Preparation and evaluation of floating tablets of pregabalin

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Abstract

Floating tablets of pregabalin were prepared using different concentrations of the gums (xanthan gum and guar gum), Carbopol 974P NF and HPMC K100. Optimized formulations were studied for physical tests, floating time, swelling behavior, in vitro release studies and stability studies. In vitro drug release was higher for tablet batches containing guar and xanthan gum as compared to the batches containing Carbopol 974P NF. Tablet batches were subjected to stability studies and evaluated by different parameters (drug release, drug content, FTIR and DSC studies). The optimized tablet batch was selected for in vivo pharmacodynamic studies (PTZ induced seizures). The results obtained showed that the onset of jerks and clonus were delayed and extensor phase was abolished with time in treated groups. A significant difference \( (p < 0.05) \) was observed in control and treated group behavior indicating an excellent activity of the formulation for a longer period (>12 h).

Keywords

Floating tablets, guar gum, pregabalin, seizure, xanthan gum

Introduction

The major advantages of gastroretentive systems are improved bioavailability of drugs which readily absorbed from GIT \(^1\), \(^2\), while the main limitation of floating systems is the requirement of high amounts of fluid in gastric systems so that formulation can float and work efficiently \(^3\), \(^4\).

Gastro-retentive systems are usually appropriate for drugs having certain properties/limitations like local action, good absorption from stomach, poor aqueous solubility, unstability at alkaline pH and/or narrow absorption window \(^5\), \(^6\), \(^7\).

Gastro-retentive systems (floating tablets, pellets or beads) were successfully developed and evaluated for several category of drugs like antihistamines (cetirizine, famotidine, ranitidine), NSAIDS (ketorolac, celecoxib), antibiotics (metronidazole, ofloxacin, amoxicillin), antidiabetics (metformin, repaglinide) and many more \(^8\), \(^9\), \(^10\), \(^11\).

Pregabalin is an antiepileptic used for treatment of partial seizures, diabetic neuropathy and post-herpetic neuralgia \(^12\), \(^13\), \(^14\). Pregabalin has many advantages over other antiepileptic drugs like lack of any pharmacokinetic interaction with other medications or enzyme induction. Pregabalin has a variable absorption through the gastrointestinal tract. It is preferably absorbed in the upper segment of the GI tract. Moreover, the shorter half life of pregabalin (4.5–7 h) too emphasizes the need for a sustained release system \(^15\), \(^16\). Hence, to ensure maximum absorption from stomach with extended period, a gastro-retentive system of pregabalin will be the most preferable dosage form.

One of the important criteria for fabrication of gastro-retentive systems is the selection of appropriate controlled drug carriers (polymers/gums). Natural gums are hydrophilic in nature, cost-effective, safe, easily available, biodegradable and biocompatible, hence preferred for the development of matrix based controlled release and delayed release drug delivery system \(^23\), \(^24\). Guar gum is a natural gum/polysaccharide (also known a galactomannan) obtained from Cyamopsis tetragonolobus composed of the sugars galactose and mannose. It is widely used as a binder and disintegrant in tablets but also used in controlled release formulation like matrix tablets. Guar gum disperses and swells immediately after putting in water. Guar gum is widely used in food industry as a stabilizer and thickener \(^26\). Xanthan gum is a polysaccharide secreted by bacterium Xanthomonas campestris produced by the fermentation of glucose, sucrose or lactose. It is used as an emulsifier and stabilizing agent in various formulations. Xanthan gum swells in water and acts as a disintegrating agent in tablets \(^27\). HPMC is a natural multifunctional carbohydrate polymer, available in various grades and viscosities. It is widely used as a thickener, tablet binder (2–5%), as coating material and controlled release agent in tablets. It retards the rate of drug release from matrix tablets \(^28\).

The present research work deals with the methodology to formulate gastro-retainive floating tablet system (consisting xanthan gum, guar gum, HPMC K100 and Carbopol 974P NF) which can help in controlling the release of pregabalin for an extended period.

