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DEVELOPMENT AND EVALUATION OF FLOATING ALGINATE BEADS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

The objective of current research work was to develop gastro-retentive floating alginate beads of tramadol hydrochloride. The beads were formulated using different concentration of hydrophilic polymer HPMC K15M and HPMC K100M, along with an effervescent agent such as calcium bicarbonate. Preformulation compatibility studies indicate that there is no interaction between the excipient and the drug. Total seven batches were prepared and floating beads ware subjected for evaluation of flow properties. All the parameter was found to be within the limit showing good flow property. Floating beads was also evaluated for entrapment efficiency, buoyancy studies, percent yield, and average particle size and in-vitro dissolution study. The drug entrapment efficiency for all batch formulation was above 90% indicating effective distribution of drug in beads. Floating lag time of all batch formulation was found in second indicating rapid buoyancy of beads after immersion in dissolution medium. Total floating time for all brads formulation was above 12 hrs. the average particle size of all beads formulation was found in the range of 1140 to 1230 µm and was found spherical in shape. The in-vitro dissolution profile of all beads formulation of Tramadol Hcl was controlled over an extended period of time. The optimized formulation of F7 containing HPMC K100M (1.5%) was consider as the best formulation with respect to its lower floating lag time, drug entrapment efficiency and in vitro drug release for 12 hrs.

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INTRODUCTION

A floating drug delivery system (FDDS) is a type of drug delivery system designed to prolong the residence time of drugs within the gastrointestinal (GI) tract, particularly the stomach. The primary objective of FDDS is to enhance the bioavailability and efficacy of drugs, particularly those with narrow absorption windows or those that degrade in the acidic environment of the stomach (Liew, 2014 and Bharat et al., 2017). In FDDS, the drug is typically incorporated into a formulation that possesses low density or contains gas-generating agents, allowing it to float on the gastric contents after ingestion. This buoyancy ensures that the drug remains in the stomach for an extended period, thereby prolonging its release and absorption (Jadhao et al., 2013). Floating alginate beads are a type of drug delivery system designed to remain buoyant on the surface of gastric fluid for an extended period of time. These beads are typically prepared using sodium alginate, a natural polysaccharide derived from brown seaweed, along with other excipients and active ingredients. The primary component of floating alginate beads, sodium alginate serves as the matrix material responsible for forming the bead structure.

Calcium salts, such as calcium chloride or calcium carbonate, are commonly used as cross-linking agents to gel the alginate and form stable beads. Drugs or other active ingredients can be incorporated into the alginate matrix to achieve controlled release or targeted delivery. Additional excipients such as gel-forming agents, pore-forming agents, and release modifiers may be included to optimize bead characteristics and drug release kinetics (Arora et al., 2005 and Deshpande, 1996). Gastroretentive floating beads are small, solid and free flowing particulate carriers, on which the drug is coated or encapsulated in the core of beads. Beads can provide controlled / sustained release properties and as such bioavailability of drugs are enhanced. Gastro retentive beads are not just to sustain the drug release, but also to enhance gastric residence of the dosage forms until the entire drugs are completely released at the desired period of time. Gastroretentive floating beads are typically designed using polymers such as alginate, chitosan, or hydroxypropyl methylcellulose (HPMC). The beads are formulated to contain a gas-generating agent like sodium bicarbonate, which releases CO2 in the acidic environment of the stomach. This gas generation reduces the density of the beads, allowing them to float on the gastric fluid. The buoyancy ensures prolonged gastric retention, providing a sustained release of the drug (Gunesh et al., 2022). Tramadol induces analgesic

effects through a variety of different targets on the noradrenergic system, serotoninergic system and opioid receptors system. Tramadol exists as a racemic mixture, the positive enantiomer inhibits serotonin reuptake while the negative enantiomer inhibits noradrenaline reuptake, by binding to and blocking the transporters. Tramadol has also been shown to act as a serotonin releasing agent. Both enantiomers of tramadol are agonists of the μ-opioid receptor and its M1 metabolite, O-demethylate, is also a μ-opioid receptor agonist but is 6 times more potent than tramadol itself.

MATERIALS AND METHODS

MATERIALS

Tramadol Hcl was obtained as gift sample from Micro Lab., Goa.., HPMC K4M & HPMC K100M were obtained from Colorcon Asia Pvt Ltd.All other chemicals are Analytical grades.

