International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN: 0974-4290
Vol.9, No.03 pp 482-490, 2016

Investigation of Ghatti Gum as a Carrier to develop Polymeric Blend Beads of Galantamine Hydrobromide

Valluru Ravi*, T.M. Pramod Kumar[1] and N. Rama Rao

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Guntur, India -522034
[1]Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore, India 570015

Abstract: Polymeric-blend beads of ghatti gum with sodium alginate containing the drug, galantamine hydrobromide were prepared by varying the gum concentrations and cross linkers viz., $CaCl_2$ and $AlCl_3$. It was found that in comparison between $AlCl_3$ and $CaCl_2$, the particle size, percent yield and drug entrapment efficiency was greater in beads prepared by $AlCl_3$ as cross linking agent. Formulation SGF6 formulations showed high percent yield which may be attributed for higher concentration of ghatti gum. SEM photographs for the prepared formulation indicated that the beads were having smooth and crack-free surface. FTIR and DSC spectra indicated that galantamine hydrobromide has not undergone any chemical interaction with the polymers and excipients used. *In vitro* drug release data indicated that formulations SGF3, SGF5 and SGF6 showed a release of about 99, 98 and 94% at the end of 12 h indicating their suitability for showing a 12 h release profile. Mathematical model fitting indicated that the best-fit model for the formulations was peppas and the release of drug from the polymer matrix followed super case-II transport. Formulation SGF6 was found to be ideal and when subjected for stability studies showed that the drug was stable.
Keywords: Ghatti gum, beads, sodium alginate, galantamine hydrobromide.

Introduction

Natural polymers and their derivatives are widely used to prepare various pharmaceutical dosage forms. Natural polymers can be modified to have tailor-made materials for preparing drug delivery systems and thus can compete with synthetic materials which are widely available in the market [1]. Oral sustained release dosage forms (DFs) are being developed for the past several decades due to their considerable therapeutic advantages [2, 3]. Natural polysaccharides hold advantages over synthetic polymers as they are non toxic, less expensive, biodegradable and easily available.

The use of biodegradable polysaccharides has gained importance in the development of controlled and sustained release drug delivery systems. Over the past few decades, natural biodegradable polysaccharides such as pectin, xanthan gum, guar gum, chitosan, carrageenans, sodium alginate (Na-alginate), hydroxypropyl methylcellulose (HPMC), agar and gellan gum have been widely used [4, 5]. These polymers can be exploited in various ways in the formulation of targeted and controlled drug delivery as they have different derivatizable groups, a wide range of molecular weight, and varying chemical composition. They can change their volume in contact with external media and form a viscous layer which serves as a protective barrier against water influx into

the system and drug efflux into the contact medium. Thus, immediate drug release is prevented, and a sustained or prolonged drug release rate can be achieved [6, 7].

Multiparticulate drug delivery systems made up of natural biodegradable polymers have been paid considerable attention for several years in controlling and sustaining of release rate of drugs. Beads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release of various active agents without major side effects. Alginic acid, also called algin or alginate, is an anionic polysaccharide distributed widely in the cell walls of brown algae. Alginates mainly consist of mannuronic acid, guluronic acid and mannuronic-guluronic blocks [8]. Dropwise addition of aqueous alginate solution to the aqueous solution containing calcium ions or other di- and polyvalent cations causes spherical gel formation termed as alginate bead. The dried alginate beads have the property of reswelling and thus they can act as sustained/controlled/extended release drug delivery system. Many researchers have done work related to alginate beads either alone or by blending with many different polymers [9-11].

Gum ghatti is a complex non-starch polysaccharide obtained as amorphous translucent mucilage from wounds in the bark of Anogeissus latifolia tree which is found in the deciduous forests of India and Sri Lanka. It has been widely employed in food, pharmaceuticals, paper and other industries primarly due to its emulsification and thickening property [12, 13]. It is a high molecular weight complex polysaccharide that occurs in nature as a mixed calcium, magnesium, potassium, and sodium salt; upon hydrolysis it yields L-arabonose, D-galactose, D-mannose, D-xylose, L-rhamnose, and D-glucuronic acid. Gum ghatti is marketed in Japan as an existing food additive, and was assigned "generally regarded as safe" (GRAS) status by the US FDA [14]. The molecular structure, functional properties and pharmaceutical applications of the gum have also been extensively studied [15]. Ghatti gum has also been used for preparing matrix tablets for domperidone [16], floating drug delivery system [17] and also as an emulsifying agent [18]. Even though, ghatti gum is an important forest product, its commercial exploitation was limited due to non-availability of scientific information, especially in relation to its application in the pharmaceutical preparations.

