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Research Article

ENHANCEMENT OF SOLUBILITY FOR CARBAMAZEPINE BY SOLID DISPERSION USING NATURAL GUMS

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ABSTRACT

The main objective of the present work is to enhance the dissolution of carbamazepine (BCS class II), poorly soluble drug by solid dispersions using different carriers. Carbamazepine solid dispersions were prepared with different techniques like solvent evaporation, kneading method, physical mixtures by using xanthan gum, modified karaya gum, mannitol and *Cochlospermum gossypium* gum in different ratios. Resultant formulations were evaluated for solubility studies, FTIR, X-ray diffraction studies, DSC, SEM and *in vitro* dissolution studies. Solid dispersion prepared by solvent evaporation method with mannitol and xanthan gum as carrier at 1:5 ratio was found to show increased solubility (1.79 ± 0.11) when compared to pure drug (0.017 ± 0.13), physical mixture (0.796 ± 0.23), kneading method (1.42 ± 0.13) and complete release (94.67 ± 1.54) when compared to pure drug (21.24 ± 0.50), physical mixtures (60.29 ± 1.28) and kneading method (89.677 ± 1.47) in 60 min.

Keywords: Carbamazepine, *Cochlospermum gossypium* gum, modified karaya gum, xanthan gum, kneading method

INTRODUCTION

The oral route is most common and preferred route for drug delivery system because of its convenience, easy for ingestion, patient compliance and drug treatment is more effective when compared to other routes of administration. Oral drug absorption mainly depends on the release of the drug substance from the delivery system i.e. dissolution rate of the drug and permeability of the drug across the gastrointestinal tract based on the physiological conditions. Poorly water-soluble drugs will have dissolution-limited absorption[1]. Drug absorption and consequently bioavailability can be improved by increasing the drug solubility. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs.

Solid dispersion refers, a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in the matrix of either amorphous particles (clusters) or in crystalline particles[2,3]. Hydrophilic excipients like PVP, cyclodextrins, PEG 4000, PEG 6000, mannitol and poloxamers can be used to enhance the dissolution of poorly soluble drugs. When solid dispersion is exposed to aqueous media, the carrier dissolves and releases the drug as fine colloidal particles, resulting in enhanced surface area, exhibiting higher dissolution rate and bioavailability of poorly water soluble drugs.

Carbamazepine, an anticonvulsant structurally similar to tricyclic antidepressants, used in the treatment of partial seizures, tonic clonic seizures, trigeminal neuralgia and other psychiatric disorders. Being a BCS class II drug, it's practically insoluble in water and exhibits dissolution limited absorption.

In the present study attempts have been made to increase the dissolution rate of poorly water soluble drug, carbamazepine by physical mixture and solid dispersion techniques using natural carriers like xanthan gum, *Cochlospermum gossypium* gum, modified karaya gum, mannitol. The prepared physical mixture and solid dispersion were characterized by FTIR, DSC, XRD, SEM. Optimized solid dispersion is formulated into immediate release tablet and they were further evaluated for pre and post compression parameter.

MATERIALS AND METHODS

Carbamazepine was obtained as a gift sample from Micro Labs, Bangalore. Karaya gum, *Cochlospermum gossypium* gum, Xanthan gum, Crospovidone, Croscarmellose sodium from Yarrow Chemical Products, Mumbai. Mannitol from Universal Laboratories, Poly vinyl pyrrolidone K30 from Corel Pharma Chem. Magnesium stearate from SD Fine Chemicals Limited. Distilled water of lab grade.
Standard graph was constructed in distilled water and 0.1N HCl to analyse the samples using UV double beam spectrophotometer. An absorption maximum was obtained at 287 nm and 288 nm which were used for the construction of standard graph.

Modification of natural carriers

The pulverized tears of karaya gum was passed through sieve no. #100. The powdered gum of 10 grams was taken in a china dish and heated at 120°C for 2 h in a hot air oven[4]. The modification of gum flowchart is shown in Figure 1.

Evaluation of modified karaya gum (MKG)

The prepared modified karaya gum (MKG) was evaluated and compared with karaya gum for the following parameters like a) swelling index, b) viscosity[5]

a. Swelling index

Measurement of Swelling index of Karaya gum is as follows- 1 gm of the gum was taken in a 100 ml measuring cylinder and the volume was made up to 100 ml with distilled water. The initial volume of the gum was noted as V_0. The swollen volume of the gum was noted as V_1.

$$\text{Swelling index} = V_1 - V_0 / V_0 \text{ X } 100 \text{ ……. Eq. 1}$$

b. Viscosity

Viscosity of the gum was measured by using Brookfield viscometer LVDV-II + Pro (Brookfield Engineering Laboratories, U.S.A). 1 gm of the gum was dispersed in 100 ml distilled water within a beaker. The dispersion was made homogenous by stirring continuously for 24 hrs on a magnetic stirrer. The viscosity of the dispersion was measured in centipoises (cps).

Preparation of solid dispersions

Preparation of physical mixture (PM)

The physical mixtures of drug with different carriers like modified karaya gum, xanthan gum, *Cochlospermum gossypium* gum and mannitol at different drug to carrier ratios in the increasing order of carrier amounts were prepared by blending method and are then passed through sieve# 60. Formulations are given in Table 1 and 2.

Preparation of solid dispersion by kneading method (KM)

The solid dispersions of drug with different carriers at different drug to carrier ratios in the increasing order of carrier amounts were prepared by kneading method. The drug and carrier were mixed; methanol was added and triturated vigorously until a damp granular mass was obtained. The mixture was then dried in hot air oven at 45ºC to form dry granules. Mixture was taken and then passed through sieve# 60 and were further evaluated. Formulations are given in Table 1 and 2.

Preparation of solid dispersion by solvent evaporation method (SM)

The solid dispersions of drug with different carriers at different drug to carrier ratios in the increasing order of carrier amounts were prepared by solvent evaporation method. Accurately weighed amount of drug and polymer were dissolved in methanol to get a clear solution. The resulting solution was subjected to evaporation at ambient temperature by stirring. The resulting solutions were kept in desiccators for at least 48 hours and then passed through sieve# 60. Formulations are given in Table 1 and 2.

Characterization of prepared physical mixtures and solid dispersions

The physical mixtures and solid dispersions prepared were analyzed for solubility, drug content and *in vitro* release of drug by dissolution studies.

Solubility measurement

Saturation solubility of carbamazepine were determined and compared with that of pure carbamazepine and physical mixtures of respective ratios. The known excess samples (carbamazepine solid dispersions, physical mixtures and pure drug) 100 mg equivalent weight of carbamazepine are added to 10 ml of distilled water and 0.1 N HCl. The samples were magnetically stirred inside a water bath at 37 ± 1°C for 48 h[6]. The samples were filtered using 0.45 µm Whatman filter paper, diluted and analyzed by UV-double beam spectrophotometer (Chemito 2600) at 287 nm and 288 nm.