Materials and methods

Materials

Pregabalin was a generous gift from Ranbaxy laboratories, Gurgaon, India. 1-Fluoro-2,4-dinitrobenzene, Xanthan gum, guar gum, Carbopol 974P NF and HPMC K100 were purchased from Himedia lab Ltd., Mumbai, India while spray dried lactose DC was purchased from Fisher Scientific, Mumbai, India. All other reagents and chemicals used were of analytical grade.
Table 1. Composition of different tablet batches.

| Batch (tablet weight in mg) | Drug (%) | Talc (%) | Mg stearate (%) | HPMC K100 (%) | Guar gum (%) | Xanthan gum (%) | Carbopol 974P NF (%) | Sodium bicarbonate (%) | Calcium carbonate (%) |
|---------------------------|----------|----------|----------------|---------------|-------------|------------------|------------------------|-----------------------|-----------------------|
| B1 (300)                  | 140      | 2        | 1              | –             | 6.6         | 10               | –                      | –                     | 12.5                  |
| B2 (560)                  | 140      | 2        | 1              | –             | 17.8        | 17.8             | –                      | 15                    | 4.7                   |
| B3 (650)                  | 140      | 2        | 1              | 35.4          | 10.7        | 25               | 15.3                   | 15                    | 3.6                   |
| B4 (560)                  | 140      | 2        | 1              | 8.3           | 10          | 23.3             | 18.3                   | –                     | 10.4                  |
| B5 (600)                  | 140      | 2        | 1              | –             | 8.3         | 35.7             | –                      | 19.6                  | 3.6                   |
| B6 (560)                  | 140      | 2        | 1              | –             | 8.3         | 26.7             | 6.7                    | 18.3                  | 10.4                  |
| B7 (600)                  | 140      | 2        | 1              | 46            | –           | –                | 20                     | 18.3                  | –                     |
| B8 (600)                  | 140      | 2        | 1              | 8.9           | 21.4        | 7.1              | –                      | 19.6                  | 11.2                  |
| B9 (560)                  | 140      | 2        | 1              | 32.1          | –           | –                | 16.1                   | 19.6                  | –                     |
| B10 (550)                 | 140      | 2        | 1              | –             | –           | –                | –                      | –                     | –                     |

Preparation of powder blends and floating tablets

Floating tablets were prepared using gums i.e. xanthan gum and guar gum, HPMC K100 and Carbopol 974P NF. Sodium bicarbonate was used as a disintegrant. Guaran gum (6.6–26.7%), xanthan gum (6.7–35.7%), HPMC K100 (8.3–46%) and Carbopol 974P NF (15.3–20%) were used as extended release polymers as well as a binder. Magnesium stearate (1%) and talc (1.8–2%) were used as lubricants and glidants, respectively. Spray dried lactose DC was used as a directly compressible excipient. The method used for tablet preparation was direct compression. Floating tablets were prepared by mixing API and all other excipients except lubricant and glidant and then sieving the powder blend to obtain uniform particle size. Then lubricant and glidant was added to blend and mixed for 15 min using 11 mm punches. Powder blend equivalent to tablet weight was weighed individually and compressed on a rotary tablet press. Table 1 shows the composition of tablets prepared.

Evaluation

**Powder blends**

**Flow properties.** Flow rate and angle of repose were determined. For determining flow rate, known weight of powder blend was poured into a funnel and the time required to pass through it was recorded. The flow rate was calculated as quotient of weight of drug and time in seconds.

Angle of repose is a measure of flow properties of powder or pellets. The powder blend was poured gently through a funnel, which was fixed at a position such that its lower tip was at the height exactly 2 cm above a hard surface. The powder blend was poured until the upper tip of the pile surface touched the lower tip height exactly 2 cm above a hard surface. The powder blend was poured gently through a funnel, which was fixed at a position such that its lower tip was at the height exactly 2 cm above a hard surface. The powder blend was poured into a funnel and the time required to pass through it was recorded. The flow rate was calculated as quotient of weight of drug and time in seconds.

**Tapped and bulk densities.** Powder blend was poured gently through a glass funnel into a 10 mL graduated cylinder until powder blend just touched the 10 mL mark and the weight of cylinder required for filling the cylinder volume was calculated. The cylinder was then tapped from the height of 2 cm until there was no more volume change. Bulk density was calculated as the quotient of the weight of pellets and volume of cylinder used. Tapped density was calculated as the quotient of the weight of the powder and its volume after tapping.