In the present study, galantamine hydrobromide (GAL) was used as a model drug, which is an analkaloid that is obtained synthetically or from the bulbs and flowers of *Galanthus caucasicus*, *Galanthus woronowii* and related genera like *Narcissus*, *Leucojum*, and *Lycoris* including *Lycoris radiate*. It is used is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, in particular those of vascular origin [19-21].

In the present study, an attempt was made to develop polymeric blend beads of sodium alginate and ghatti gum containing GAL as model drug. This is a novel study and was not carried out elsewhere by any researcher. The overall objective of the present investigation is to investigate the utility of ghatti gum, a natural and biodegradable gum in pharmaceutical preparations as a carrier in formulating sustained drug delivery systems. Different formulations were prepared by varying the concentration of gums and the prepared beads were evaluated for particle size, scanning electron microscopy (SEM), percent yield, entrapment efficiency, differential calorimetry (DSC), Fourier transform infrared spectrophotometer (FTIR), *in vitro* drug release studies, diffusion coefficient (n) and stability studies.

Materials and Methods

Materials

Galantamine hydrobromide was received as gift sample from Dr. Reddy's Laboratories, Hyderabad, India. It is a white to almost white powder, slightly soluble in water, fairly soluble in hot water, and freely soluble in alcohol, acetone, and chloroform. Ghatti gum was purchased from Girijan Co-operative Society, Govt. of Andhra Pradesh, Hyderabad, India. Sodium alginate was purchased from Sigma Aldrich, Mumbai, India. All other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Purification of gum [15]

First the foreign extraneous matter like bark etc was separated from the gum, then powdered using mixer grinder and passed through sieve # 80. The powdered gum was dispersed in distilled water to get a 1% solution, kept in sonicator for 10 min until it was clear and added to equimolar mixture of acetone and ethanol (2:1 v/v) to

give precipitation of gum. Precipitated polymer was kept in an oven for drying, powdered and evaluated for general characteristic properties.

Preparation of polymer blend beads [22, 23]

Required amount of drug, galantamine was homogenously dispersed in an aqueous solution of sodium alginate and ghatti gum. The resulting dispersion was extruded through 23 Guage hypodermic needle into $CaCl_2$/ $AlCl_3$ solution. Six formulations were prepared by varying the concentration of gums and cross linking agents as given in Table 1.The prepared beads were, then collected by filtration, washed with deionized water, air dried at room temperature for 12 h and dried at 40°C in a hot air oven to constant weight and kept in a dessicator until further use.

Table 1: Formulation chart for ghatti gum-sodium alginate polymer blend beads

Formulation code	GG%: SAL%	Drug load (% w/w of total polymer)	Gelation time (h)	Conc. of $AlCl_3$ (% w/v)	Conc. of $CaCl_2$ (% w/v)
SGF1	1:1.5	10	0.5	--	10
SGF2	1:1	10	0.5	--	10
SGF3	1.5:1	10	0.5	--	10
SGF4	1:1.5	10	0.5	10	--
SGF5	1:1	10	0.5	10	--
SGF6	1.5:1	10	0.5	10	--

UV/Visible spectroscopy

The wavelength of maximum absorbance (λ_{max}) of galantamine hydrobromide drug in pH 7.2 phosphate buffer was determined by scanning a known concentration of sample solution in the wavelength region 200–400 nm by using Shimadzu 1601 UV/Visible spectrophotometer. The λ_{max} was found to be 221 nm and this wavelength was used for further studies.

Particle size analysis [24, 25]

The particle size analysis was carried out by using optical microscope. Samples were dispersed in liquid paraffin and observed under optical microscope. Stage micrometer was used to calculate calibration factor. Averages of 50 beads were counted and size was determined.

Scanning electron microscopy (SEM) [24]

SEM photographs were taken for the prepared beads with a scanning electron microscope, at the required magnification in room temperature. The photographs were observed for morphological characteristics and to confirm the spherical nature of beads.