Drug–excipient compatability studies

Fourier Transformer Infrared Spectroscopy (FTIR)

FTIR was used to study the spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of tablets. By preparing potassium bromide (KBr) discs using a Shimadzu corporation (model – 8400S Koyto, Japan) FTIR spectra were recorded. Few mg of sample was mixed with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure[7] for preparing Potassium bromide (KBr) discs. The IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 min by mounting the resultant disc in a suitable holder in IR spectrophotometer. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in compound.

Differential scanning calorimetry (DSC)

DSC was used for studying the physical nature of the drug, polymer and optimized formulations. Shimazdu DSC-60 differential scanning calorimeter (DSC) was used for performing DSC analysis. The instrument was calibrated with indium standard. Weighed and placed 3-5 mg samples in a closed, hermetic sample pans with pin hole. By heating the sample from 0˚C to 350˚C at a constant rate of 10°C/ min thermograms were obtained. A dry purge of nitrogen gas (50 ml\min) was used for all runs. The melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of any new peak and peak shape were noted[7].

Powder X-Ray diffraction analysis (PXRD)

The crystallinity of the drug, polymer and optimized mixtures were studied by powder XRD. The powder XRD analysis was performed using Shimadzu XRD-7000 using copper K α (λ=1.5406 Aº) radiation[7]. The data were recorded over a scanning 20 range of 5º to 50º at a step time of 0.045 steps/0.5 sec.

Surface morphology by scanning electron microscopy (SEM)

The morphology and surface properties of drug, polymer and optimized formulations were visualized using scanning electron microscopy (JSM- 6360A, JEOL, Tokyo, Japan). The samples were lightly sprinkled on a double-sided adhesive tape stuck to aluminium stub. The stubs were then coated with platinum to a thickness of about 10 Aº under an argon atmosphere using a gold-sputter module in a high-vacuum evaporator[7]. Afterwards, the stubs containing the coated samples were placed in the scanning electronic microscopic chamber.

***In vitro* dissolution studies**

In vitro drug release of pure drug, physical mixtures and solid dispersions were determined using USP II apparatus - Paddle type (Electrolab TDT-08L, Mumbai). The dissolution test was performed using 900 ml distilled water at 37 ± 0.5˚C. The speed of rotation was set at 75 rpm. At time points of 10, 20, 30, 40, 50, 60 min. 5 ml samples were withdrawn and same volume was replaced with fresh media. UV-double beam spectrophotometer

(Chemito 2600) was used for checking absorbance at 287 nm and drug release was determined from standard curve[8].

Pre formulation studies for immediate release tablets

Physical and chemical properties of a drug substance alone and when combined with excipients were investigated by pre formulation testing. It is the first step in the rational development of dosage forms. The overall objective of pre formulation testing is to generate information useful to the formulation in developing stable and bioavailability dosage forms. The use of pre formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Preparation of a mixed blend of drug excipients

All the ingredients were passed through sieve no. # 60. Required quantity of each ingredient was taken for each specified formulation and all the ingredients were subjected to grinding to a required degree of fineness. The powder blend was subjected to pre compression parameters[9].

Angle of repose

This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the loose powder can be measured by angle of repose. Angle of repose is calculated by the following formula.

$$\Theta = \tan^{-1}(h/r) \quad \text{……. (Eq. 3)}$$

Where Θ = angle of repose, r = radius of the pile, h = height of the pile

Bulk density

Bulk density is defined as a mass of powder divided by the bulk volume. The bulk density (*b) was calculated using the formula.

$$\text{Bulk density (*b)} = \text{Mass/Volume} \quad \text{……. (Eq. 4)}$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The tapped density (*t) was calculated using the formula.

$$\text{Tapped density (*t)} = \text{Mass/Volume} \quad \text{……. (Eq. 5)}$$

Carr's index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which is calculated using the formula, correlation between carr's index and flow properties is given in Table 3

$$\text{C.I (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{. (Eq. 6)}$$

Hausner's ratio

It's an index of ease of powder flow. It was calculated by the using the formula given below and correlation of Hausner's ratio with flow properties is given in Table 3

$$\text{Hausner's ratio} = \text{tapped density/bulk density} \quad \text{……. (Eq. 7)}$$

Preparation of carbamazepine immediate release tablets

Tablets were prepared using optimized solid dispersion of carbamazepine SMMXG5 with disintegrants. All ingredients were triturated individually in a mortar and passed through #60 sieve. Then required quantity of all ingredients were weighed and mixed uniformly in geometrical ratio for 10 min. Finally magnesium stearate was added and mixed for 5 min. This uniformly mixed blend was compressed into tablets containing 100 mg drug using 11.9 mm convex surface punches on a Rimek-1 rotary machine by direct compression method[10]. Formulations of carbamazepine solid dispersions (SMMXG5) tablets are given in Table 4.

Evaluation of carbamazepine immediate release tablets

The prepared tablets can be evaluated for various parameters like weight variation, thickness, hardness, friability, *in vitro* disintegration time, content uniformity, *in vitro* drug release studies[11].

Weight variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated. (Table 5)

Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. Screw guage was used for measuring the thickness of tablet which is related to the hardness of tablet. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging. Screw guage was used for measuring the thickness in millimeters (mm) individually for 10 pre weighed tablets. The average thickness and standard deviation were reported.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The force required to break a tablet into pieces by compression, which is the tablet crushing load. Tablet hardness tester (Monsanto hardness tester) was used to measure crushing load. The average reading was noted by testing three tablets from each formulation batch randomly

Friability

Roche Friabilator (Electrolab, India) was used for determining friability of the tablets. This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 min dropping the tablets at a distance of 6 inches with each revolution. 20 tablets were weighed and placed in the friabilator and subjected to 100 revolutions. Soft muslin cloth was used for dusting the tablets and reweighed. The friability (F %) is given by the formula.

$$F\% = (1 - W_0/W) \times 100 \quad \text{……. (Eq. 8)}$$

Where, W_0 = wt. of the tablet before test, W = wt, of the tablets after test

Disintegration time

Disintegration time of tablets was determined in a tablet disintegration test apparatus, using 0.1 N HCl at 37°C ± 0.5°C as medium.

Content uniformity

Ten tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 100 mg weighed and dissolved in 100 ml of 0.1 N HCl filtered and drug content analyzed spectrophotometrically at 288 nm.

***In vitro* drug release studies**

In vitro drug release of immediate release tablets of carbamazepine was determined using USP II apparatus - Paddle type (Electrolab TDL-08L). 900 ml of 0.1 N HCl at 37˚C ± 0.5°C was used for performing dissolution test. 75 rpm was set as the speed of rotation of paddle. At time points of 10, 20, 30, 40, 50, 60 min. 5 ml samples were withdrawn and same volume was replaced with fresh media. At a wave length of 288 nm, absorbance of solution was checked by UV spectrophotometer (ELICO-164 double beam spectrophotometer, Hyderabad, India) and drug release was determined from standard curve.