**Physiochemical interaction.** To determine the compatibility of pregabalin with different excipient FTIR spectroscopy and DSC thermal analysis were performed. FTIR spectra were obtained using a KBr pellet in FTIR spectrophotometer (Shimadzu-8400S, Kyoto, Japan). Transmittance (\% T) was recorded in the spectral region of 500–4500 cm\(^{-1}\) using a resolution of 4 cm\(^{-1}\) and 40 scans. DSC analysis was used to characterize the drug by examining endothermic transitions from the thermogram obtained. It involved the heating signal to a sample and a reference. DSC (TA Instruments, New Castle, DE) analyses were carried out on a nitrogen flow of 50 mL/min and a heating rate 10 °C/min from 20 to 300 °C.

**Tablet batches**

**Visual inspection.** Visual inspection of the tablets was done to check the surface texture of the tablets. Tablets were observed for various defects for example capping (partial and complete separation of top or bottom crown of tablets), lamination (laminar separation of tablet layers), mottling (unequal distribution of color in tablets), picking and sticking.

**Weight variation.** Twenty tablets were taken from each batch. Each tablet was weighed individually and average weight of the tablet batch was calculated. Then percentage deviation from average weight was calculated for each tablet as per IP 2010.

**Diameter and thickness.** Diameter and thickness were measured for all batches with a vernier caliper. This helps in determining the uniformity of the tablet batches.

**Hardness and friability.** Hardness of tablet batch was tested by Monsanto hardness tester. Hardness of the tablets should be 3–8 kg/cm\(^2\). Friability of tablet batch was tested using Roche’s friabilator. Tablet weight 6–6.5 g was taken in Roche’s friabilator and rotated for 100 revolutions at 25 rpm. After friability tablets were dusted to remove any powder adhered to tablets and was weighed. Percentage friability was calculated as given in formula:

\[
\% \text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

Percentage friability for new and old batches should be below 0.8 and 1%, respectively.

**Drug content.** Ten tablets were powdered in a mortar pestle. Tablet weight equivalent to 10 mg was taken and dissolved in 100 mL water in a volumetric flask. To 1 mL of stock solution of drug, 0.4 mL of 0.00117 M FDNB (1-fluoro-2,4-dinitrobenzene) and 1 mL of borate buffer was added. Test tubes were heated in a water bath for 45 min at 60 °C. After cooling, 0.15 mL of 1 N HCl was added and the volume was made up to 10 mL with acetonitrile. Absorbance was taken in UV-visible spectrophotometer against suitable blank. All determinations were done in triplicate. FDNB was used for analysis (UV-visible
spectrophotometer) of pregabalin only as the drug (pregabalin) does not contain any chromophore group. FDNB is a common reagent used for analysis of amino acids or compounds containing free amine group\(^3\).  

**Swelling index and floating time.** Tablets were taken in a beaker containing 150 mL of 0.1 N HCl. Tablets were weighed before putting in the beaker (which was taken as initial weight). The swelled tablets were taken out and weighed after blotting at 1, 2, 4, 6, 8, 10 and 24 h. Swelling index was calculated using the formula:

\[
\text{Swelling index} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100
\]

Floating time was calculated as the time taken by tablet to float in 0.1 N HCl and taken as lag time\(^3\).  

**Dissolution studies.** The dissolution studies were performed using USP dissolution apparatus type 2 (at 50 rpm) using 0.06 N HCl as the dissolution medium. Samples were taken at different time intervals and analyzed using a UV spectrophotometer (\(\lambda_{\text{max}} = 355 \text{ nm}\)) after derivatizing with Sanger’s reagent. Derivatization was done by adding 1 mL of dissolution sample with 0.4 mL of Sanger’s reagent and 1 mL borate buffer. The mixture was then heated for 45 min at 60°C. After cooling, 0.15 mL of 1 N HCl was added and the volume was made up to 10 mL with acetonitrile. Dissolution studies were performed in triplicate and the average drug released was calculated.  

**Stability studies.** Stability studies were conducted to determine the effect of time and storage conditions on the physical and chemical stability of the product. Stability program is designed to determine the shelf-life or expiry date of the product under normal storage conditions in its intended package. Stability testing of the optimized tablet batch was performed by storing the tablet at 40°C and 65% relative humidity in stability chamber for one month. Samples of the tablet batch were taken at different time points (0, 10, 20 and 30 days) and analyzed by dissolution studies, drug content estimation, FTIR spectrum and DSC spectra studies.  