Yield of the process [23-26]

Determining whether the preparation procedure chosen for incorporating a drug into the polymers is efficient is of prime importance. The raw materials, amount of active compound, and other process parameters are deciding factors for the yield of the product during the preparation of beads. The yield was determined by weighing the beads and then finding out the percentage yield with respect to the weight of the input materials, i.e., weight of drug and polymers used. The formula for calculation of % yield is as follows

% Yield = (Weight of drug + Weight of polymers) x 100/ Weight of beads

Drug entrapment efficiency [25]

Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the beads. 100 mg of beads were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffer. They were shaken for 1 h on a mechanical shaker, crushed and further shaken for 1 h.

From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution is diluted to 10 ml and absorbance was measured at 221 nm. The drug content was calculated by using the formula-

Amount of drug = Conc. from standard graph x Dilution factor/ 1000

Percentage drug entrapment efficiency was found out by calculating the amount of drug present in 100 mg of beads. It is further calculated by using formula-

% Drug entrapment efficiency = Experimental drug content x 100/ Theoretical drug content

***In vitro* drug release studies [24, 25]**

To understand the release kinetics of drug from beads, release studies were carried out using USP dissolution apparatus, basket type at 100 rpm and at 37 ± 0.5˚C. The release studies were carried out for 12 h in simulated intestinal condition (pH 7.2 phosphate buffer). A 10 ml aliquot of the dissolution solution was withdrawn at regular intervals of time and analyzed for drug content using a UV– visible spectrophotometer at 221 nm. A 10 ml of the fresh buffer solution was replaced back to the dissolution vessel so as to maintain the sink conditions.

Peppas model fitting [27, 28]

Koresmeyer-Peppas model is one of the mathematical expression to evaluate the mechanism of drug delivery. The Koresmeyer-Peppas equation is as follows;

$$M_t/ M_\infty = 1- A (\exp^{-kt}) \quad (2)$$

$$\log (1 - M_t/M_\infty) = \log A – kt/2.303 \quad (3)$$

where, M_t/M_∞ is the fractional amount of drug released and t is the time in hrs. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of In ($1- M_t/M_\infty$) versus time t respectively where, Mt is the amount of drug release at time t; M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and A is the diffusional exponent indicative of the mechanism of drug release. To find out the release exponent, the log value of percentage drug dissolved was plotted against log time for each batch according to the above equation. If A is equivalent to 0.5 indicates Fickian (case I) release; greater than 0.5 but less than 1 for non-Fickian (anomalous) release and A is greater than 1 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.

Fourier Transform Infrared Spectroscopy (FTIR) [21]

FTIR spectra of the pure galantamine hydrobromide and the optimized formulation were recorded using a Fourier transform infrared spectrophotometer (FTIR 8400 Shimadzu, Japan). Samples were prepared as KBr pellets using a hydraulic pellet press and scanned from 4000 to 400 cm^{-1}.

Stability studies [17]

Stability studies of the optimized formulation of galantamine hydrobromide beads was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies have been measured at 40 ºC/75% RH for 3 months (Thermolab, Mumbai, India). Drug formulation was analyzed every 15 days for its physical appearance and % drug content.

Differential Scanning Calorimetry (DSC) [21]

All dynamic differential scanning calorimetric (DSC) studies were carried out using DuPont thermal analyzer with 2010 DSC module. Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids, and heated at a constant rate of 5 °C/min over a temperature range from ambient temperature to 300 °C. DSC thermograms were recorded for pure galantamine drug and the optimized formulation.

Results and Discussion

The data obtained for particle size analysis, percent yield and drug entrapment efficiency is given in Table 2. From the table, it is clear that the particle size increased with increase in concentration of ghatti gum in the formulation. When $CaCl_2$ is used as cross linking agent, the particle size for the formulations was in the order 0.64, 0.71 and 0.98 mm for SGF1, SGF2 and SGF3 respectively. Similarly when $AlCl_3$ cross linker is used the particle size was 0.66, 0.79 and 1.04 mm for SGF4, SGF5 and SGF6 respectively. In comparison to $AlCl_3$ and $CaCl_2$, the particle size was higher in beads prepared using $AlCl_3$ as cross linking agent (particle size of SGF6 is more than SGF3).