Stability studies

The optimized formulation was subjected to stability studies at room temperature in a dry place (desiccator) for period of three months. Tablets were analyzed for the hardness, disintegration time, friability, drug content and *in vitro* drug release[12]

RESULTS AND DISCUSSION

Evaluation of modified karaya gum

Swelling index

From mean readings of three determinations[4,13] swelling index was calculated. Swelling index of Karaya gum was found to be 233.3 ± 1.2 and modified Karaya gum was found to be 150 ± 0.3. Least percentage of swelling index was shown by the mucilage of modified karaya gum than Karaya

Viscosity

Brookfield viscometer LVDV-II + pro (spindle 062) was used for measuring the viscosity of gums. Karaya gum was found to be more than Modified karaya gum. Viscosity of the gums at different RPMs is given in the Table 6

From Figure 2, it was observed that the swelling index and the viscosity of parent karaya gum were more when compared with the modified karaya gum. Hence, it leads the gums to certain chemical changes in them on modification of gums i.e. heating to higher temperatures. The viscosity of karaya gum is directly proportional to its volatile acetyl content. Hence, it is assumed that the removal of volatile acetyl content in the gum will reduce the viscosity of the gum. The results indicated that the viscosity of the modified karaya gum was markedly lower when compared to the karaya gum. Due to swelling nature of carrier, the extensive surface of the carrier is increased during dissolution and dissolution rate of deposited drug is markedly enhanced.

Evaluation of solid dispersions

Solubility studies

The solubility study was carried out in water and 0.1N HCl. There is significant increase in the solubility of solid dispersions in distilled water as compared to carbamazepine Solubility of pure drug was found to be 0.290 ± 0.35 and 0.017 ± 0.13 in 0.1N HCl and Water respectively.

The improvement in solubility may be due to changing in the crystal forms, different habit, structure, surface modification. In some instances, solvents included into the crystals forms solvates changing the surface properties and the reactivity of drug particles and intern all energy of the molecules playing an important role in increasing solubility of drug.

Trials has been made with different drug to polymer ratios (1:2-1:10 ratios), the solubility studies of carbamazepine physical mixtures, kneading method and solid dispersion is shown in Table 7.

Pure carbamazepine yielded the lower solubility due to its hydrophobic property causing the powder to float on the surface of the media and preventing its surface to make contact with medium. Hence the enhancement of the solubility by solid dispersion technique compared with that of pure drug, could presumably explained by the following factors: swelling ability of the carrier, low viscosity of the carrier, a decrease in crystallinity and size of the drug crystals in the solid dispersion and improved drug wettability[4,6]. Due to high ratio of gum and to overcome the problem half of the proportion of xanthan gum was replaced with mannitol (drug: xanthan gum, 1:5 ratio) out of 5 parts 2:3 ratio of xanthan gum: mannitol to facilitate the convenience for preparation of tablets. Solubility on using the combination of xanthan gum and mannitol was found to be 0.796 ± 0.23, 1.42 ± 0.13 and 1.79 ± 0.11 by physical mixture, kneading method and solvent evaporation method respectively.

Drug-excipient compatibility studies

Fourier transformer infrared spectroscopy analysis (FTIR)

FTIR studies were done to verify if there was any interaction between the pure drug and various excipients employed. The different spectra are given below in Figure 3

From the above IR spectra the peaks representing the pure drug were similar in formulation spectra (SMMXG5) indicating there was no interaction of the pure drug with excipients used in formulation or pure drug is not altered functionally during formulation development[14-16] as shown in Table 8 and Figure 3

Differential scanning calorimetry (DSC)

The physical nature of the prepared solid dispersion of carbamazepine with SMMXG5 was studied by DSC. The melting point, peak onset and appearance of any peak were noted. Similarly, the pure drug was analyzed by DSC in same manner and the melting point and onset of peak values were noted. The thermo grams of the solid dispersions were superimposed with the pure drug to compare the results.

Table 1: Formulation of carbamazepine and gum mixtures by physical mixture, kneading method, solvent evaporation method

Physical mixture					
Formulations	**Ratio of D:C**	**Drug (mg)**	**Modified Karaya gum (mg)**	***Cochlospermum gossypium* (mg)**	**Xanthan gum (mg)**
PGG2	1:2	100	66.6	66.6	66.6
PGG4	1:4	100	133.3	133.3	133.3
PGG6	1:6	100	200	200	200
PGG8	1:8	100	266.6	266.6	266.6
PGG10	1:10	100	333.3	333.3	333.3
Kneading method					
KGG2	1:2	100	66.6	66.6	66.6
KGG4	1:4	100	133.3	133.3	133.3
KGG6	1:6	100	200	200	200
KGG8	1:8	100	266.6	266.6	266.6
KGG10	1:10	100	333.3	333.3	333.3
Solvent evaporation method					
SMGG2	1:2	100	66.6	66.6	66.6
SMGG4	1:4	100	133.3	133.3	133.3
SMGG6	1:6	100	200	200	200
SMGG8	1:8	100	266.6	266.6	266.6
SMGG10	1:10	100	333.3	333.3	333.3

Note: D – carbamazepine, C - carrier

Table 2: Formulation of carbamazepine and xanthan gum with mannitol by all three methods

Methods	Formulation	Ratio of D: C	Drug (mg)	Xanthan gum (mg)	Mannitol (mg)
Physical mixtures	PMXG5	1:5	100	200	300
Kneading method	KMXG5	1:5	100	200	300
Solvent evaporation method	SMMXG5	1:5	100	200	300

Note: D – carbamazepine, C – carrier (xanthan gum + mannitol)

Table 3: Correlation of Hausner's ratio, angle of repose and compressibility index with flow properties of powder

S. No	% Compressibility Index	Powder flow	Angle of repose (Ɵ)	Hausner's ratio
1	<10	Excellent	25-30	1.00-1.11
2	16-15	Good	31-35	1.12-1.18
3	16-20	Fair	36-40	1.19-1.25
4	21-25	Passable	41-45	1.26-1.34
5	26-31	Poor	46-55	1.35-1.45
6	32-37	Very Poor	56-65	1.46-1.59
7	>38	Extremely Poor	>66	>1.60

Table 4: Formulations of carbamazepine immediate release tablets

Ingredients (mg)	F1	F2	F3	F4
SMMXG5 (drug equivalent to 100 mg)	600	600	600	600
PVP K30	16.5	16.5	16.5	16.5
Croscarmellose sodium (CCS)	16.5	-	30	-
Crospovidone (CP)	-	16.5	-	30
Mg. Stearate	3.5	3.5	3.5	3.5
Total weight (mg)	636.5	636.5	650	650