METHOD

Drug Excipients Compatibility Studies: These studies aim to identify any chemical, physical, or mechanical interactions that could affect the stability, efficacy, or safety of the final dosage form. By assessing compatibility early in the development process, formulation scientists can make informed decisions regarding excipient selection, formulation design, and process optimization. Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (Shimadzu, Japan). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug (Rouge et al., 1991 and Manjanna, 2009).

After completing the homogenization process, solution was kept stand for 15 min without stirring and then sonicate for 10 min using bath sonicator to remove the air bubbles formed during homogenization. In another beaker, 100 ml of water containing glacial acetic acid (2 %v/v) and calcium chloride (5%w/v) solution was prepared in which sodium alginate solution containing drug was dropped with the help of 29-gauge hypodermic needle fitted with 10ml syringe into previously prepared calcium chloride solution, by keeping the distance of 10 cm from the syringe tip and surface of calcium chloride solution during dropping the alginate solution. Drug loaded alginate beads were immediately form in calcium chloride solution, which was then allowed to incubated for 30 min. After complete incubation beads were separated by filtering the solution. Obtained beads were washed three times with distilled water and dried at 40℃. Prepared beads were stored in tight container before further use in their characterization. The composition of different formulation of Tramadol Hcl floating beads is shown in the table 1 (Mohammad Abu TaherRasel 2012 and SantanuChakraborty et al., 2010).

Evaluation Floating Beads

Micrometrics Properties: Flow properties of Floating Beads of Tramadol Hcl were determined by measurement of angle of repose, bulk density, and tapped density, compressibility index (CI) and hausner's ratio (Tekade, 2013).

Drug Loading and Drug Entrapment Efficiency (%): Drug Entrapment Efficiency was determined by comparing the whole weight of beads formed against the combined weight of the copolymer and drug. An accurately weighed sample of beads (100mg) was crushed in a mortar. The crushed material was dissolved in 75ml of 0.1N Hcl, then made up to 100ml. This mixture was filtered and analyzed by UV spectrophotometer at λ max 270.5 nm against 0.1N Hcl as blank.

Table 1. Formulation of Floating Beads of Tramadol Hcl

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Tramadol Hcl	100	100	100	100	100	100	100
HPMC K4M (%)	-	0.5	1	1.5	-	-	-
HPMC K100M (%)	-	-	-		0.5	1	1.5
Sodium Alginate (%w/v)	3	3	3	3	3	3	3
Calcium Chloride (%w/v)	5	5	5	5	5	5	5
Glacial Acetic acid (%v/v)	2	2	2	2	2	2	2
Calcium Carbonate (%w/w)	3	3	3	3	3	3	3

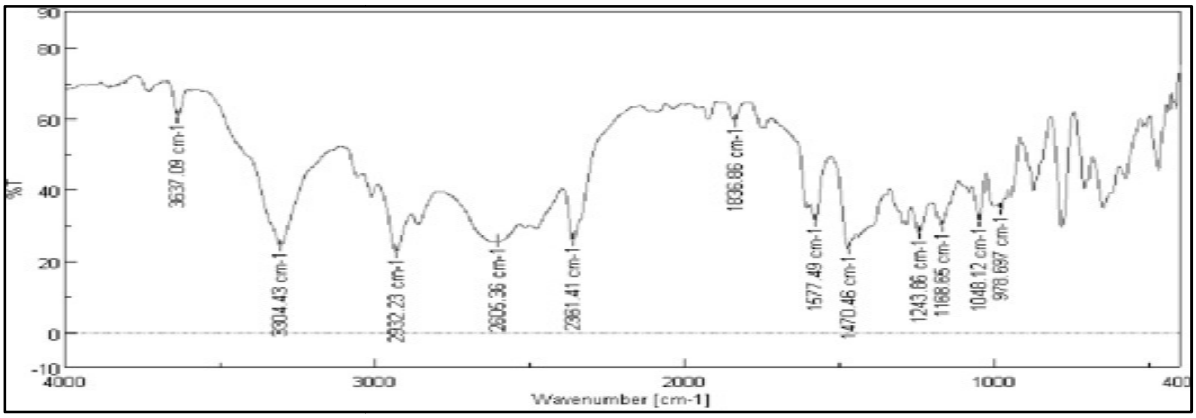

Figure 1. IR spectra of pure drug Tramadol Hcl

Formulation of Tramadol Hcl Floating Alginate Beads: Floating alginate beads of Norfloxacin were prepared by ionotropic gelation technique using different proportion of polymers as shown in Table 7.1. Sodium alginate (3%w/v) was accurately weighed and dissolved in slightly warmed distilled water. The sodium alginate solution was homogenized by stirring on magnetic stirrer for 45 min before formulation. HPMC K4M and HPMC K100M and calcium carbonate (gas forming agent) were then dispersed in alginate solution under constant stirring for uniform mixing. Drugs was accurately weighed and added or disperse in alginate solution during homogenization.

