ORIGINAL ARTICLE

Formulation development and evaluation of novel oral jellies of carbamazepine using pectin, guar gum, and gellan gum

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Medicated jelly formulations are more suitable for pediatric, geriatric and dysphagic patients, which offer rapid dissolution and absorption of drugs thereby early onset of action. The aim was to develop and evaluate oral jelly formulations of carbamazepine (CBZ). Carbamazepine oral jellies were prepared to employ pectin, guar gum and gellan gum alone and pectin-guar gum combination. Preformulation studies, organoleptic, physical characteristics, drug content, pH, spreadability, rheological properties, syneresis, taste masking, *in vitro* dissolution testing, drug release kinetics and stability studies were conducted. The Fourier transform infrared and differential scanning calorimeter studies showed that there was no interaction between drug and excipients. The pH of all the formulations was found between pH 6.37 ± 0.03 and 6.83 ± 0.04. The concentration of gelling agents influenced the spreadability. Syneresis was observed in jellies made from guar gum alone, whereas those made from pectin and guar gum it was absent. The optimized formulations (F3, F11 and F15) masked the bitter taste of CBZ and demonstrated acceptable flavor and mouth feel. All formulations showed more than 50% drug release in 15 min except those made of gellan gum alone. The formulations F3, F11 and F15, were found stable for 90 days as per International Conference on Harmonization stability protocol. Carbamazepine jellies made from pectin (F3, 1.2%), gellan gum (F11, 1.5%) and pectin-guar gum (F15, 1:0.4%) were found more successful and could be employed to improve the palatability and acceptability by pediatric, geriatric and dysphagic patients. The jellies could be useful to overcome the problems of poorly soluble CBZ.

Key words: *Carbamazepine, dysphagic patients, medicated jelly, natural polymers*

INTRODUCTION

Development of novel drug delivery techniques that minimize toxicity and improve efficacy offers prospective benefits to patients and opens new avenues for pharmaceutical companies. Patient compliant dosage forms show beneficial over conventional ones, especially if the drug delivery problems of pediatric, geriatric and dysphagic patients are addressed. Although the spectrum of dosage forms available to these patients; such as syrups, suspensions, chewable tablets, dispersible tablets and powders for reconstitution; many questions and expectations are still to be addressed such as stability, dosage wastage, improper measurement, reconstitution, dose dumping, ease of administration, patient nonacceptance and so on. Therefore, there is a scope for more patient-friendly delivery systems which involve easy administrative methods, especially by oral route. Pediatrics patient compliance with convenient administration and more palatable and elegant dosage forms are gaining significant importance in the design of novel drug delivery systems.[1]

Oral jellies as unit dosage forms can offer a better solution to address these problems.[2] Jellies are transparent or translucent nongreasy semisolid solutions

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or suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. These are meant for oral or external application to mucous membranes and can be ingested without water.[3-6] Medicated jelly formulations are more suitable for pediatric, geriatric and dysphagic patients, offering rapid dissolution and absorption of drugs thereby early onset of action. The dysphagic patients can be choked by water while consuming liquid formulation, and this problem can be eliminated by administering liquid formulations with high viscosity in the form of jellies.[7,8] A number of jelly products have been developed that aim to improve compliance by aiding swallowing.[9-12] Gelling agents usually employed are tragacanth, sodium alginate, pectin, starch, gelatin; cellulose derivative such as hydroxypropyl methyl cellulose, methylcellulose, carbomers, polyvinyl pyrrolidone and polyvinyl alcohol at different concentrations using various additives.[3,13,14] Commercial oral jelly formulations of calcium gluconate, amlodipine, acyclovir, alendronate, donepezil hydrochloride, sildenafil and tadalafil are available in some countries, but scarcely any products found in those patients who really need them.[7,15,16]

Natural polymers are gaining importance as carriers of drugs in recent times. The advantages of these polymers over commercially available polymers are that they are biodegradable, biocompatible, nontoxic, low cost and environment friendly and locally available, better patient tolerated and edible.[17] Pectin and guar gum are recognized as viscosity enhancing agents and approved by US Food and Drug Administration (FDA) and are official in United States Pharmacopoeia (USP).[18] They are popularly used as food additives and confectionaries and are generally regarded as safe.[19] Gellan gum is a naturally derived polysaccharide from *Pseudomonas elodea*, composed of glucuronic acid, rhamnose and glucose, and O-acetyl moieties. It is an excellent gelling polymer, which can be used for a variety of applications in pharmaceutical formulations.[20,21]