Note: F1, F2 - with 2.5% disintegrant F3, F4 - with 5% disintegrant

Table 5: Percentage deviation allowed for the tablets

Pharmaceutical form	Avg. weight	%deviation
Tablets	130 mg or less	10
	More than 130 mg	7.5
	More than 324 mg	5

Table 6: Viscosity of karaya gum and modified karaya gum

Name of the gum	RPM	Viscosity (cps)
Karaya gum	20	367 ± 1.5
	40	353 ± 1.32
	60	348 ± 0.45
	80	340 ± 0.9
	100	337 ± 1.3
Modified karaya gum	20	230 ± 0.11
	40	221 ± 1.17
	60	219 ± 0.58
	80	217 ± 0.33
	100	215 ± 1.7

Values are expressed as mean ± SD, n = 4

Table 7: Solubility studies of physical mixture, kneading method, solid dispersions

Polymers used	Solubility for different ratios (mg/ml)				
	1:2	1:4	1:6	1:8	1:10
Physical mixture					
Xanthan gum (XG)	0.753 ± 0.008	0.770 ± 0.011	0.781 ± 0.009	0.792 ± 0.007	0.799 ± 0.14
Cochlospermum gossypium (KG)	0.625 ± 0.011	0.645 ± 0.009	0.648 ± 0.007	0.683 ± 0.008	0.689 ± 0.12
Modified karaya gum (MKG)	0.513 ± 0.011	0.532 ± 0.009	0.547 ± 0.007	0.552 ± 0.14	0.565 ± 0.21
XG+KG+MKG	0.725 ± 0.011	0.745 ± 0.009	0.748 ± 0.007	0.783 ± 0.008	0.785 ± 0.12
Kneading method					
Xanthan gum (XG)	1.09 ± 0.012	1.290 ± 0.006	1.401 ± 0.008	1.420 ± 0.009	1.451 ± 0.41
Cochlospermum gossypium (KG)	0.975 ± 0.008	0.989 ± 0.008	1.09 ± 0.008	1.201 ± 0.10	1.212 ± 0.21
Modified karaya gum (MKG)	0.954 ± 0.11	0.970. ± 0.11	0.982 ± 0.11	1.001 ± 0.10	1.023 ± 0.11
XG+KG+MKG	0.995 ± 0.008	1.10 ± 0.008	1.25 ± 0.008	1.40 ± 0.10	1.42 ± 0.21
Solid dispersion					
Xanthan gum (XG)	1.578 ± 0.14	1.598 ± 0.16	1.657 ± 0.15	1.786 ± 0.16	1.805 ± 0.22
Cochlospermum gossypium (KG)	1.496 ± 0.006	1..52 ± 0.009	1.565 ± 0.012	1.580 ± 0.008	1.591 ± 0.010
Modified karaya gum (MKG)	0.986 ± 0.16	0.998 ± 0.11	1.097 ± 0.16	1.122 ± 0.10	1.234 ± 0.11
XG+KG+MKG	1.52 ± 0.14	1.54 ± 0.16	1.60 ± 0.15	1.64 ± 0.16	1.72 ± 0.22

Table 8: Interpretation of carbamazepine FTIR scan

S. No.	Region in cm^{-1}	Type of vibration	Functional group present
1	3465.84	N-H stretching	Amine
2	3159.18	C-H stretching	Aromatic
3	1690	C=O stretching	Amide
4	1595.02	C-N stretching	Aliphatic amines
5	1488.49	C=C stretching	Aromatic

Table 9: Pre compression parameters of the powder blend of all formulations

Formulations	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)
F1	31.5 ± 0.61	0.345 ± 0.29	0.399 ± 0.11	1.15 ± 0.41	13.53 ± 0.71
F2	32.4 ± 0.77	0.340 ± 0.03	0.398 ± 0.02	1.17 ± 0.02	14.57 ± 0.56
F3	30.31 ± 0.14	0.344 ± 0.01	0.395 ± 0.03	1.14 ± 0.07	14.97 ± 0.02
F4	31.33 ± 0.12	0.340 ± 0.04	0.389 ± 0.01	1.14 ± 0.09	12.59 ± 0.01

Note: Values are expressed as Mean ±SD, n = 3

Table 10: Evaluation of different formulations of carbamazepine immediate release tablets

Parameters	Formulations			
	F_1	F_2	F_3	F_4
Weight variation (mg)	636.5 ± 0.11	635.5 ± 0.23	650 ± 0.24	649 ± 0.21
Hardness (Kg/cm^2)	3.6 ± 0.21	3.5 ± 0.11	3.2 ± 0.24	3.4 ± 0.19
Friability (%)	0.45 ± 0.12	0.44 ± 0.24	0.54 ± 0.14	0.42 ± 0.11
Disintegration time (min)	8.00 ± 0.24	9.02 ± 0.41	2.01 ± 0.21	3.02 ± 0.11
Drug content	99.3 ± 1.72	98.8 ± 1.67	99.51 ± 0.15	99.22 ± 0.24
Content uniformity	99.2 ± 0.10	98.5 ± 0.01	99.5 ± 0.21	98.8 ± 0.11

Note: F1, F2-2.5% Disintegrant (DT). F3, F4-5% Disintegrant

Table 11: Evaluation of physicochemical properties during stability studies

Parameters	Time	
	0 (Initial)	3rd month
Hardness (Kg/cm^2)	3.2 ± 0.24	3.1 ± 0.11
Disintegration time (min)	2.01 ± 0.21	2.5 ± 0.13
Drug content (%)	99.51 ± 0.15	99.1 ± 0.21
Friability (%)	0.54 ± 0.14	0.56 ± 0.15