Table 2: Average particle size for the prepared polymer-blend beads

Formulation code	Mean particle size (mm)*	% Yield mean ± SD*	Entrapment efficiency (%) Mean± SD*
SGF1	0.64	68.76 ± 1.22	76.5 ± 1.25
SGF2	0.71	71.33 ±1.39	80.6 ±1.46
SGF3	0.98	78.54 ±1.71	87.3 ±1.81
SGF4	0.66	71.14 ±1.23	80.7 ±1.46
SGF5	0.79	78.26 ±1.57	85.9 ±1.72
SGF6	1.04	82.57 ±1.26	91.1 ±1.68

*Mean, n=50

From the table, it is clear that the percent yield increased with increase in concentration of ghatti gum in the formulations. When $CaCl_2$ is employed as cross linking agent, the percent yield for the beads was in the order 68, 71 and 78% for SGF1, SGF2 and SGF3 respectively. SGF3 formulation showed high percent yield compared to SGF1 and SGF2. This may be attributed for increase in concentration of ghatti gum in SGF3.

Similarly, when $AlCl_3$ cross linker was used the percent yield was 71, 78 and 82% for SGF4, SGF5 and SGF6 respectively. SGF6 formulation showed high percent yield compared to SGF4 and SGF5. This may be attributed for higher concentration of ghatti gum in SGF3. In comparison to $AlCl_3$ and $CaCl_2$, the percent yield was more in beads prepared used $AlCl_3$ as cross linking agent (percent yield of SGF6 is more than SGF3).

From the results, it is clear that the entrapment efficiency increased with increase in concentration of ghatti gum in the formulations. When $CaCl_2$ was used as cross linking agent, the drug entrapment efficiency by the beads was in the order 76, 80 and 87% for SGF1, SGF2 and SGF3 respectively. SGF3 formulation showed high drug entrapment efficiency compared to SGF1 and SGF2. This may be attributed for higher concentration of ghatti gum in SGF3.

Similarly when $AlCl_3$ cross linker was used the entrapment efficiency was 80, 850 and 91% for SGF4, SGF5 and SGF6 respectively. SGF6 formulation showed high percent yield compared to SGF4 and SGF5. This may be attributed due to higher concentration of ghatti gum in SGF3. In comparison of $AlCl_3$ and $CaCl_2$, the drug entrapment efficiency was high in beads prepared used $AlCl_3$ as cross linking agent (percent yield of SGF6 is more than SGF3). This result shows that $AlCl_3$ is an effective cross linker for preparing the polymer-blend beads. It is also evident that by increasing the concentration of ghatti gum in the preparation, drug leaching from the prepared beads can be prevented.

Scanning electron microscopy was carried out to observe the surface morphology and texture of the beads. The SEM microphotographs of SGF6 are given in Figures 1 and 2. From the photographs it was observed that the beads were having a smooth and crack free surface. The IR spectra of pure galantamine hydrobromide (A) and formulation SGF6 (B) are shown in Figure 3. The FTIR spectra obtained indicated that no chemical interaction occurred between the drug, polymers and the excipients used in formulating the polymer-blend bead. But, a slight shift in absorption peaks position was noticed which indicated that physical interaction might have occurred between drug and the polymer.

