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FABRICATION AND DEVELOPMENT OF SOLID DISPERSION OF CARBAMAZEPINE USING CROSCARMELLOSE AS CARRIER

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ABSTRACT

Relatively insoluble candidate drug like carbamazepine (CBZ) often exhibit incomplete or erratic absorptions; and hence wide consideration is given to improve aqueous solubility of such compound. Carbamazepine is a water insoluble antiepileptic drug. Being a BCS class –II drug, its absorption is dissolution rate limited. Solid dispersions were prepared to enhance the dissolution rate of the drug. Carbamazepine solid dispersions were prepared by the solvent evaporation method using different ratios of crosscarmellose as carrier to improve physicochemical characteristics of Carbamazepine. The prepared solid dispersions were evaluated for its flow ability, solubility characteristics and dissolution behavior. Flow ability studies of powders showed that solid dispersion technique improve flow properties compared with pure drug. Solid dispersion technique found to be effective in increasing the aqueous solubility of Carbamazepine. The dissolution of carbamazepine and solid dispersion were investigated using UV spectroscopy. Dissolution was carried out in 900ml containing 1% sodium Lauryl sulphate and 1%methanol using a standard USP II dissolution apparatus. Solid dispersion gave faster dissolution rates than the pure drug. Finally, solid dispersion of carbamazepine: cross carmellose sodium prepared in 1:7 ratio showed excellent physicochemical characteristics and was selected as the best formulation in this study.

KEYWORDS: Relatively insoluble candidate crosscarmellose formulation in this study.

INTRODUCTION

The therapeutic effectiveness of a drug depends upon the ability of a drug dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response.[1] Many potential drug candidates are characterized by low oral bioavailability. Often poor drug dissolution or solubility, rather than a limited permeation through the epithelia of the GIT are responsible for low oral bioavailability. Several attempts have been made to increase the dissolution rate and bioavailability of poorly soluble drug. Poorly soluble drugs exhibit erratic dissolution and hence variable bioavailability. Thus, improvement in their dissolution characteristics is prerequisite of formulation development.[3,4] The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs. Many hydrophilic excipients like PVP, cyclodextrins, PEG 4000, PEG 6000, mannitol and poloxamers can be used to enhance the dissolution of poorly soluble drugs. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. Carbamazepine is a poorly soluble drug. So in the current research solid dispersion of carbamazepine is prepared using croscarmellose sodium and the method employed is solvent evaporation technique.[2]

MATERIALS AND METHODS

Carbamazepine and croscarmellose sodium was a gift sample from Orchid Pharma, Chennai.

Experimental Work

Standard curve of Carbamazepine[5]

Maximum wavelength, √max, of carbamazepine was determined spectrophotometric ally and was found to be 287.2nm.The primary solution of carbamazepine was prepared by dissolving 40mg of carbamazepine in 100ml of distilled water containing 1% sodium lauryl sulphate and 1% methanol. From this, 10ml was taken and diluted to 100ml (40 µg/ml).From this, various concentrations such as 2, 4, 6, 8, 10µg/ml were prepared and the absorbance was read at 287.2nm.

Solubility Determination of Carbamazepine[6]

Solubility studies of Carbamazepine in different solvents or buffer solutions were carried out to know the solubility and to decide the appropriate medium. A small amount of drug was placed in contact with a fixed

amount of solvent in sealed glass tubes. The tubes were shaken well. The saturated solution was filtered and the filter ate was suitably diluted and analyzed for the carbamazepine content by UV spectroscopy at 288nm.

Preparation of solid Dispersion –Solvent Evaporation Technique[7]

Carbamazepine with croscarmellose sodium containing five different weight ratio (1:1, 1:3, 1:5, 1:7, 1:9) were prepared separately using solvent evaporation technique. Carbamazepine and CCS were accurately weighed, pulverized and then mixed thoroughly by light trituration in a glass mortar until a homogeneous mixture was obtained. To this the solvent (1% SLS and 1% methanol) was added drop wise until a tacky mass was formed. The solvent was allowed to evaporate at 50oc.The prepared solid dispersion were milled to pass through sieve mesh no.35.

Evaluation of prepared solid dispersion

The prepared powders were mixed with 1% magnesium stearate as lubricant. Flow properties of powders are important parameters in mixing and passing through hoper, especially during tableting and capsule filling. Therefore, for investigating prepared solid dispersion, their flow property, angle of repose and compressibility were determined.