Values are expressed as Mean ± SD, n = 3

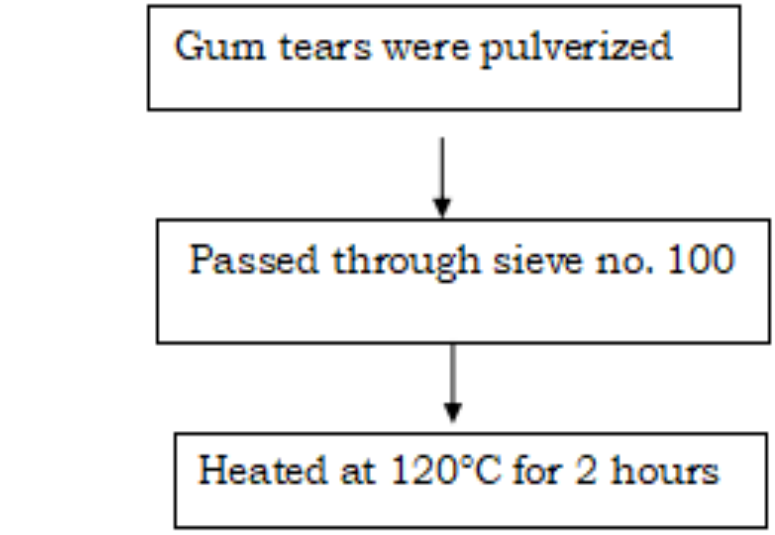


Figure 1: Flow chart of the modification of karaya gum

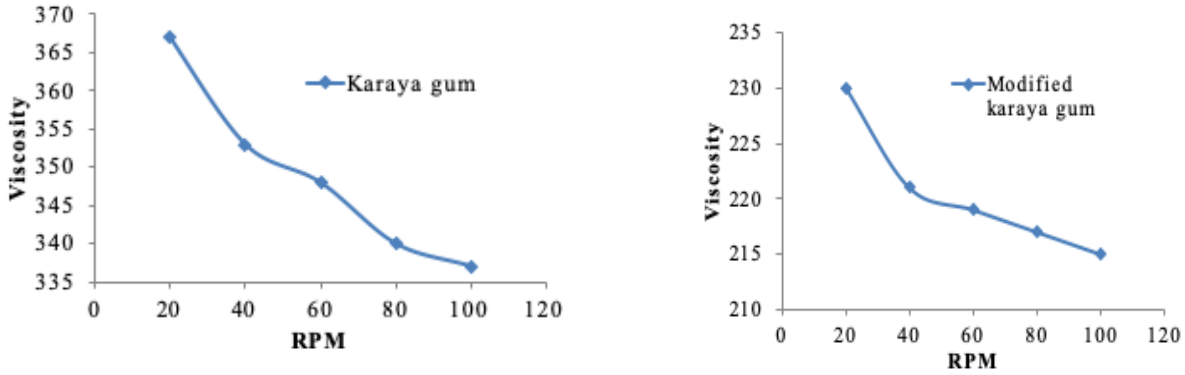
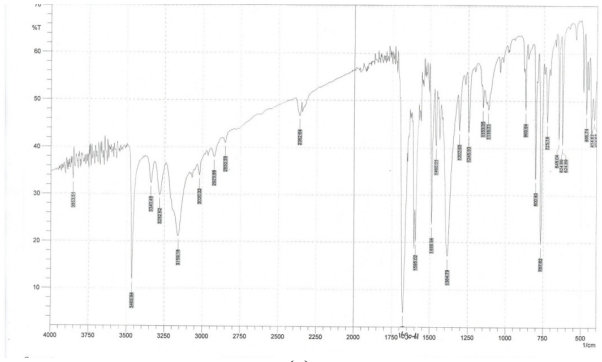
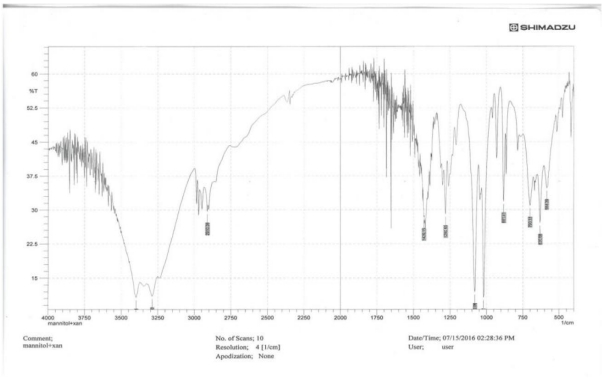


Figure 2: Rheogram of RPM vs. viscosity for (a) karaya gum (b) modified karaya gum



(a)



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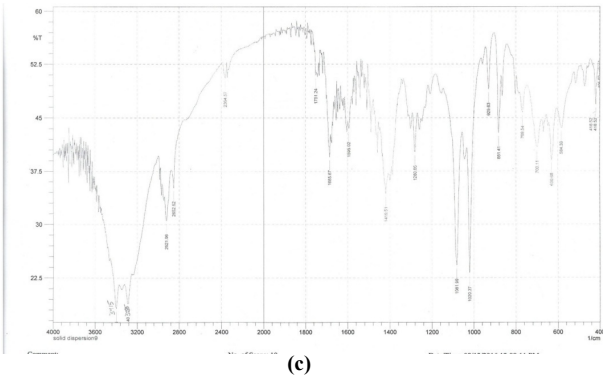
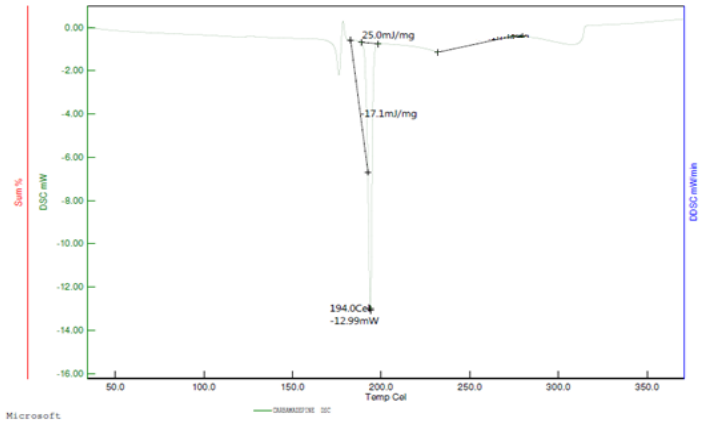
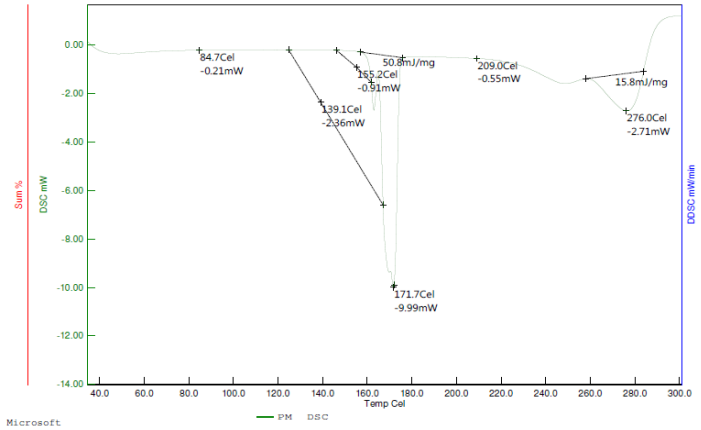


(c)

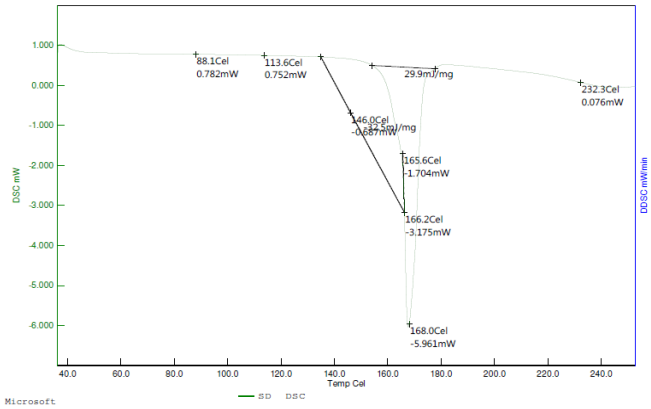
Figure 3: IR spectra of (a) carbamazepine (b) xanthan gum + mannitol (c) SMMXG5