Carbamazepine (CBZ) (5H-dibenzo [*b, f*] azepine-5-carboxamide) is an anticonvulsant used in epilepsy, neuralgia and psychosis. Its absorption from the gastrointestinal tract is slow and erratic; more rapid on a full stomach and slower from solid dosage forms than from solution.[22] It is white to yellowish-white crystalline powder, practically insoluble in water (17.7 mg/L at 25°C) and belongs to class 2 of biopharmaceutical classification system of drugs. It is highly lipophilic with an aqueous solubility of 0.078 mg/mL and poor bioavailability of 42-58% after oral administration. It is a bitter drug with an unpleasant aftertaste.[23] In the light of scanty, research found on patient friendly jelly formulations of CBZ, designing a suitable dosage form is still a challenge to formulators.

In the present study novel patient-friendly oral jelly formulations of CBZ were developed and characterized employing natural gelling agents: Guar gum, gellan gum, pectin alone and in combination of guar gum and pectin.

MATERIALS AND METHODS

Materials

CBZ was gratis sample from Alkem Laboratories Ltd., Mumbai, India. Pectin (mol. wt. 30,000-100,000) and Guar gum (mol. wt. 22,000) were purchased from Loba Chemie Pvt., Ltd., Mumbai, India. Gellan gum (mol. wt. 500,000), polyethylene glycol (PEG) 400, sodium lauryl sulfate (SLS), citric acid, sucrose, methyl paraben and propyl paraben were obtained from Merck Specialties Pvt. Ltd., Mumbai, India. Cremophor RH 40 from BASF, Germany; acesulfame potassium from Gangwal Chemicals Pvt. Ltd, Mumbai, India; raspberry flavor from CEC Pvt. Ltd., Ponpadi, India; CBZ tablets 200mg (Tegretol®, Novartis Ltd., Mumbai, India) were obtained. All other reagents used were of analytical grade.

Preformulation studies

The preformulation studies were carried out for CBZ: Organoleptic characteristics, melting point, solubility, loss on drying, identification tests, drug-excipient compatibility. Visual examination of CBZ powder was carried out by transferring 50 mg on to white paper, spreading and examining visually in day light. Melting point was determined using digital melting point apparatus (DVMP-202, Sunshine Instruments, Coimbatore, India). Loss on drying was determined using digital infrared moisture balance (Labline, Mumbai, India).

The solubility was determined by the equilibrium solubility method; wherein an excess of the drug was placed in a solvent system and shaken at a constant temperature (30°C ± 2°C) over a long period until equilibrium was obtained. In the present study, the solubility of CBZ was tested in PEG400 and cremophor RH40:PEG400 (1:10), distilled water, aqueous buffers (pH 1.2, 6.8, 7.4 and 7.5) and organic solvents (methyl alcohol, chloroform, acetone and ether) at 30°C ± 0.2°C. The drug content in the solution was determined for the degree of solubility in the solvents.

Identification tests

Identification of CBZ was carried out by transferring 5 mg to a test tube, adding 1 mL of formaldehyde/sulfuric acid TS. To another test tube 10 mg of CBZ was transferred, and 2 mL of nitric acid (~1000g/L) TS was added and heated in the water bath for 1 min.[24]

Drug-excipient compatibility studies

The drug and excipients were mixed together in 1:1 ratio and placed in borosilicate colored glass vials. These vials were sealed and placed in an oven maintained at 40°C and 75% RH. The samples were observed after 15, 30 and 45 days for any color change or lump formation.

Fourier transforms infrared (FTIR) spectra (4000-400 cm^{-1} and resolution of 4 cm^{-1}) of the pure drug and its mixtures of gelling agents were measured by preparing dispersion

in dry KBr using attenuated total reflectance FTIR spectrophotometer (Bruker, UK). The absorption maxima in the spectra obtained were compared, and the presence of additional peaks corresponding to the functional groups was noted.

The heat characteristics of CBZ and drug-polymer mixtures were analysed using a Shimadzu® Differential scanning calorimeter (DSC)-60 (Shimadzu, Kyoto, Japan). The behavior was studied by heating the samples (2 mg) from 25°C to 400°C at a heating rate of 10°C/min under nitrogen flow at 10 cm^3/min^{-1} using an empty aluminum pan as a point of reference.