**In vivo pharmacodynamic studies.** Pentylentetrazol (PTZ), a non-competitive GABA antagonist is used in seizure assays as a method of assessing the excitability of the central nervous system and GABA activity. This model is highly sensitive, and hence preferred widely for comparing different chemicals under standardized conditions\(^2\).  

PTZ test was performed to determine the pharmacodynamic activity of test formulation. Onsets of jerks, onsets of seizures, duration of extensor and death or recovery were noted in rats. All animal experiments were carried out after approval of the protocol by the Institutional Animal Ethical Care Committee (IAEC), Panjab University, Chandigarh, India, and conducted according to the Indian National Science Academy (INSA) guidelines for the use and care of experimental animals. SD rats (150–200 g) were fasted overnight for PTZ test. Each animal received the oral dose (2.8 mg/kg) of the test formulation (50 mg mini-tablets) following intraperitoneal administration of PTZ (65 mg/kg) after 1 h. Animals were observed carefully to check the onset of jerks, onset of clonus, duration of extensor and death or recovery. The same procedure was followed after 4, 8, 10 and 12 h following oral treatment with test formulation.  

**Statistical analysis.** Simple analysis of variance (one-way ANOVA, GraphPad Prism 5, GraphPad Software Inc., La Jolla, CA) was used to determine statistically significant differences between the results and values with \(p < 0.05\) were considered statistically significant as analyzed by the Dunnett multiple comparison test.  

**Results and discussion**  

**Evaluation of powder blends**  

**Flow properties**  

Angle of repose for tablet batches ranged between 29.391 ± 0.663 and 30.112 ± 0.742 as shown in Table 2 which indicated the excellent flow of powder blend. Flowability of powder is of immense importance in the production of pharmaceutical dosage forms like tablets. This ensures uniform/reproducible filling of tablet dies which improves weight uniformity and allows the tablet to produce more consistent physico-chemical properties. Angle of repose is a constant three-dimensional angle relative to horizontal base of a cone like pile formed. Angle of repose between 25° and 30° depicts excellent flow properties\(^3\).  

**Tapped and bulk densities**  

The tapped and bulk density of powder blends ranged from 0.829 ± 0.029 to 0.988 ± 0.052 g/cm\(^3\) and 0.621 ± 0.031 to 0.753 ± 0.052 g/cm\(^3\), respectively (Table 2). Hausner ratio for different powder blends ranged between 1.306 ± 0.019 and 1.452 ± 0.147. The Carr index for the powder blends of the tablet batches were founded between 0.218 ± 0.038 and 0.241 ± 0.069 as shown in Table 2. According to USP 2011, value of Carr index must be less than 10 for excellent flow properties of powders\(^3\). Bulk density determines the packing properties of powder while and Hausner ratio and Carr index indicates the flow behavior of powder.  

**Physicochemical interaction**  

No significant interactions were found between pregabalin and the excipient (gums and polymers) as confirmed by FTIR spectra and DSC thermogram. FTIR spectra of the physical mixture (drug + excipient) retains all important peaks of drug like –N–H stretching (2956.92 cm\(^{-1}\)), –OH stretching (2620.77 cm\(^{-1}\)) and –C = O (1645.23 cm\(^{-1}\)), Supplementary Figure S1).  

Thermograms of physical mixture (pregabalin + excipient) retained the sharp endotherm of the drug which showed the absence of any significant interactions between the drug and excipient (Supplementary Figure S2).  

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**Table 2. Angle of repose and flow rate of tablet batches.**

| Batch | Angle of repose (degrees) ± SD | Flow rate (g/s) ± SD | Tapped density (g/cm\(^3\)) ± SD | Bulk density (g/cm\(^3\)) ± SD | Hausner ratio ± SD | Carr index ± SD |
|-------|-------------------------------|---------------------|---------------------------------|-------------------------------|-------------------|-----------------|
| B7    | 30.112 ± 0.742                | 7.039 ± 0.418       | 0.888 ± 0.013                   | 0.680 ± 0.014                 | 1.367 ± 0.095     | 0.233 ± 0.022   |
| B8    | 29.673 ± 1.136                | 6.259 ± 0.448       | 0.829 ± 0.029                   | 0.621 ± 0.031                 | 1.335 ± 0.026     | 0.241 ± 0.069   |
| B9    | 29.391 ± 0.663                | 7.740 ± 0.767       | 0.933 ± 0.061                   | 0.714 ± 0.024                 | 1.306 ± 0.019     | 0.234 ± 0.032   |
| B10   | 29.672 ± 1.297                | 7.516 ± 0.423       | 0.988 ± 0.052                   | 0.753 ± 0.018                 | 1.310 ± 0.042     | 0.218 ± 0.038   |
Evaluation of tablet batches