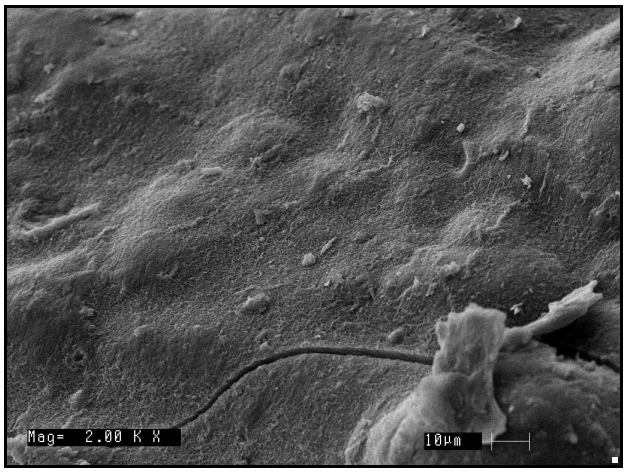

Figure 1: SEM microphotograph showing the surface of prepared SGF6 beads

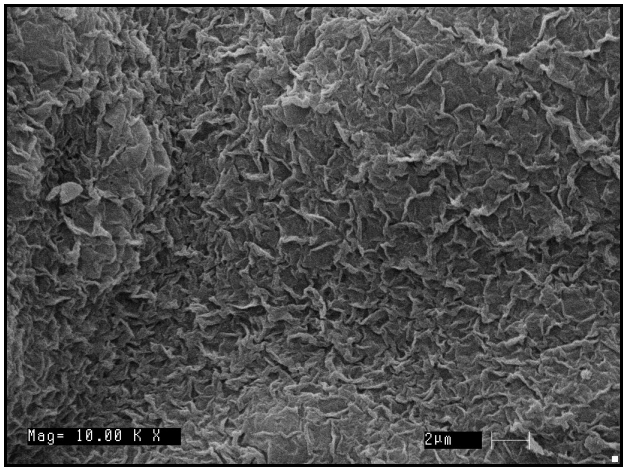

Figure 2: SEM microphotograph of the bead indicating a smooth crack-free surface

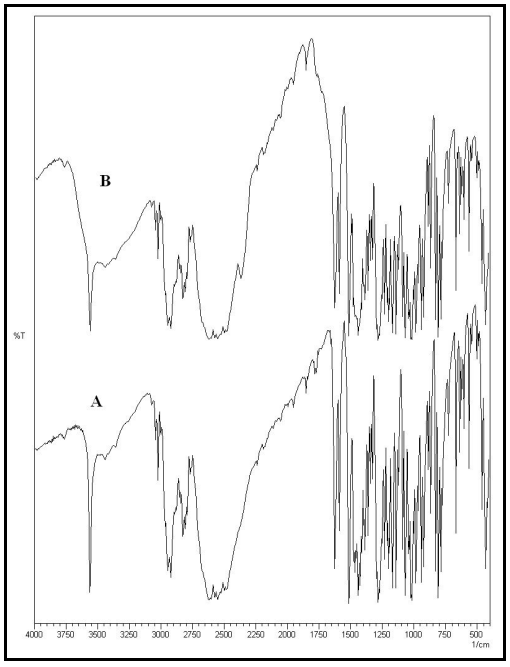

Figure 3: FTIR spectra of pure drug (A) and formulation SGF6 (B)

The *in vitro* drug release data of galantamine hydrobromide from the prepared polymer-blend beads is shown in Figure 4. From the figure, it is clear that beads prepared using $CaCl_2$ as cross-linker showed burst drug release. Formulations SGF1-SGF3 showed a drug release of 50, 46 and 41% of drug at 4 h. Formulations SGF1 and SGF2 released the entire amount of drug in 8 and 10 h respectively and thus could not sustain the release of drug for 12 h. On the other hand, formulations prepared using $AlCl_3$ as cross-linker showed very less release at the end of 4 h. Formulations SGF4-SGF6 showed drug release of 40, 36 and 31% at the end of 4 h. But, SGF4 showed complete drug release within 10 h, indicating its unsuitability to design for 12 h release. Formulations SGF3, SGF5 and SGF6 showed a release of about 99, 98 and 94% at the end of 12 h indicating their suitability for showing a 12 h release profile.

In vitro release studies data of prepared beads (formulations SGF3, SGF5 and SGF6) was fitted into various mathematical models to determine the best-fit model. The best fit model with the highest regression coefficients (R^2) for all the formulations is given in Table 3 and the best-fit model was found to be Peppas model. When the *in vitro* release data was fitted to the Korsmeyer-Peppas equation, the release exponent values (n) obtained in all the cases were found to be more than 1. This result indicated that the release of drug from the polymer matrix formulations was found to be super case-II transport, i.e., drug release by both diffusion and relaxation of polymer chain. From the table, it was concluded that, formulation SGF6 with R2 value of 0.9968 is the optimized formulation for 12 h study period.

Table 3: Model fitting data for the prepared formulations

Release model		Formulation code		
		SGF3	**SGF5**	**SGF6**
Zero order	**R^2**	0.8475	0.8952	0.9031
First order	**R^2**	0.9044	0.9348	0.8227
Hixson Crowell	**R^2**	0.8348	0.8324	0.8343
Matrix	**R^2**	0.8346	0.8646	0.8952
Peppas	**R^2**	0.9926	0.9934	0.9968
	n	1.123	1.215	1.361
Best fit model		Peppas	Peppas	Peppas

Table 4: Stability study data of optimized formulation SGF6

Time in weeks	% Drug content in SGF6 mean ± SD* at 40 ± 0.5°C and 75% RH
0 (Initial)	101.62 ± 1.28
1	100.48 ± 1.83
2	100.74 ± 2.78
3	99.28 ± 1.43
4	9946 ± 2.46
5	98.82 ± 1.43
6	98.36 ± 2.46

*Standard deviation n=3

DSC thermograms of the pure drug and its optimized formulation were recorded to evaluate whether the drug has undergone any degradation during the study period. A sharp endothermic peak at 270 °C was obtained for galantamine hydrobromide. From the DSC data obtained (Figure 4), it was evident that the melting point of galantamine hydrobromide has not appeared in the prepared beads. Hence, it may be inferred that the drug has dispersed in micron level in the prepared beads.