Preparation of oral medicated jellies

The jellies loaded with CBZ were prepared using gelling agents: Pectin, guar gum, gellan gum alone and pectin-guar gum combination of various concentrations. Formulations, F1-F6 were prepared using pectin (0.8, 1.0, 1.2, 1.4, 1.6 and 1.8%). Guar gum (1.0, 1.25, 1.5 and 1.75%) was used to prepare F7-F10. Gellan gum was employed in the concentrations of 1.5, 1.75, 2.0 and 2.25% for F11–F14. Pectin-guar gum combinations were employed to prepare the formulations, F15-F18. CBZ (1%) and other excipients were present in all formulations. Cremophor RH40 (1%) and PEG400 (10%) were used as solubility enhancers of CBZ; citric acid 1% as a pH modifier; simple syrup (60%) and acesulfame potassium (0.3%) as sweetening agents; methyl paraben (0.18%) and propyl paraben (0.02%) as preservatives; raspberry flavor (2%) and purified water (up to 100%) as vehicle were used. All ingredients were calculated on the basis of % w/w.

Accurately weighed polymer powder was dispersed in 10 mL of purified water maintained at 90°C throughout preparation. The dispersion was stirred using a magnetic stirrer (2MLH, Remi Equipment Pvt. Ltd., Mumbai, India) for 20 min to facilitate hydration of gelling agent. CBZ was taken in another beaker and solubilized using PEG400 and CremophorRH 40. Then simple syrup was added to it under continuous stirring. Then acesulfame potassium, citric acid, and preservatives were added under continuous stirring. Raspberry flavor was added to this under continuous stirring at 60°C. The final weight was adjusted with purified water, mixed, transferred to polyethylene molds, sealed and allowed to cool at room temperature (25°C ± 5°C) to form a jelly like texture.

Characterization of formulations

Physical observation

The prepared jellies were observed visually for clarity, odor, texture and presence of any particles. The texture was evaluated in terms of stickiness and grittiness by mild rubbing the gel between two fingers.

Weight variation and drug content

The average weight of ten jellies was taken to determine weight variation. The jellies were taken out of the molds in a beaker and weighed individually, pooled and mixed. Then gel equivalent to 100mg of CBZ was taken in 100 mL volumetric flask, dissolved and made up to the volume using 1% SLS solution. A stability indicating analytical method was employed for the determination of CBZ.[25,26] The drug content was estimated by UV/Vis spectrophotometer (Aquamate Plus, Thermo Scientifics, Mumbai, India) at 287.5 nm after filtering the sample through Whatman filter paper (qualitative no. 4, 110 mm diameter, Sigma-Aldrich, Bangalore, India).

Determination of pH

The pH of prepared jellies was measured using a digital pH meter (LI 120, Elico Ltd., Hyderabad, India) at room temperature (25°C ± 5°C). For this purpose, 0.5 g of jelly was dispersed in 50 mL of distilled water to make a 1% solution, and the pH was noted.

Spreadability

Spreadability of jellies was determined by an apparatus suggested by a multimer, which was fabricated and used for the study. It consisted of the wooden block provided with two glass slides. Lower slide fixed on a wooden block and upper slide with one end tied to a glass slide and the other end tied to weighing the pan. About 2.5 gm of jelly was placed between two slides, and 1000 gm weight was placed over it for 5 min to press the sample to an uniform thickness. Eighty gm of jelly was added to pan, and the time (s) required separating the two slides was taken as a measure of spreadability. A shorter time interval to cover a distance of 7.5 cm considered as better spreadability and was calculated by the formula,

$$S = \frac{ML}{T}$$

where, *S* is the spreadability, *M* is the weight tide to upper slide, *L* is the length of glass slide (7.5 cm) and *T* is the time taken to separate two slides.[8]

Viscosity

Viscosity of jellies was measured in triplicate by Brookfield® viscometer (DV II+, Brookfield Engineering, Massachusetts, USA) using spindle LV4 at the rotation of 3 rpm at room temperature (25°C ± 5°C). The jelly was squeezed out from the polyethylene mold by making a cut of uniform size on the mold and viscosity was measured.[8]

Syneresis

Syneresis is the contraction of the gel upon storage and separation of water from the gel. It is more pronounced in the gels, where lower concentration of gelling agent is employed. It is one of the major problems associated with low acylated guar gum gels.[8] All the jellies were observed for signs of syneresis at room temp (25°C ± 5°C) and 8°C ± 1°C. The formulations showing signs of syneresis were rejected and not considered for further studies.