Floating lag time: In this parameter 100 mg of beads formulation were added into the 900 ml dissolution vessel containing 0.1N HCl at 37^0C. It was the time taken by beads to emerge on surface of dissolution medium is noated as floating lag time (Rathod Sayali, 2021).

Total Floating Time: In this parameter 100 mg of beads formulation was added into the 900 ml dissolution vessel containing 0.1N HCl at 37^0C. The time for which the formulation remains constantly

floating on surface of dissolution medium was referred as duration of floating (Jadhaom).

Particle Size Analysis: The particle sizes of drug loaded beads were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out as triplicate (Jadhao).

Determination of Percentage Yield: The prepared beads were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of the beads. Percentage Yield was determined using following formula (Bharat, 2014).

Percentage yield = Actual weight of product / Total weight of drug and polymer X 100

In-vitro Dissolution Studies: In-vitro dissolution studies were performed for all the formulations using USP type II apparatus. An accurately weighed floating alginate beads were taken into 900ml 0.1 N Hcl buffer (pH 1.2). The temperature was maintained at 37℃±0.5℃ and stirred at a speed of 50 rpm. At specified time intervals 5 ml of sample was withdrawn, at the same time 5 ml of fresh dissolution media was added to maintain sink condition. The collected samples were filtered if necessary and analyzed at 270.5 nm using UV spectrophotometer against 0.1 N Hcl buffer (pH 1.2) taken as blank (Tekade, 2017 and Swarnkar Kedar Prasad, 2012).

Stability study: The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40°C and 75% RH for the period of 3 months. The beads formulation was evaluated before and after 3 months for change in floating behaviours, drug content and in -vitro drug release (Swarnkar Kedar Prasad, 2012 and Menon Thulasi, 2013).

RESULTS AND DISCUSSIONS

Compatibility Studies (FT-IR): Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and Tramadol Hcl. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

Evaluation of Floating Beads

Flow Properties of Floating Beads: The results of micromeritic properties of beads were showed in table 8.2. Bulk density values for all batch beads was obtained in the range from 0.54 - 0.57 gm/cc and the tapped density values obtained in the range from 0.61 - 0.65 gm/cc. Angle of repose value for all the formulation ware found in the range between 25.51 – 20.15$^{\theta}$ showing good flow properties for all batch of alginate beads. The compressibility index and Hausner's ratio was further calculate to determine the flowability of beads. The % compressibility index value for all batch beads was found in the range of 11.29 to 13.84 indicating excellent to good flow properties for all batch. Hausner ratio for all batch powder blend was found below 1.25 showing excellent flow properties of beads of all batches. Thus from the micromeritics study it was found that all batch formulation exhibiting the good flow and were non aggregated.

Drug Loading and Drug Entrapment Efficiency (%)

The drug entrapment efficiency of floating beads was found in the range 90.12±0.52 to 95.10±0.72 %. The drug entrapment efficiency of all batch of beads formulation was found to be increased progressively with increasing concentration of coating polymers. Batch F7 showed highest drug entrapment efficiency. Drug loading for all batch of beads was found to be optimum in the range of 28.12±1.22 to 38.34±1.10 %. The results are shown in Figure 3.

