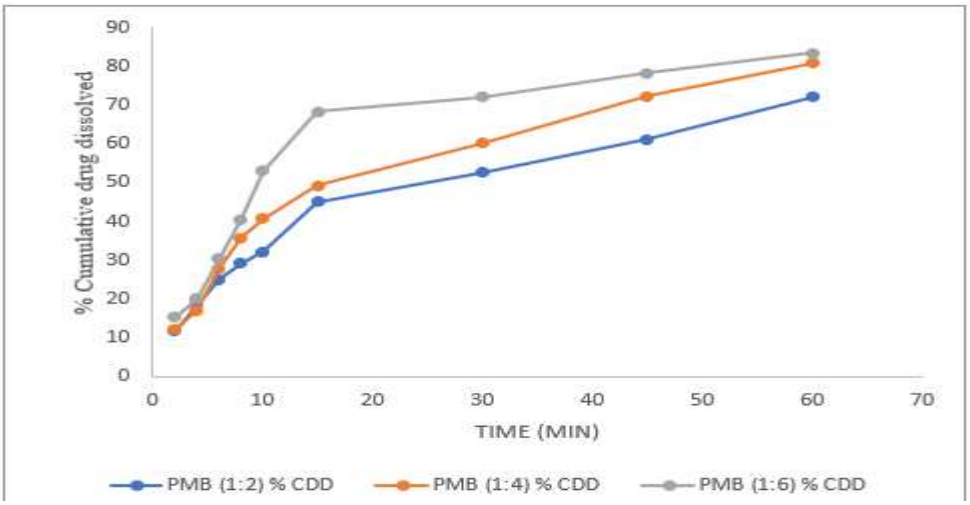

Figure 6 Cumulative % drug dissolved v/s time plot of batch I physical mixture (%CDD-PMA)

Table 6 Dissolution rate studies of batch N physical mixture

S.no.	Time (min)	PMB (1:2) % CDD	PMB (1:4) % CDD	PMB (1:6) % CDD
1	2	10.66	13.1	15.88
2	4	12	17.46	22.78
3	6	17.52	27.46	32.45
4	8	28.23	34.4	45.87
5	10	35.46	42.8	52.78
6	15	44.46	52.02	63.46
7	30	57.8	62.7	72.98
8	45	67.23	75.23	80.56
9	60	75.23	85.08	87.26
% CDD= % cumulative drug dissolved; PMB= Physical mixture				

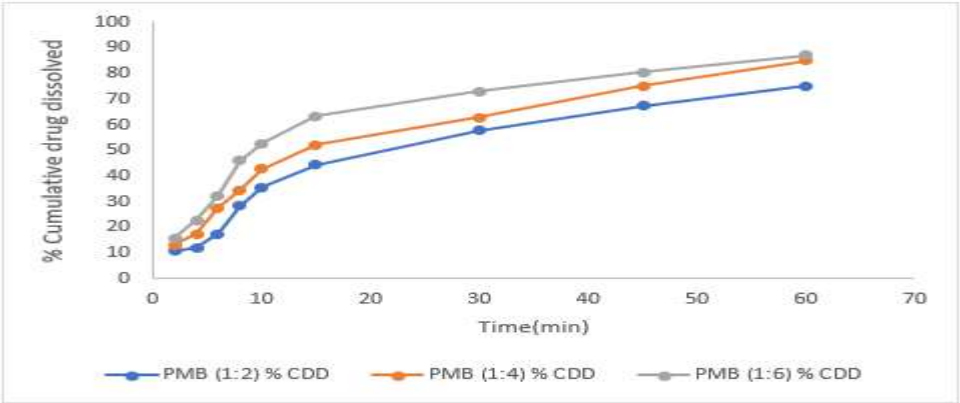

Figure 7 Cumulative % drug dissolved v/s time plot of batch I physical mixture (%CDD-PMA)

Table7 Dissolution rate studies of batch Q physical mixture

S.no.	Time (min)	PMB (1:2) % CDD	PMB (1:4) % CDD	PMB (1:6) % CDD
1	2	9.58	11.32	15.88
2	4	10.98	15.75	22.78
3	6	15.62	25.23	32.45
4	8	26.45	32.44	45.87
5	10	34.46	42	52.78
6	15	44.46	50.45	63.46
7	30	54.66	61.42	72.98
8	45	67.23	73.45	80.56
9	60	73.9	83.98	87.26
% CDD= % cumulative drug dissolved; PMB= Physical mixture				

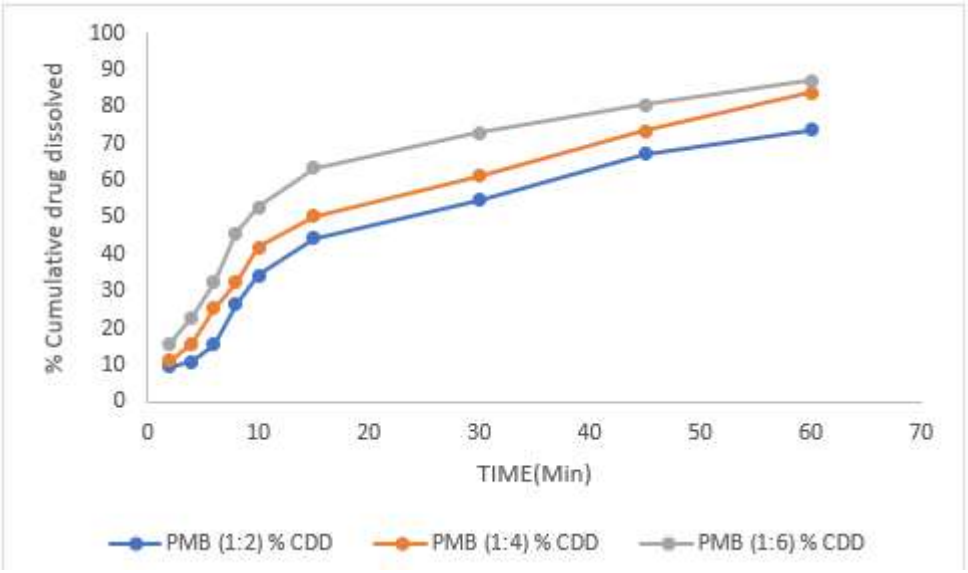

Figure 8 Cumulative % drug dissolved v/s time plot of batch I physical mixture (%CDD-PMA)

The cumulative drug dissolved in 30 min. in case of, physical mixture Batch- D ,Batch-I, Batch-N and Batch-Q found.

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 solubilisers. The solubilizes were dissolved in water and then drug was added, a clear yellow solution was formed. The excess water was evaporated from this solution and solid dispersion was obtained which was later dried completely, pulverized and packed. 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. Different Physical Mixture were prepared with different drug and solid solubiliser ratio. were compared for dissolution studies with different ratio of physical mixture Physical mixture containing drug, polymer in various ratios showed very good drug release profile.

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