Taste and palatability

Human taste panel study of CBZ jellies consisted of a double-blind crossover study by estimating the gustatory responses.[27] It was carried out on a trained panel of six healthy adult human volunteers of age group 25-30 years and body weight 65-78 kg. The study protocol followed the ethical principles for medical research involving human subjects (declaration of Helsinki) as developed by the World Medical Association and the Ethical Guidelines of Institutional Ethical Committee (institutional protocol number: NCPA/IEC/2012-13/03). Proper consent of volunteers was taken after explaining them the study matter in the vernacular. They were asked to maintain a standard dietary condition (avoid high calories and junk foods), definite water intake, normal physical activity, avoidance of strenuous exercise and work overload for the 4 days of dosage form intake.

A dose of the jelly equivalent 10 mg of CBZ was given to every volunteer to place in the mouth for 30 s and spat out. The bitterness was recorded immediately and at intervals of 1 min up to 10 min. A numerical five level bitterness intensity scale was used: 0 = tasteless, 1 = acceptable, 2 = slight, 3 = moderate and 4 = strong. Palatability was measured by "+" if palatable and "−" if nonpalatable.[28,29]

In vitro dissolution testing

In vitro dissolution was studied using USP 28 dissolution Apparatus II (Disso 2000; Labindia Analytical Instruments Pvt. Ltd., Thane, India) in 1% SLS (900 mL, 37°C ± 0.5°C) dissolution medium at 75 rpm.[26] 5 mL samples were withdrawn at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min using a prefilter. The sample was replaced by an equal volume of SLS solution to maintain constant volume throughout. The CBZ dissolved was determined using a calibration curve at 287.5 nm after suitable dilution.[25] The percentage of CBZ released at 30 and 60 min was calculated from the dissolution data.

The mechanism of drug release from jellies was analyzed by fitting the data into zero-order, first-order, Highuchi and Koresmeyer-Peppas kinetic models.[30-32] The similarity factor (f_2) measures the closeness between two dissolution profiles; FDA has set the standard of f_2 values range 50–100 to indicate that they are similar. The dissolution profile of marketed formulation was compared to those of prepared jellies using f_2 at 0.25 and 0.5 h dissolution time points.[33,34]

Stability studies

The stability studies of optimized jelly formulations were packed in aluminum foils, transferred to high-density polyethylene containers, tightly closed, and stored at room temperature (25°C ± 5°C), 8°C ± 1°C and 40°C ± 2°C/75 ± 5% relative humidity for 90 days as per International Conference on Harmonization guidelines.[33] The samples were characterized for change in various parameters such as appearance, pH, viscosity, sugar crystallization, stiffness, syneresis and drug content at the end of 90 days. A freshly made sample was used as a reference standard for subjective evaluations. The statistical significance of the difference was assessed by Student's *t*-test where the values of $P < 0.05$ were considered as significant.

RESULTS AND DISCUSSION

Preformulation studies

The procured CBZ was white amorphous powder and odorless with slightly bitter taste. Melting was observed at 192°C ± 0.5°C. Preliminary chemical examination of CBZ showed positive reactions with formaldehyde/sulfuric acid and nitric acid resulting in the formation of yellow and orange colors to the solutions respectively thus complying with WHO specifications.[24] Loss on drying of CBZ was found 0.34% ±0.02%. It was insoluble in water and ether: Soluble in 1% SLS, 30% PEG400, propylene glycol, dichloromethane and Cremophor RH40:PEG400 (1:10). Although propylene glycol was found as better cosolvent in preformulation studies, it was reported to induce seizures and hence not employed as cosolvent in the present study. SLS was also avoided because it is not recommended for the oral formulations in pediatrics.[35] Using of PEG400 or cremophor RH40 was found not suitable as cosolvent because CBZ was precipitated when the solution was mixed with water. High concentration (30%) of PEG400 did not yield in precipitation, but it had affected the consistency of jellies. Hence a combination of PEG400 and cremophor RH40 was tried at different proportions.[36] Finally cremophor RH40 and PEG400 in the ratio of 1:10 was optimized as solubilizer, cosolvent and plasticizer.