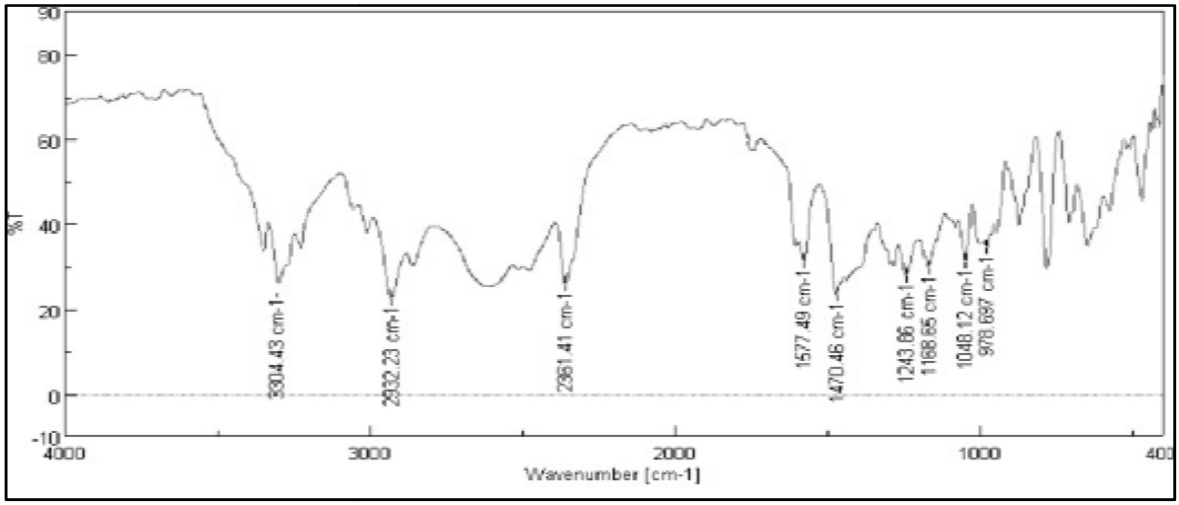

Figure 2 IR Spectra of Tramadol Hcl and HPMC

Table 2. Micromeritics properties of Floating Beads (F1 to F7)

Batch	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	26.14±0.17	0.55±0.16	0.62±0.56	11.29	1.12
F2	25.51±0.32	0.54±0.15	0.62±0.43	12.90	1.14
F3	24.16±0.17	0.56±0.33	0.64±0.31	12.50	1.14
F4	25.44±0.22	0.54±0.21	0.62±0.10	12.90	1.14
F5	21.32±0.54	0.57±0.24	0.65±0.16	12.30	1.14
F6	23.18±0.19	0.56±0.81	0.65±0.25	13.84	1.16
F7	20.15±0.15	0.54±0.35	0.61±0.16	11.47	1.12

(SD ± Mean of n=3)