Angle of Repose[8]

The flow property of the drug was compared to that of the formulation giving the maximum release by fixed funnel method. The angle of repose was measured by passing the sample through a sintered glass funnel, the tip of which was fixed at 2cm from the surface. The radius of the formed heap was then measured.

Carr's Compressibility index

Approximately 100ml of powder (Vb) was gently poured into a tarred graduated cylinder and the initial volume (bulk density, db) and the weight of the material (M) was recorded. The graduated cylinder was placed on a tap density tester and and the final volume was recorded after 200 taps (vt). The data obtained were used to calculate bulk density (db) and tap density (dt) of the powders which were used to determine the percent compressibility index. Lower percent compressibility values represent better flow. Percent compressibility index were determined by using following equation: I=100x (Tap density-bulk density)/Tap density.

Drug Content

The content of carbamazepine in each molar ratio of solid dispersion was determined using UV spectroscopy. Accurately weighed solid dispersion, equivalent to 100mg of carbamazepine was transferred to a 100ml volumetric flask and diluted to 100ml with the dissolution medium and sonicated for 30 minutes for complete solubilisation of the drug. The solution was filtered with Whatmann filter paper. 1ml of this solution was taken and this absorbance was measured spectrophotometric ally at 288nm.Concentration of carbamazepine was determined using calibration curve of drug in solvent.

Invitro -Dissolution Study

The method indicated the use of USP apparatus 2 (paddles) at 75rpm and 900ml 1.0% sodium lauryl sulfate solution containing 1% methanol as dissolution medium at 37oC±0.5oC. The samples of 5ml were withdrawn at 15, 30, 45 and 60min and were replaced with equal volume of fresh media. Aqueous samples were passed through 0.45µ membrane filter and diluted before absorbance was measured at 288nm using UV-VIS spectrophotometer.

Fourier Transform Infrared Spectroscopy

The pure drug showed characteristic absorption bands cm-1 at 3460.22 (N-H), 1674.14 (C=O), 1597.98 (ArC=C), 1382.58 (C-N) and 3157.70 (ArC-H).Croscarmellose sodium showed characteristic absorption bands cm-1 at 3462.04 (O-H stretch), 1599.13 (C=O), 1423.32 (ArC=C) and 2899.86 (C-H).

RESULTS AND DISCUSSION

Standard curve of carbamazepine

Standard curve of carbamazepine was plotted using UV Spectrophotometer.

Table 1: Standard curve of carbamazepine.

concentration	absorbance
o	0
2	0.1992
4	0.4003
6	0.5906
8	0.8084
10	1.0097

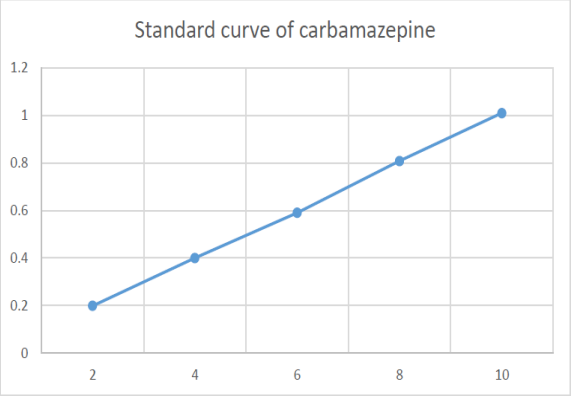

Figure No. 1: Standard curve of Carbamazepine.

2. Solubility Determination of Carbamazepine

Solubility study data of carbamazepine in various solvents and buffers were carried out.

Table. 2: solubility data of Carbamazepine in Different solvents.

Solvents	Concentration(mg/ml)
0.1 N hydrochloric acid	0.528
Phosphate buffer pH7.4	0.833
Phosphate buffer pH7.2	0.928
1% Sodium Lauryl Sulphate	6.58
Methanol	8.64
Acetone	8.11
phosphate buffer pH 6.8	2.18

3. Preparation of Solid Dispersion-Solvent Evaporation Method

Solid dispersion of ratios 1:1, 1:3, 1:5, 1:7 and 1:9 were prepared by solvent evaporation method.

4. Angle of Repose

Table no. 3: Flow property of drug and dispersion.

Sl. No.	Samples	Angle of repose
1.	Drug	37°57′
2.	1:1	26°77′
3.	1:3	20°12′
4.	1:5	27°99′
5.	1:7	24°66′

The flow property of carbamazepine and the formulation was determined.