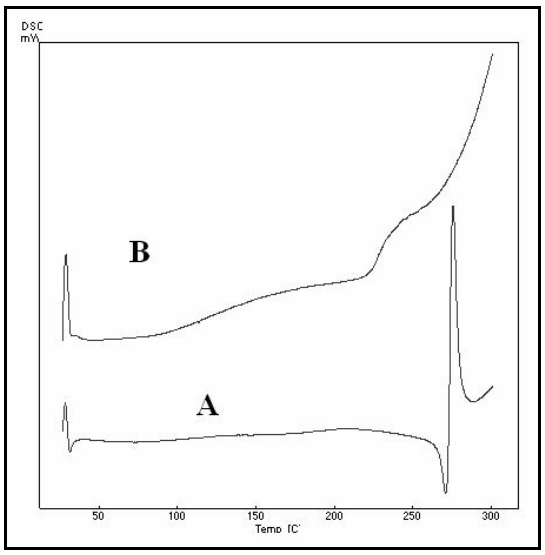

Figure 4: DSC spectra of pure drug (a) and formulation SGF6 (b)

Conclusion

Polymeric-blend beads of ghatti gum with sodium alginate were prepared by varying the gum concentrations and cross linkers viz., $CaCl_2$ and $AlCl_3$. It was found that in comparison between $AlCl_3$ and $CaCl_2$, the particle size, percent yield and drug entrapment efficiency was greater in beads prepared by $AlCl_3$ as cross linking agent. SGF6 formulations showed high percent yield which can be attributed for higher concentration of ghatti gum used. SEM photographs for SGF6 indicated that the beads were having smooth and crack-free surface. FTIR and DSC spectra indicated that galantamine hydrobromide has not undergone any chemical interaction with the polymers and excipients used. *In vitro* drug release data indicated that formulations SGF3, SGF5 and SGF6 showed a release of about 99, 98 and 94% at the end of 12 h indicating their suitability for showing a 12 h release profile. Mathematical model fitting indicated that the best-fit model for all the formulations was peppas and the release of drug from the polymer matrix followed super case-II transport. Formulation SGF6 was found to be ideal and when subjected for stability studies showed that the drug was stable.

References

1. Cottrell I.W., Kang K.S. and Kovaca P., Handbook of Water Soluble Gums and Resins, In: R. L. Davidson (ed.), McGraw Hill, Kingsport Press, New York, 1980, pp. 24-29.
2. Hoffman A., Pharmacodynamic aspects of sustained release preparations, Adv. Drug Deliv. Rev., 1998, 33, 185-199.
3. Brahma N. Singh and Kwon H. Kim., Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention, J. Control. Rel., 2000, 63, 235-259.
4. Shweta Arora, Kaved Ali, Alka Ahuja, Roop K. Khar and Sanjula Babota, Floating drug delivery systems: A review, AAPS PharmSciTech, 2005, 6, 372-390.
5. Streubel A., Siepmann J., and Bodmeier R., Floating microparticles based on low density foam powder, Int. J. Pharm., 2002, 241, 279-292.
6. Hoffman A., and Stepensky D., Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy, Crit. Rev. Ther. Drug Carrier Syst., 1999, 16, 571-639.
7. Yong-Dan Tang, Venkataraman S.S., Freddy Y.C. Boey and Li-Wei Wang, Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form, Int. J. Pharm., 2007, 336, 159-165.
8. Mutasem O. Taha, Wissam Nasser, Adel Ardakani, and Hatim S. AlKhatib, Sodium lauryl sulfate impedes drug release from zinc-crosslinked alginate beads: Switching from enteric coating release into biphasic profiles, Int. J. Pharm., 2008, 350, 291-300.
9. Thaned Pongjanyakul and Satit Puttipipatkhachorn, Xanthan–alginate composite gel beads: Molecular interaction and *in vitro* characterization, Int. J. Pharm., 2007, 331, 61-71.