Drug-excipient compatibility studies

Physical examination of individual drug-excipient mixtures stored at 40°C and 75% RH was carried out for 45 days. The initial color of the drug-excipient mixtures observed as white to brownish for pectin and white to greenish white for guar gum. All other excipients along with CBZ showed white to off white color. No characteristic changes were observed in color or physical state for all the samples at 15, 30 and 45 days.

Fourier transforms infrared overlay spectra of the pure drug and drug-excipient mixtures were obtained and are shown in Figure 1. Characteristic peaks of pure CBZ were observed at 1599.41 cm^{-1} (aromatic –C = C– stretching), 852.66 cm^{-1} (aromatic –C–H bending), 1727.50 cm^{-1} (carbonyl –C = O stretching in amide), 3510.53 cm^{-1} (asymmetric $–NH_2$ stretching in amide) and 3406.47 cm^{-1} (symmetric $–NH_2$ stretching in amide) which were in compliance to those of standard values. No additional peaks corresponding to functional groups were obtained. There were no significant deviations found between the peaks of CBZ and those of drug-excipient mixtures that indicated the stability of the drug in the presence of all excipients.

The DSC thermogram of pure drug demonstrated a sharp endothermic peak at 195.18°C corresponding to the melting point of the crystalline form of CBZ. Whereas the thermograms of the mixtures of the drug using various gelling agents showed varying deviations in the characteristic peaks between 180°C and 200°C [Figure 2]. This shifting of endothermic peaks to lower temperatures could be due to the formation partial drug-polymer complexes which also indicate a reduction in drug crystallinity due to complexation.

Preparation of oral medicated jellies

The jellies of CBZ were successfully prepared using gelling agents: Pectin, guar gum, gellan gum alone and pectin-guar gum combination of various concentrations. Earlier few attempts were made on jellies as swallowing aids.[8,11] Cremophor RH40 and PEG400 were employed as solubility enhancers of CBZ that were in conformity with earlier studies.[36-38]

Characterization of jelly formulations

Physical observation

Physical observation of jellies is important to justify the patient acceptance and compliance of the products. The observed parameters are summarized in Table 1. All the jellies were transparent except those prepared using guar gum. The jellies were slightly liquid to thick in nature with varying degrees of consistency. A nonsticky texture was observed in all formulations, except those of guar gum. Formulation F18 was thick and sticky due to the presence of high concentration of guar gum. Their color and odor were in an acceptable range.

Weight variation and drug content

The weight variation was found between 2.45%±0.58% and 3.79%±0.83% in all prepared jelly formulations. The drug content was found in the range of 97.63% ±0.63%–99.23% ±0.66%, which was in conformity with the pharmacopoeial specification of 95-105%.

Table 1: Evaluation of appearance, consistency and texture of prepared jellies

Formulation*	Property of jellies		
	Appearance	Consistency	Texture
F1	Transparent	Slightly liquid	Nonsticky
F2	Transparent	Acceptable	Nonsticky
F3	Transparent	Acceptable	Nonsticky
F4	Transparent	Acceptable	Nonsticky
F5	Transparent	Acceptable	Nonsticky
F6	Transparent	Slightly thick	Slightly sticky
F7	Cloudy	Slightly liquid	Slightly sticky
F8	Cloudy	Slightly liquid	Slightly sticky
F9	Cloudy	Slightly liquid	Slightly sticky
F10	Cloudy	Acceptable	Nonsticky
F11	Transparent	Acceptable	Nonsticky
F12	Transparent	Acceptable	Nonsticky
F13	Transparent	Acceptable	Nonsticky
F14	Transparent	Acceptable	Nonsticky
F15	Transparent	Acceptable	Nonsticky
F16	Transparent	Acceptable	Nonsticky
F17	Transparent	Slightly thick	Nonsticky
F18	Transparent	Thick	Slightly sticky

*Formulations of pectin (F1-F6), guar gum (F7-F10), gellan gum (F11-F14) and pectin-guar gum combination (F15-F18)