5. Carr's compressibility index.

Sl. No	Samples	Carr's index
1.	Drug	21.12
2.	1:1	16.18
3.	1:3	11.10
4	1:5	10.00
5.	1:7	12.80

6. Drug content in solid dispersion

Table No.4: Drug content in Solid dispersion.

Solid dispersion	Drug content (%)
1:01	95.35
1:03	94.34
1:05	96.32
1:07	98.61
1:09	95.35

Drug content of solid dispersions were determined.

7. Invitro -Dissolution Study

Table 5: Dissolution data of Solid dispersion at Various Time intervals.

	15thmin (%)	30thmin (%)	45th Min (%)	60thmin (%)	75thmin (%)	90thmin (%)	105thmin (%)	120th Min (%)
Drug	2.066	3.2	4.0	7.2	8.8	8.8	9.6	10.4
1:1	4.0	6.4	8.0	13.6	25.6	33.866	36.8	38.4
1:3	5.6	13.6	32.1	39.2	47.2	54.13	60.266	66.4
1:5	16.8	23.2	35.46	42.4	50.4	54.4	67.2	70.66
1:7	32.0	60.0	63.2	68	77.6	80.33	83.2	88.8
1:9	5.6	7.2	18.4	28.8	36.8	41.33	43.2	46.4

An increase in the dissolution of the drug was found in the solid dispersion compared to the pure drug. As the ratio of the polymer increased, dissolution also increased and 1:7 showed maximum release (88.8%) at 120th minute but after a certain carrier concentration the release was found to decrease (1:9).

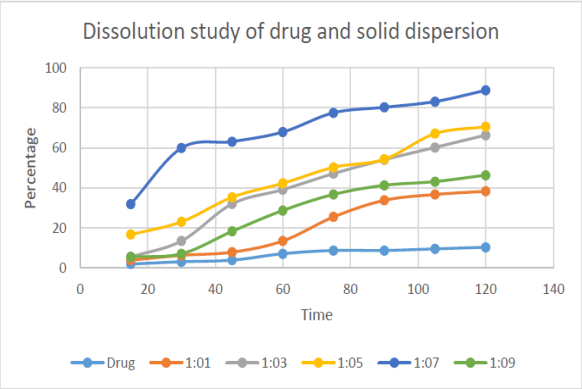

Figure. No 5: Dissolution study of Solid dispersion at Various Time intervals.

8. Fourier Transform Infrared Spectroscopy

The IR spectra of pure carbamazepine and the polymer revealed that there are similar absorption bands in the formulations. Hence it was concluded that drug-polymer solid dispersions were formed.

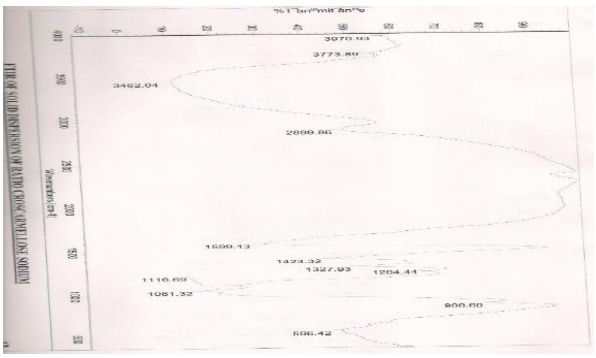

Figure No. 3: IR spectra of Cross carmellose sodium.

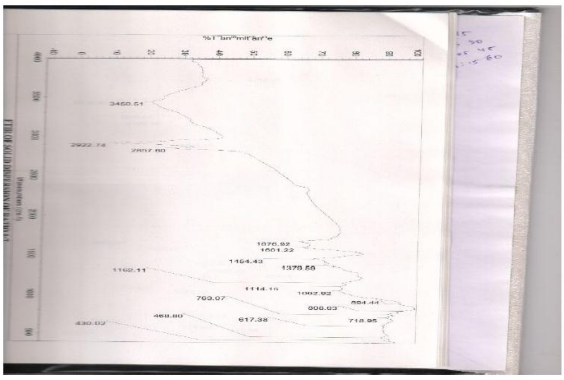

Figure No. 4: IR spectra of solid dispersion 1:1.

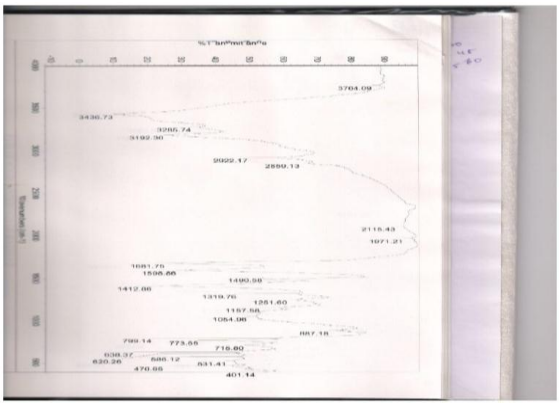

Figure No. 5: IR spectra of carbamazepine.