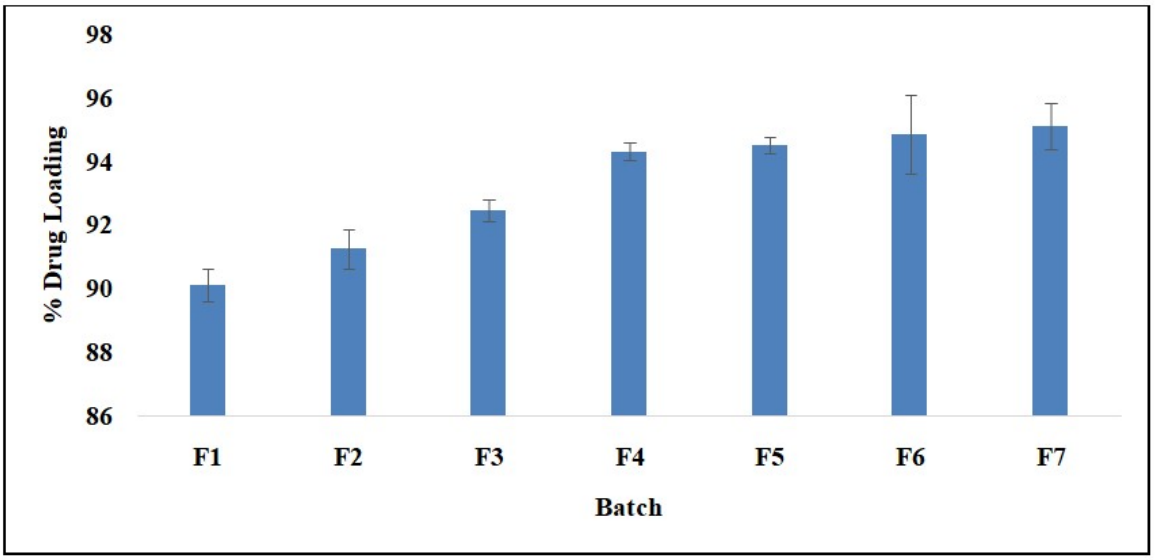

Figure 3. % Drug Entrapment Efficiency of Batch F1 to F7

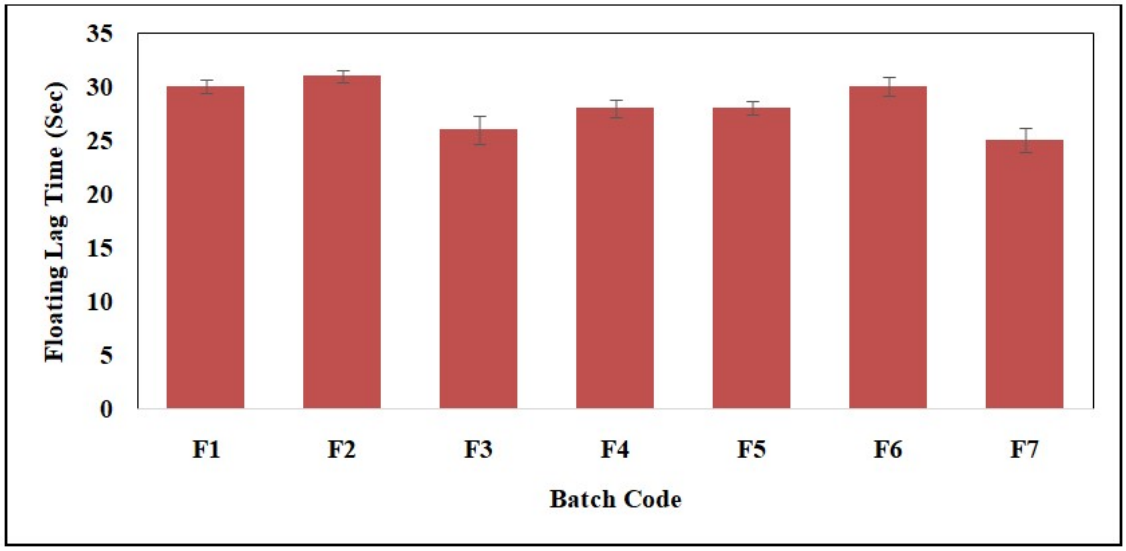

Figure 4. Floating lag time of Batch F1 to F7

Table 3: Characterizations of Floating Beads of Tramadol HCl (F1 to F7)

Batch	Drug Loading (%)	Drug Entrapment Efficiency (%)	Floating Lag Time (Sec)	Total Floating Duration (Hr)	Mean Particle Size (µm)	Percent Yield (%)
F1	36.12±0.25	90.12±0.52	30±0.60	> 12 hrs	1140±0.06	85.41
F2	38.34±1.10	91.24±0.61	31±0.55	> 12 hrs	1160±0.04	86.30
F3	32.45±0.67	92.45±0.34	26±1.30	> 12 hrs	1190±0.03	88.10
F4	30.26±0.54	94.30±0.27	28±0.80	> 12 hrs	1210±0.02	92.65
F5	28.12±1.22	94.51±0.25	28±0.58	> 12 hrs	1170±0.03	90.72
F6	30.63±1.24	94.84±0.41	30±0.85	> 12 hrs	1210±0.04	93.26
F7	34.16±0.52	95.10±0.72	25±1.16	> 12 hrs	1230±0.05	95.34

(SD ± Mean of n=3)

Floating Lag Time: Floating lag time of all the prepared beads formulations was observed by visual examination. All the prepared formulations show Floating lag time from 25 seconds to 31 second. It was observed that the gas generated was trapped in the beads within the gel formed by hydration of polymer, thus decreasing the density beads and make them buoyant. Batch F7 showed fastest floating lag time of 25 second, after entering in 0.1 N HCl and show floating for more than 12 hrs. The results are shown in figure 4.

Total Floating Duration: Floating lag time was determined after immersing 100 mg of beads into the 900 ml dissolution vessel containing 0.1N HCl at 37^0C. All prepared formulation showed effective total floating duration more than 12 hours and found to be fulfilling the need of floating drug delivery system.

The total buoyancy time of all formulation was more than 12 hrs. It was observed that as the concentration of the polymer increases the floating increase. The results are shown in Table 8.3.

Particle Size Analysis: The mean particle sizes of drug loaded floating beads were measured by an optical microscope. The average particle size of floating beads was found in size range of 1140 to 1220 µm. All batch beads are found spherical in shape. The results are showed in Table 8.3.