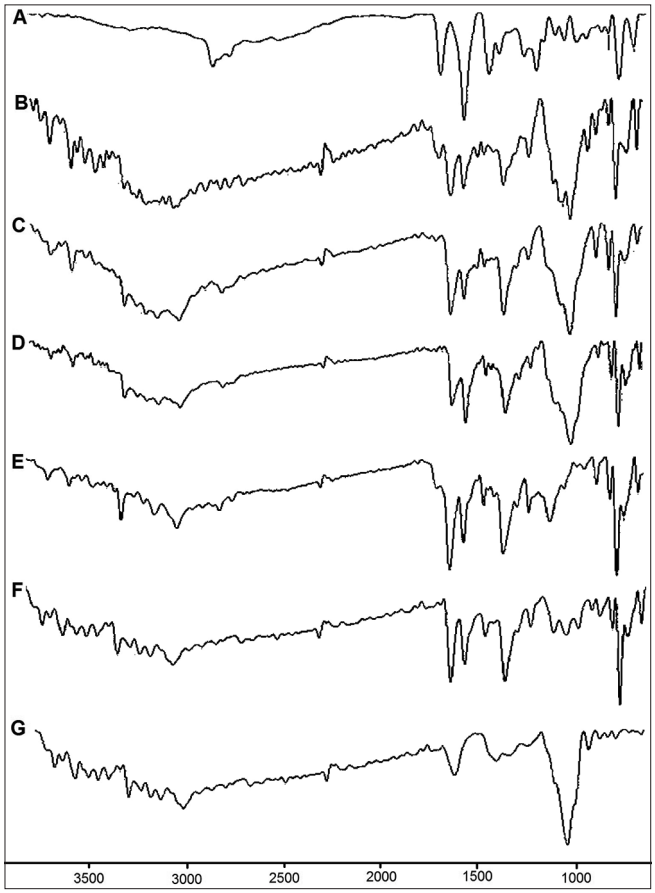

Figure 1: Fourier Transform Infrared spectra of (A) pure carbamazepine (CBZ), mixtures of CBZ using (B) pectin, (C) guar gum, (D) gellan gum, (E) citric acid, (F) sucrose, and (G) pectin-guar gum combination

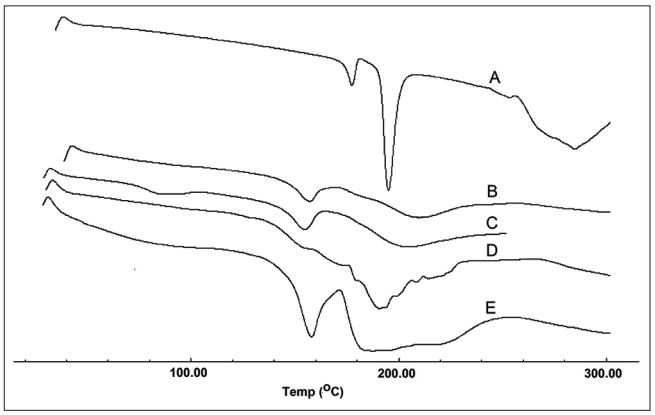

Figure 2: Differential scanning calorimeterthermograms of (A) pure carbamazepine (CBZ), mixtures of CBZ using (B) pectin, (C) guar gum, (D) gellan gum and (E) pectin-guar gum combination

pH of jelly formulations

The results of various evaluation parameters of prepared jelly formulations are summarized in Table 2. The pH of the formulation influences the taste and stability of oral jellies. The pH of the prepared formulations was found in the range of 6.37 ± 0.03-6.83 ± 0.04 which was slightly acidic. Sucrose may precipitate in the presence of citric acid on standing.[39] Therefore, a minimum quantity of citric acid was added just to maintain the pH.

Spreadability

The spreadability of all the formulations was carried out and the time required to cover a distance of 7.5 cm on the slide was determined and found between 4.05 ± 1.00 and 14.46 ± 3.00 s. It was directly proportional to polymer concentration and shorter in jellies of guar gum compared to those of other polymers used in the study.

Viscosity

The viscosities of CBZ jellies were found between 5849 ± 47 and 12778 ± 81 cps and varied depending on the type and concentration of polymer. Jellies prepared from guar gum alone showed low viscosity, but those prepared in combination with pectin, the viscosity was increased and were found suitable as jelly formulations. The jellies of pectin and gellan gum employed alone showed higher viscosities. The concentration of the polymer directly influenced the viscosity.