Physical evaluation

Tablets were evaluated visibly and diameter–thickness of various batches was determined using vernier calliper. Uniformity in tablet diameter and thickness was observed, which shows uniformity in tablet batches. Diameter of different tablet batches was found to be 1.12 ± 0.01 to 1.32 ± 0.04 mm. Thickness of tablet batches was found to be 0.48 ± 0.02 to 0.69 ± 0.02 mm. Hardness was determined using Monsanto hardness tester which was found in the range of 2.67 ± 0.52 to 14 ± 0.26 kg/cm². Variation in hardness value was due to different concentrations of HPMC K100, guar gum, xanthan gum and Carbopol 974P used in different batches. All these materials act as binders which result in difference in hardness. Tablet batch 1 with hardness 2.67 did not contain HPMC K100 whereas tablet batch 3 with hardness 14 contained highest concentration of HPMC K100. Weight variation was determined. Drug content of each tablet batch was found in the range of 96.23 ± 0.43 to 100.34 ± 0.96%. Friability was determined using Roche’s friabilator. Friability of different batches was found in range of 0.06–4.48% (batch B1, B3 and B4 failed friability test). Observations of weight, diameter, thickness, friability, hardness and drug content are given in Table 3.

Swelling index

Swelling index is an important criterion in controlled release systems. Due to swelling of various polymers present in the formulation, drug release is prolonged. Drug diffusion is controlled by gel diffusion barrier. Swelling index of various tablet batches (which passed the physical evaluations test) were determined by weighing the tablet at different time intervals after tablet batches (which passed the physical evaluations test) were put into 0.1 N HCl at 37°C determined by weighing the tablet at different time intervals after tablet batches (which passed the physical evaluations test) were put into 0.1 N HCl at 37°C. Batches B2, B5 and B6 were dissolved within 3 h in the disintegrating medium while other batches exhibited good swelling behavior. Experimental data showed that swelling index of tablet batches (B8 and B10) with Carbopol 974P NF and HPMC K100 was higher as compared to tablet batches with gums and HPMC K100 (batch B7 and B9; Figure 1). Due to swelling of gums, Carbopol 974P NF and HPMC K100 tablets showed drug release for extended periods. Gums and Carbopol 974P NF present in matrix tablets retarded the drug release and prevented burst effect. However, decrease in concentration of gums, Carbopol 974P NF and HPMC K100 content in tablet batches increased the drug release in the medium. By decreasing the ratio of Carbopol 974P NF and HPMC K100 content (B8 and B10), swelling index was found to be decreased in comparison to B7 and B9. Swelling index of batch B9 was found to be slightly lower than batch B7 because of the low percentage of guar gum in B9 (21.4%) as compared to B7 (26.7%). Floating lag time of tablet batches ranged between 2 and 35 min while duration of floating for different batches ranged between 15 min and 24 h. Figure 2 depicts the swelling behavior and floating property of pregabalin tablets at various time points.

In vitro drug release studies

In vitro drug release studies of tablet batches containing gums and HPMC were performed in water using USP dissolution apparatus 2, i.e. paddle type apparatus at 50 rpm and 37°C. The cumulative release percentage from different batches were observed as 84.49 ± 2.27% (B7), 68.96 ± 3.82% (B8), 89.60 ± 1.07% (B9) and 85.21 ± 1.54% (B10) after 24 h (Figure 3). While the burst effect observed was 26.29 ± 2.29, 14.61 ± 2.01, 34.65 ± 0.48 and 36.95 ± 1.12% of batches B7, B8, B9 and B10, respectively. Release kinetics of these batches exhibited linearity with the Korsmeyer–Peppas model (r² > 0.9) suggesting the release of drug from tablet occurred by diffusion through a matrix system.