(a)

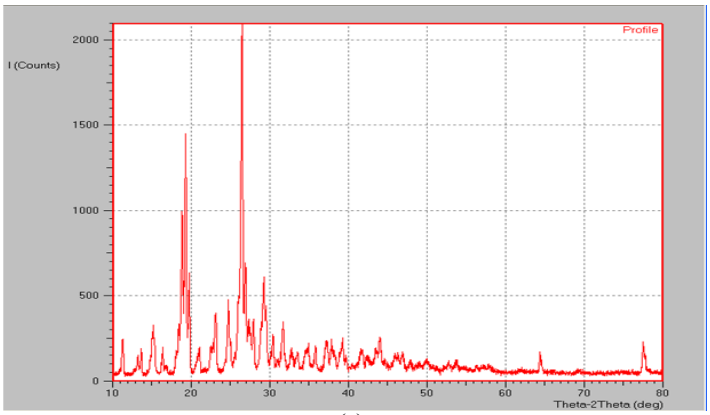


(b)

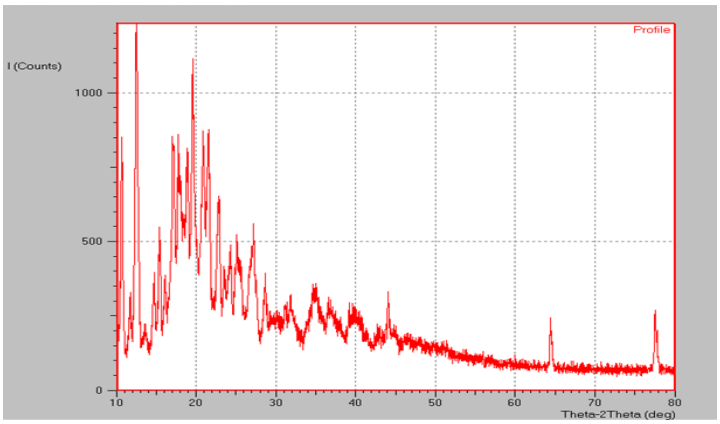


(c)

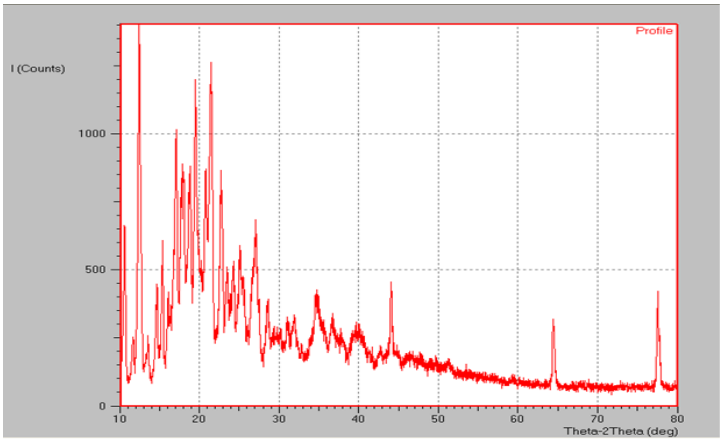
Figure 4: DSC thermograms of (a) Carbamazepine (b) Physical mixture (c) SMMXG5



(a)

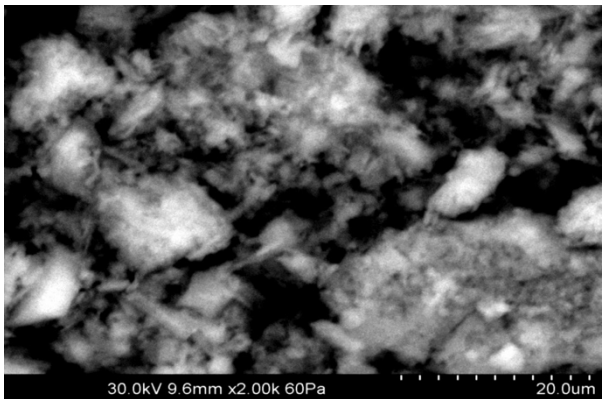


(b)

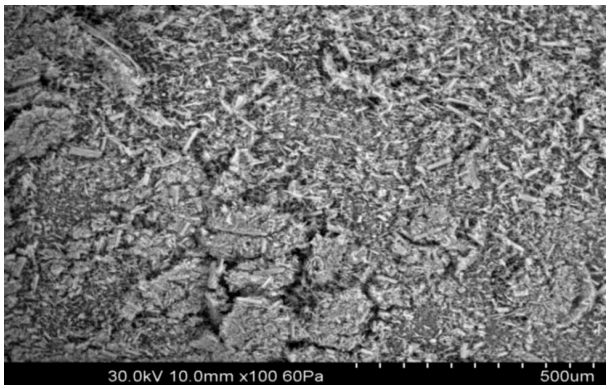


(c)

Figure 5: P-XRD pattern of (a) Carbamazepine (b) Xanthan gum + mannitol (c) SMMXG5