Syneresis

Gels experience syneresis or de-swelling due to the release of liquid, resulting in shrinkage of gels and reduce quality.[40] Syneresis was more pronounced in the gels, where lower concentration of gelling agent was employed. It was observed after 24 h of jelly preparation. The formulations F1, F7, F8 and F9 showed syneresis at room temperature (25°C ± 5°C) whereas those of F1 and F7 showed at 8°C ± 1°C [Table 2]. A reduction in the free energy of the system affects the water hold-up in the gels.[41] Syneresis was not noticed at room temperature probably due to binding of free water by co-solute.[42,43] In the preformulation studies, jellies containing guar gum and pectin combination did not show syneresis. Hence, in order to reduce syneresis of guar gum jellies, pectin was used as co-solute.

Taste and palatability

The results of taste masking studies of formulation F3, F11 and F15 on human volunteers are presented in Table 3. All the volunteers reported the jelly formulations as nonbitter. Formulation F3 showed better palatability. The reason of reduction of bitterness could be due to lower diffusion of CBZ by gelling agents from the jelly to the taste buds. The bitterness of CBZ was significantly masked by the presence of additives used. Aftertaste and mouth feel were found significantly improved. Sweetness and flavor were variable

Table 3: Results of taste masking determination and palatability of optimized jelly formulations

Form of CBZ	Intensity of bitterness after time (min)					
	0.5	1	2	5	10	15
Pure drug	2	2	3	3	2	1
F3	0+	0+	0+	0+	0+	0+
F11	0	0	0	0	0	0
F15	0	0	0	0	0	0

+: Palatability, CBZ: Carbamazepine

Table 2: Results of various evaluation parameters of prepared jelly formulations

Formulation[a]	Percentage drug content	pH of the jelly	Viscosity (cps)	Spreadability[b] (s)	Syneresisc	
					Room temp (25°C±5°C)	8°C±1°C
F1	98.86±0.33	6.51±0.02	5849±47	6.37±0.11	+	+
F2	99.23±0.66	6.83±0.04	7334±52	9.07±0.25	–	–
F3	98.36±0.38	6.52±0.03	8678±39	10.31±0.32	–	–
F4	98.23±0.66	6.73±0.05	9989±44	12.01±0.37	–	–
F5	99.13±0.20	6.61±0.08	11997±54	13.37±0.59	–	–
F6	98.53±0.41	6.80±0.05	12778±41	14.28±1.25	–	–
F7	97.86±0.12	6.83±0.04	5999±48	4.03±0.09	++	+
F8	98.13±0.75	6.47±0.03	7678±39	4.31±0.16	–	–
F9	97.96±0.36	6.49±0.04	9334±33	6.03±0.38	–	–
F10	97.83±0.79	6.45±0.05	11737±28	7.12±0.44	–	–
F11	98.53±0.49	6.82±0.03	6678±42	9.07±0.35	–	–
F12	98.43±0.41	6.61±0.05	7576±39	10.31±0.48	–	–
F13	98.30±0.58	6.72±0.04	8678±41	12.42±1.19	–	–
F14	99.06±0.33	6.71±0.04	9998±29	14.25±1.31	–	–
F15	98.83±0.32	6.37±0.03	5899±27	9.07±0.33	–	–
F16	98.16±0.46	6.47±0.03	7634±35	10.31±0.49	–	–
F17	97.63±0.63	6.76±0.04	8768±31	12.01±1.15	–	–
F18	98.46±0.98	6.60±0.04	9698±36	12.48±1.28	–	–

All values expressed as ±SD, *n*=3. [a]Formulations of pectin (F1-F6), guar gum (F7-F10), gellan gum (F11-F14) and pectin-guar gum combination (F15-F18).[b]Time interval to cover distance of 7.5cm. [c]+:Positive, –: Negative,++: More occurrence. SD: Standard deviation