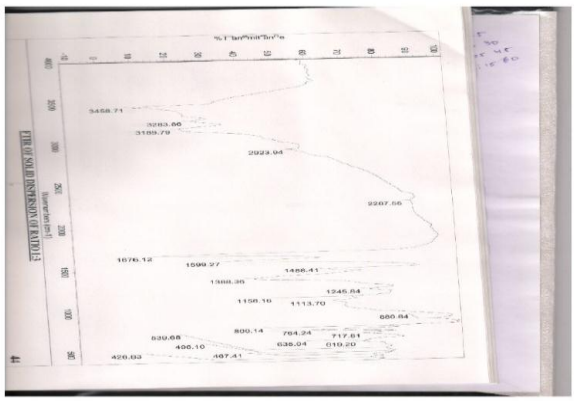

Figure No. 6: IR spectra of solid dispersion 1:3.

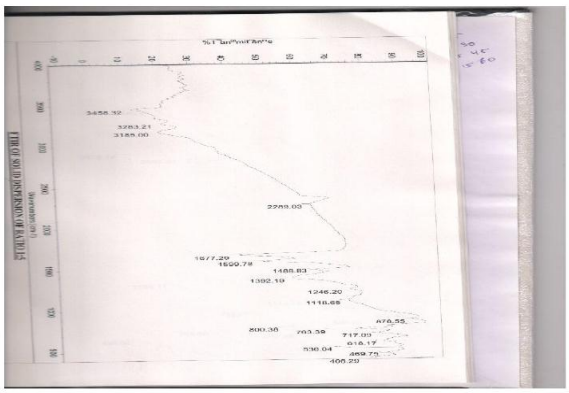

Figure No. 7: IR spectra of Solid dispersion1:5.

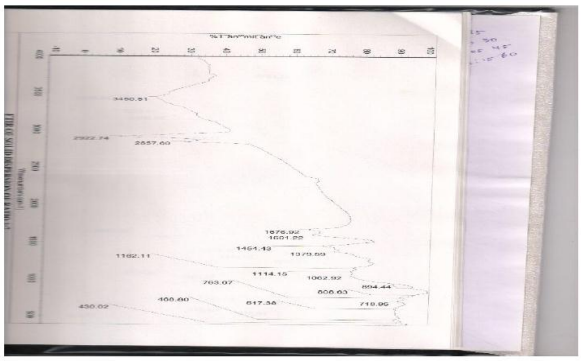

Figure No. 8: IR spectra of Solid dispersion1: 7.

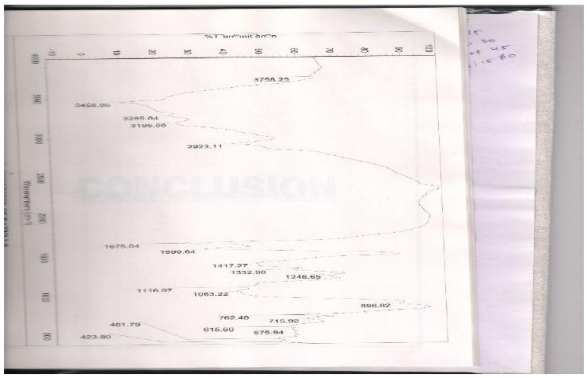

Figure No. 8: IR spectra of solid dispersion 1:9.

CONCLUSION

Carbamazepine-croscarmellose sodium solid dispersions were obtained by solvent evaporation method in 5 molar ratios (1:1,1:3,1:5,1:7,1:9). 1% Sodium lauryl sulphate and 1% methanol in 100ml distilled water was used as the solvent, as carbamazepine is practically insoluble in water and ether and freely soluble in acetone, chloroform, alcohol, dioxane and propylene glycol. The flow property of carbamazepine and the formulation giving the maximum release was determined. The drug content study was performed for various ratios. Dissolution study of the drug from the solid dispersion was found to increase compared to the pure drug up to certain ratio of the carrier (1:7). The formulation of solid dispersion of carbamazepine and crosscarmellose sodium was configured by FTIR. The prepared solid dispersions are suitable for formulation into dosage forms such as tablets and capsules.

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