10. Yongmei Xu, Changyou Zhan, Lihong Fan, Le Wang and Hua Zheng. Preparation of dual crosslinked alginate–chitosan blend gel beads and in vitro controlled release in oral site-specific drug delivery system, Int. J. Pharm., 2007, 336, 329-337.
11. George Pasparakis and Nikolaos Bouropoulos, Swelling studies and *in vitro* release of verapamil from calcium alginate and calcium alginate–chitosan beads, Int. J. Pharm., 2006, 323, 34-42.
12. Ji Kang, Steve W. Cui, Jie Chen, Glyn O. Phillips, Ying Wu and Qi Wang, New studies on gum ghatti (*Anogeissus latifolia*) part I. Fractionation, chemical and physical characterization of the gum, Food Hydrocolloid, 2011, 25, 1984-1990.
13. Cesar A. Tischer, Marcello Iacomini, Ricardo Wagner and Philip A.J. Gorin, New structural features of the polysaccharide from gum ghatti (*Anogeissus latifolia*), Carbohyd. Res., 2002, 337, 2205-2210.
14. Cheryl A. Hobbs, Carol Swartz, Robert Maronpot, Jeffrey Davis, Leslie Recio and Shim-mo-Hayashi, Evaluation of the genotoxicity of the food additive, gum ghatti, Food Chem. Toxicol., 2012, 50, 854-860.
15. Anand S. Deshmukh, Mallikarjuna Setty C., Arvind M. Badiger and Muralikrishna K.S., Gum ghatti: A promising polysaccharide for pharmaceutical applications, Carbohyd. Polym., 2012, 87, 980-986.
16. Gurpreet Arora, Malik K, Rana V., and Singh I., Gum Ghatti-A pharmaceutical excipient: development, evaluation and optimization of sustained release mucoadhesive matrix tablets of domperidone, Acta. Pol. Pharm., 2012, 69, 725-737.
17. Valluru Ravi, Pramod Kumar T.M., and Siddaramaiah. Investigation of ghatti gum as a carrier to develop sustained release floating tablets of diltiazem hydrochloride, Thai J. Pharm. Sci., 2012, 36, 155-164.
18. Cushman D.R., and Schick J.W., Modified natural gums, U.S. Patent US 3891620, 1975.
19. Guk-Hee Suh, Modeling the Cost-Effectiveness of Galantamine for Mild to Moderately Severe Alzheimer's Disease in Korea, Value in Health, 2009, 12, S49-S54.
20. Steven H. Ferris, Switching previous therapies for Alzheimer's disease to galantamine, Clin. Therap., 2001, 23, A3-A7.
21. Joseph Coyle and Paul Kershaw, Galantamine, a cholinesterase inhibitor that allosterically modulates nicotinic receptors: effects on the course of Alzheimer's disease, Biol. Psychiatry, 2001, 49, 289-299.
22. Rajat Ray, Siddhartha Maity, Sanchita Mandal, Tapan K Chatterjee and Biswanath Sa, Development and evaluation of a new interpenetrating network bead of sodium carboxymethyl xanthan and sodium alginate for ibuprofen release, Pharmacol. Pharm., 2010, 1, 9-17.
23. Jakir Ahmed Chowdhury, Sheikh Tasnim Jahan, Md. Masud Morshed and Jewel Mallick, Development and evaluation of diclofenac sodium loaded alginate cross-linking beads, Bangladesh Pharm. J., 2011, 14, 31-39.
24. Kulkarni A.R., Soppimath K.M., Aminabhavi T.M., and Rudzinski W.E., *In-vitro* release kinetics of cefadroxyl loaded sodium alginate interpenetrating network beads, Eu. J. Pharm. Biopharm., 2001, 51, 127-133.
25. Piyakulawat P., Praphairaksit N., Chantarasiri N., and Muangsin N., Preparation and evaluation of chitosan/carrageenan beads for controlled release of sodium diclofenac, AAPS PharmSciTech, 2007, 8, 1-10.
26. Chavanpatil M.D., Jain P., Chaudhari S., Shear R., and Vavia P.R., Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin, Int. J. Pharm., 2006, 316, 86-92.
27. Korsmeyer R.W., Gurny R., Doelker E., Buri P., and Peppas N.A., Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm., 1983, 15, 25-35.
28. Peppas N.A., Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv., 1985, 60, 110-111.

*****