Table 4: *In vitro* drug release and kinetics for prepared jellies

Formulation[a]	Dissolution (%w/w) at time (min)[b]		Zero-order		First-order		Similarity factor (f_2)
	30	60	r^2	K_0 (mg/h)	r^2	K_1 (h^{-1})	
F1	85.61±4.38	[c]	0.824	1.693	0.931	0.080	29.917
F2	77.83±3.65	98.69±4.75	0.861	1.396	0.908	0.059	37.824
F3	75.51±3.29	97.53±4.37	0.871	1.391	0.945	0.052	39.638
F4	72.53±4.35	96.04±3.76	0.888	1.397	0.968	0.048	42.367
F5	69.71±3.91	94.22±4.14	0.884	1.325	0.944	0.039	47.428
F6	64.41±3.83	91.74±3.88	0.922	1.348	0.969	0.036	55.819
F7	86.77±4.66	[c]	0.837	1.712	0.968	0.062	22.086
F8	81.30±4.21	[c]	0.873	1.704	0.880	0.075	23.576
F9	71.04±3.89	98.20±4.51	0.891	1.404	0.910	0.055	41.230
F10	67.39±3.22	93.89±4.37	0.912	1.361	0.961	0.041	49.792
F11	86.77±4.18	97.86±3.86	0.743	1.335	0.977	0.057	30.815
F12	80.97±3.47	93.56±4.61	0.823	1.365	0.987	0.043	37.452
F13	69.88±3.27	88.09±3.69	0.863	1.256	0.989	0.032	49.233
F14	53.15±3.11	83.62±3.88	0.948	1.233	0.978	0.025	82.045
F15	70.21±4.26	96.21±4.27	0.898	1.385	0.947	0.046	44.479
F16	65.90±4.32	93.39±4.61	0.924	1.366	0.956	0.039	53.291
F17	60.77±3.68	91.74±4.48	0.943	1.344	0.969	0.034	65.587
F18	57.79±2.28	88.26±3.44	0.960	1.335	0.961	0.029	77.070
MP	57.96±2.42	81.14±3.39	0.931	1.000	0.991	0.028	[d]

[a]Formulations of pectin (F1-F6), guar gum (F7-F10), gellan gum (F11-F14) and pectin-guar gum combination (F15-F18). [b]Values ±SD, n=3. [c]Dissolution completed at 50 min. [d]Not applicable.%w/w: Mean weight percentage of drug dissolved, r^2: Correlation coefficient, MP: Marketed product, SD: Standard deviation

but in acceptable limits. Raspberry flavor was chosen to help in masking the bitter taste of CBZ.[43]

In vitro dissolution testing

The *in vitro* dissolution study was carried out to compare CBZ release kinetics from the prepared jellies. The results are summarized in Table 4. It showed higher values of correlation coefficients (r^2) for first-order kinetics (>0.947) which indicated that the rate of drug release was dependent on the initial concentration from the jellies. Higher values were obtained for Higuchi plots that showed the drug release from tablets was diffusion controlled. To verify the mechanism of drug transport, first 60% drug release data was fitted in Korsmeyer–Peppas model and the obtained n values were between 0.5 and 1.0 which indicated that the diffusion mechanism was non-Fickian where the drug from the swollen polymer was assumed to move linearly with time.[44] The rate of dissolution of CBZ from F3, F11 and F15 was higher and in conformity with the biopharmaceutics classification system classification concept for immediate release formulations (>85% in 30 min).

Stability studies

A physically stable medicated oral jelly should retain its viscosity, color, clarity, taste, and odor throughout its shelf-life. The stability studies were carried out on formulations F3, F11 and F15 by comparing the initial samples to those under study period and the results are summarized in Table 5. The Student's t-test revealed no significant ($P < 0.05$) changes in physical characteristics and drug content of optimized jelly formulations of CBZ during stability studies.

Table 5: Results of stability studies on optimized formulations after 90 days*

Formulation	Temperature (°C)	Viscosity (cps)	pH	Drug content (%w/w)
F3	8±1	8718±69	6.37±0.05	98.01±0.58
	RT	8726±65	6.37±0.03	97.15±0.84
	40±2	8760±58	6.36±0.02	96.54±0.72
F11	8±1	6728±49	6.71±0.04	98.11±0.61
	RT	6740±44	6.70±0.04	97.31±0.37
	40±2	6750±35	6.70±0.06	96.16±0.44
F15	8±1	5873±24	6.13±0.05	98.33±0.52
	RT	5884±37	6.11±0.04	97.73±0.39
	40±2	5877±29	6.14±0.03	97.24±0.63

*Physical appearance, stiffness, sugar of crystallization and syneresis were not altered after testing period.RT, 25±5°C. All values expressed as ±SD; n=3. SD: Standard deviation, RT: Room temperature

CONCLUSION

In the present study, the jellies loaded with CBZ were successfully formulated using pectin, gellan gum and pectin-guar gum as gelling agents. The optimized formulations showed acceptable physico-chemical properties and stability. Formulations F3, F11 and F15 could be effectively employed for oral delivery of poorly soluble CBZ for pediatric, geriatric and dysphagic patients as alternatives to solid oral dosage forms.

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