(a) PMXG5



b) SMMXG5

Figure 6: SEM photographs of (a) PMXG5 (b) SMMXG5

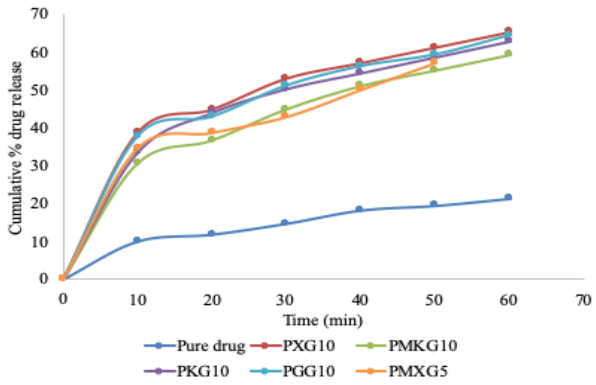


Figure 7: Dissolution profiles by physical mixture

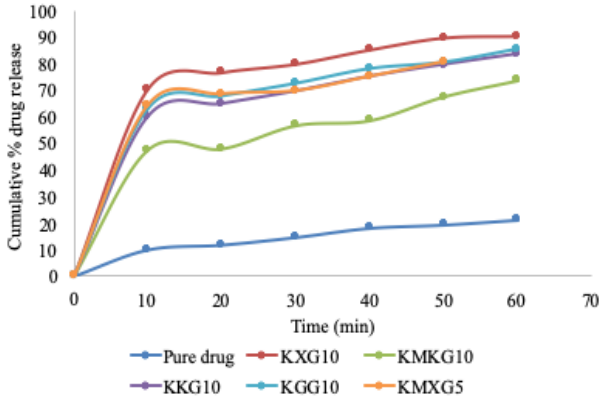


Figure 8: Dissolution profiles by kneading method

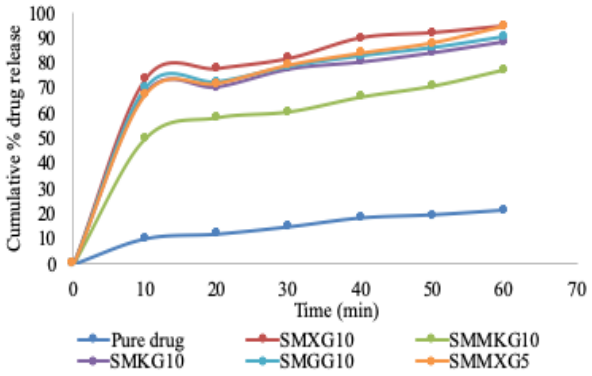


Figure 9: Dissolution profiles of SD by solvent evaporation method

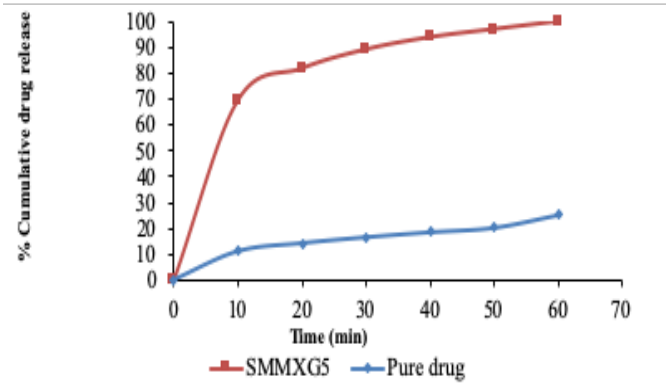


Figure 10: Dissolution profile of SMMXG5 in 0.1 N HCl

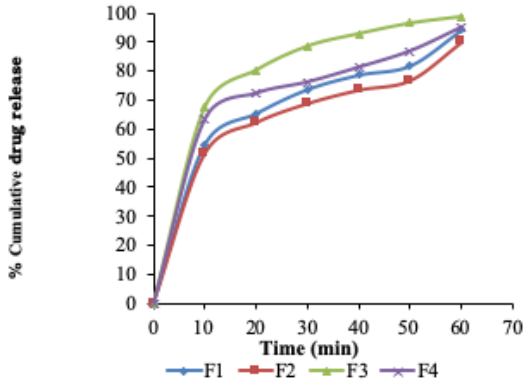


Figure 11: Dissolution profile of carbamazepine tablet

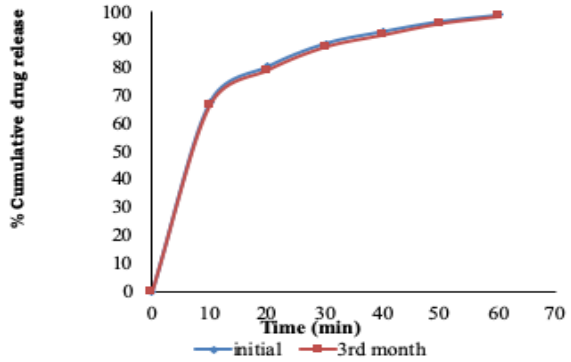


Figure 12: Dissolution profile of optimized formulation F3 during stability studies

DSC of the pure drug showed as a sharp endothermic peak at 194.0 cal corresponding to its melting point. Thermal traces of physical mixture or SD showed peak shifted to lower melting point. The peak appeared at 171.7 cal and 166.2 cal respectively. The differences in thermal behavior of carbamazepine in form of PM and SD suggested the reduced drug crystallinity of the prepared SDs than the pure form of drug[14-18]. Thermograms are shown in Figure 4

Powder x-ray diffraction analysis (P-XRD)

The crystallinity of the prepared solid dispersions of carbamazepine is studied by P-XRD. The pure drug and solid dispersions were also analyzed by XRD in same manner and the peak intensity and presence of new peaks were noted. The diffraction spectrum of pure carbamazepine showed that the drug is highly crystalline powder and possesses sharp peaks. The decrease in intensity of the diffractogram in case of the SD and the peaks of carbamazepine disappeared completely. It could be attributed to the destruction of its crystal lattice, because of melting of drug into carrier[15-18] as shown in Figure 5.

Surface morphology by scanning electron microscopy (SEM)

The surface morphology of carbamazepine SD on xanthan gum with mannitol and PM were observed by using an analytical scanning electron microscope. The SEM of physical mixture dusting of drug powder on the carrier was observed as shown in Figure 6 (a) while the SEM of solid dispersion as shown in Figure 6 (b) drug was found to be in amorphous state.

The physical mixture of the drug and carrier showed the presence of drug in the crystalline form. It was easy to recognize the polymer particles from that of the drug. In case of SD, it was difficult to distinguish the presence of carbamazepine crystals. Carbamazepine crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The result could be attributed to dispersion of the drug in the molten mass of the polymer[6].

Dissolution studies

Dissolution studies of all formulations were performed according to the parameters given below. The pure drug showed only 21.24 % in 60 minutes.

***In vitro* drug release from physical mixtures**

Drug release studies of physical mixtures shown in 60 min as shown in Figure 7. Formulation containing 1:10 (drug: carrier ratio) showed maximum release of drug in 60 min when compared with other ratios.

From Figure 7, it was observed that 1:10 ratio of drug: xanthan gum (PXG10) showed greater release (53.15%) than pure drug (14.70) in 30 min. The percentage drug released by PMs carbamazepine with xanthan gum showed increased release when compared to pure drug due to greater hydrophilicity of carriers[13]. So, it is considered for further studies. It was observed that 1:10 parts of drug: modified karaya gum showed greater release (44.97%) compared to pure drug (14.70) in 30 min. 1:10 ratio of drug: *Cochlospermum gossypium* showed greater release (50.20%) compared to pure drug (14.70) in 30 min. 1:10 parts of Drug: Combination of xanthan, modified karaya and *Cochlospermum gossypium* gum showed greater release (51.15%) compared to pure drug (14.70) in 30 min. 1:5 ratio of drug: mannitol and xanthan (PMXG5) showed greater release (42.97%) compared to pure drug (14.70) in 30 min[19,20].

The percentage drug release of carbamazepine with carriers showed increased release when compared to pure drug due to the drug with hydrophilic carrier results in greater wetting and increasing surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media[21,22].