It was observed that tablet batch prepared with natural gums (guar gum and xanthan gum), i.e. batch B7 and B9 showed higher cumulative drug release as compared to tablet batches prepared with synthetic polymers like Carbopol 974P NF and HPMC (B8 and B10). The reason might be the high swelling capacity of Carbopol 974P NF as compared to gums, which resulted in a lower drug release rate. Moreover, natural gums like guar gum and xanthan gum also act as a disintegrating agent that resulted in high drug release as compared to batches prepared with Carbopol 974P NF (B8 and B10). The above observations suggested B9 as the most optimized batch, which was further selected for stability studies and animal activities.

Stability studies

Stability testing of tablet batch B9 was performed by storing the tablet batches at 40°C and 65% relative humidity in stability...
chamber for 1 month. These conditions were taken according to the conditions specified for accelerated stability studies in ICH guidelines.

**Dissolution studies**

Dissolution was performed to observe any increase or decrease in drug release from tablet batches after different time intervals (0, 10, 20 and 30 days). No statistically significant difference ($p > 0.05$) was observed during one month period in drug release profile of batch B9 (Figure 4).

**Drug content**

Drug content of tablet batch B9 kept for stability studies was found to be $98.25 \pm 0.81\%$ after 30 days of storage indicating that the drug was stable in developed batch B9.

**Physiochemical interaction**

FTIR spectra showed no change in functional group peaks of the drug which indicated the stability of batch B9. Similarly, DSC thermogram of batch B9 showed insignificant changes in endothermic peaks (Supplementary Figures S3 and S4).

**In vivo pharmacodynamic studies**

Animals were treated with pregabalin tablets (batch B9) except control group and PTZ injection was given after 1 h (Group 1), 4 h (Group 2), 8 h (Group 3), 10 h (Group 4) and 12 h (Group 5) and observations were noted.

Control group (Group 1) showed the faster onset of jerks and clonus as compared to treated group, i.e. $76 \pm 7.94$ and $108.33 \pm 10.41$ s, respectively. Duration of extensor phase was found to be $237.3 \pm 56.05$ s. Severity of jerks and clonus was very high in the control group. All the animals of the control group died within an hour of the PTZ injection (100% mortality).

Group 1 treated with the formulation B9 showed late onset of jerks ($160.33 \pm 17.62$ s) and clonus ($211 \pm 7.33$ s), respectively, after 1 h of oral dosing. Duration of extensor was found to be $43 \pm 6.32$ s after 1 h of oral dosing with formulation B9. For group 2 (after 4 h), the Onset of jerks and clonus after 4 h (Group 2) was found to be $85 \pm 5.30$ s and $273 \pm 1.68$ s, respectively, with no extensor phase. The onset of jerks and clonus after 10 h (Group 4) was found to be $234.33 \pm 9.90$ and $360 \pm 55.8$ s, respectively, with no extensor phase. Severity of jerks and clonus decreased after 4 h (Group 2). After 12 h of oral dosing, no jerks, clonus and extensor phase was observed in treated animals and hence, showed
no mortality. Therefore, data showed that tablet batch B9 gave prolonged effect up to 12 h in treatment of seizures. Statistically significant difference ($p<0.05$) was observed in animals treated with tablet batch B9 and control group after 1, 4, 8 10 and 12 h (Figure 5).

It was clear from the observations that all the phases of epilepsy diminished after oral dosing of pregabalin tablet (batch B9) as the formulation exhibited the extended pharmacodynamic efficacy against PTZ induced seizures.

Thus, formulation batch B9 containing guar gum (21.4%), xanthan gum (7.1%) and HPMC K100 (8.9%) was found to be stable and highly effective in the treatment of partial seizures.

Conclusion

Floating tablets of pregabalin were successfully prepared (using different concentrations of gums and polymers) and evaluated. Tablet batch B9 (primarily consisting of natural gums) exhibited excellent properties like higher floating time (>24h with a lag time of about 7 min) with extended drug release profile and good stability. Furthermore, it displayed excellent efficacy against partial seizures for prolonged periods. Besides excellent biocompatibility, natural gums also serve the properties of binder, disintegrant, emulsifier and stabilizer. Hence, exploitation of natural gums for fabrication of floating tablets could be highly beneficial in controlling the release of drugs from the designed matrix systems.

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Declaration of interest

The authors report no declarations of interest.

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Supplementary material available online
Supplementary Figures S1–S4