Drug release study of solid dispersion by kneading method

Solid dispersions prepared by kneading method were subjected to drug release studies in 60 min as shown below From Figure 8, it was observed that 1:10 ratio of drug: xanthan gum KSD (KXG10) showed greater release (80.10) than pure drug (14.70) in 30 min. The percentage drug release by KSDs of carbamazepine with xanthan gum showed increased release when compared to pure drug and PMs in their respective ratios due hydration capacity of carrier by kneading method. The affinity between the hydrophilic inert carriers and dissolution fluids facilities rapid penetration into the particles, further enhancing the dissolution process[13]. So, it is considered for further studies.

1:10 ratio of drug: modified karaya gum showed greater release (56.9%) compared to pure drug (14.70) in 30 min. 1:10 ratio of drug: *Cochlospermum gossypium* showed a release of 69.9% in 30 min. 1:10 ratio of Drug: Combination of xanthan, modified karaya and *cochlospermum gossypium* gum showed 72.9% release in 30 min. The percentage drug release of carbamazepine with modified karaya gum, *Cochlospermum gossypium* gum and gum combinations showed increased release when compared to pure drug and PMs in their respective ratios due to the drug getting wet due to carrier by kneading method[19,20]. The ratio 1:5 of drug: mannitol and xanthan (KMXG5) showed greater release (70.10%)

than pure drug (14.70) in 30 min. The percentage drug released from xanthan gum and mannitol was greater than the PMs due to absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, amorphous state, further enhancing the dissolution process[21,22].

Drug release study of solid dispersion by solvent evaporation method

Solid dispersions prepared by solvent evaporation method were subjected to drug release studies in 60 min as shown below. From Figure 9, it was observed that 1:10 ratio of drug: xanthan gum (SMXG10) SD showed greater release (81.79%) than pure drug (14.70%) in 30 min. The percentage drug released by SDs of carbamazepine with xanthan gum showed increased release when compared to pure drug and PMs in their respective ratios which may be due to greater hydration capacity of this carrier[13]. The affinity between the hydrophilic inert carriers and the dissolution fluids facilitates rapid penetration into the particles, further enhancing the dissolution process. It was observed that 1:10 ratio of drug with modified karaya gum in SMMKG10 showed greater release (60.55%) compared to pure drug (14.70%) in 30 min. 1:10 ratio of drug with *Cochlospermum gossypium* in SMKG10 showed greater release (77.6%) compared to pure drug (14.70%) in 30 min[19,20]. 1:10 ratio of drug with gums combination in SGG10 showed greater release (78.6%) than pure drug (14.70%) in 30 min. 1:5 ratio of SMMXG5 showed greater release (79.13%) compared to pure drug (14.70%) in 30 min.

From Figure 10, it was observed that 1:5 ratio of SMMXG5 (solid dispersion of xanthan gum and mannitol) showed greater release (89.13%) compared to pure drug (16.52%) in 30 min in 0.1 N HCl. The percentage drug released by SDs showed increased release when compared to pure drug, PMs, KSDs in their respective ratios due to increased wettability of drug due to the hydrophilic polymer

Preparation and evaluation of carbamazepine immediate release tablets

Pre compression parameters

The angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index were performed on the formulations prepared are given in Table 9.

The angle of repose ranged between 30.31 ± 0.14 to 32.4 ± 0.77 indicating fair flow property. Carr's index calculated from bulk density and tapped density ranged from 12.59 ± 0.01 to 14.97 ± 0.02 refers fair flow property. Hausner's ratio ranged from 1.14 ± 0.07 to 1.17 ± 0.02 infers excellent or fair flow property.

Evaluation of different formulations of carbamazepine immediate release tablets

The optimized solid dispersions (1:5) ratio prepared by solvent evaporation method has shown excellent properties, maximum solubility and drug release in 60 min. Hence by direct compression technique, conventional tablets of the formulations were prepared according to Table 6. Various parameters like weight variation, hardness, friability, content uniformity, disintegration time, assay and *in vitro* drug release studies were evaluated for all the formulations.

Evaluation of prepared immediate release carbamazepine tablets were conducted and the results for weight variation were found in the range of 635.5 to 650 mg (< limits 10% deviation), hardness 3.2 to 3.6 well in I.P limits of 4-8, friability of 0.42 to 0.54% which was within the limits of 0.5-1% disintegration time of 2.01 to 9.02 min. (< limits of 15 min), drug content and content uniformity 98.5 to 99.51% (< 2%). This indicates that the evaluation parameters for all the formulations are within the limits. The results are given in the Table 10**.**

***In vitro* dissolution studies**

The most important evaluation parameter that needs to be optimized is drug release study by *in vitro* dissolution.

Figure 11 depicts the dissolution profile of carbamazepine tablets in 0.1 N HCl. Different ratios of disintegrants were used in the preparation of tablets. F1 and F2 (2.5% disintegrant) were prepared using 2.5% w/w disintegrant of CCS and CP respectively, whereas F3 and F4 (5% disintegrant) were formulated with 5% w/w disintegrants of CCS and CP. Finally total contents of the binder and disintegrant were optimized and the immediate release tablet was prepared by direct compression technique that was able to release the drug within 60 min. The formulation F3 (which contains binder PVP K30 at 2.5% w/w, CCS as disintegrant at 5% w/w and 0.5% w/w lubricant called magnesium stearate) was observed to release 88.6% in 30 min. As the concentration of disintegrant was increasing, faster the disintegration of tablets was observed. Hence, F3 was considered as optimized formulation.

Stability studies

The carbamazepine tablet (F3) was subjected to stability studies under normal conditions, results are shown in Tables 11 and Figure 12

The stability of F3 formulation was determined by performing stability studies for three months at room temperature in a dry place (desiccator). F3 formulation was found to be stable, with insignificant change in the hardness, disintegration time, friability, drug content and *in vitro* drug release as shown in Figure 12**.**

CONCLUSION

Enhancement of carbamazepine solubility with different hydrophilic carriers like xanthan gum, *Cochlospermum gossypium*, modified karaya gum and mannitol was observed by the preparation methods of physical mixture, kneading and solvent evaporation.

It was observed that SMMXG5 of carbamazepine with xanthan gum and mannitol at 1:5 ratio prepared by solvent evaporation method showed increased release rate 89.13% in 30 min. The optimized SMMXG5 formulation was characterized by FTIR, XRD, DSC, shape and surface properties by SEM studies. Compatibility of drug and excipients is evident from these studies.

The SMMXG5 solid dispersion was formulated into immediate release tablet by using different disintegrants, crospovidone and croscaramellose sodium. The tablets were evaluated for physicochemical properties. The results indicated that the tablet complied with the official specifications. Solubility enhancement and increased drug release was observed for the prepared formulations and tablets were compared to that of the pure drug.

In conclusion, it can be stated that the objective of study has been achieved. Solid dispersion technique was successful in improving the dissolution rate of carbamazepine. The hydrophilic carriers like xanthan gum and mannitol were successful in improving the dissolution rate of carbamazepine by solvent evaporation method.

Tablets prepared using SMMXG5 showed improved dissolution rate.

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