Determination of Percentage Yield: The yield of beads were determined by comparing the whole weight of beads ormed against the combined weight of the polymer and drug and excipients. Percentage Yield for all batches of floating beads was found to be

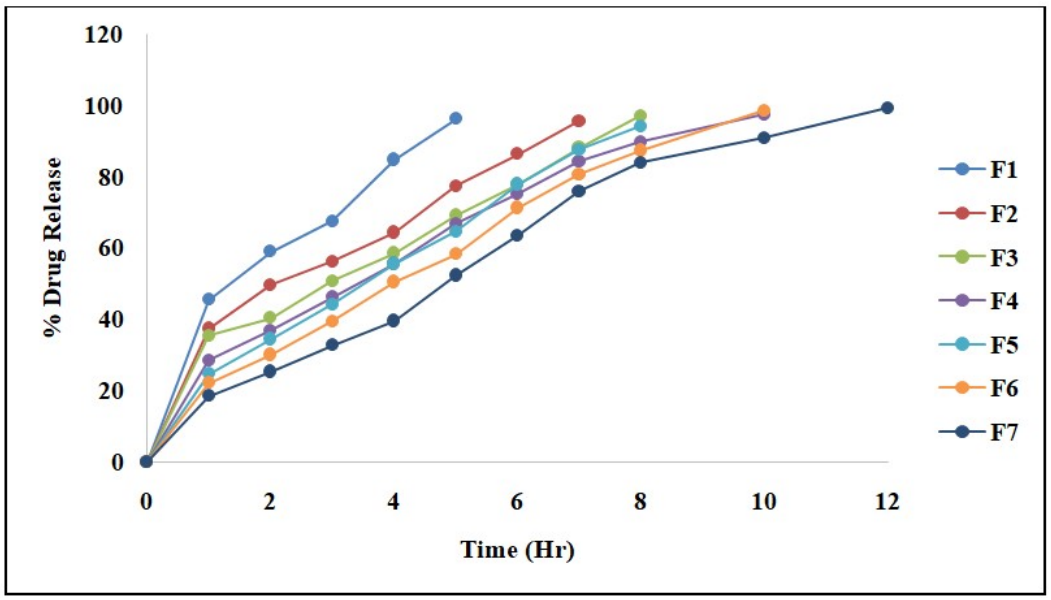

Figure 5. Comparative in vitro Dissolution Profile of formulation F1to F7

Table 4. Stability data of Optimized formulation F7

Formulation Code	Parameter	Before storage (0 month)	After storage (3 month)
F7	Floating lag Time (Sec)	25±1.16	27±1.o6
	Total Floating Time (hr)	> 12 hrs	> 12 hrs
	% Drug Release	99.12 ±1.23	98.38±1.45

85.41 to 95.34 %. The optimized batch F7 showed highest percent yield as 95%. The results are showed in Table 3.

In-Vitro Dissolution Study

In vitro drug release study of prepared floating beads of Tramadol Hcl was determined in 0.1 N Hcl as dissolution medium. Formulations F1 prepared without the addition of rate controlling polymer showed drug release of 96.36 % in 5 hrs. Batch F2, F3 and F4 prepared using HPMC K4M in concentration of 0.5%, 1% and 1.5 % showed 95.47, 96.98 and 97.14 % drug release respectively in 7, 8 and 10 hrs. All three formulation fails to sustained the drug release up to 12 hrs. Formulation F4, F5, and F6 prepared with HPMC K100M in concentration of 0.5%, 1% and 1.5 % showed 94.14%, 98.35% and 99.12 % drug release respectively in 8 hr, 10 hrs and 12 hrs. From the dissolution study it was observed that high viscosity grade polymer HPMC K100 M effectively controlled the release of drug for extended period of time as compare to less viscosity grade HPMC K4M. All batch beads formulation showed sustaining the release of drug. All batch formulation showed sustaining the drug release for extended period of time. Among the different formulations, batch F7, prepared with HPMC K100M at concentration of 1.5%, showed sustained release of drug for the periods of 12 hrs. From the results it was observed that, as the concentration of both grade of polymer increases, the drug release decreases. Data for in vitro drug release of floating beads was shown Figure 5.

Stability Study

Tramadol Hcl Floating beads formulation showing promising results in term of lowest floating lag time and sustained drug release, was selected for stability studies. According to ICH guidelines, optimized formulations F7 were stored at 40^0C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated for appearance, floating lag time, total floating time and In vitro drugrelease. At the end of 3 months no significant difference was observed in tested parameters. From the stability study it was concluded that Tramadol Hcl Floating beads formulation F7 was found to be stable. The results of stability data were shown in Table 4.

CONCLUSION

The Floating alginate beads of Tramadol Hcl can be prepared by ionotropic gelation method by using sodium alginate and HPMC K15M, HPMC K100M as rate controlling polymer and calcium bicarbonate as a gas generating agent. All the prepared beads formulation was found to be spherical and in micron size range.IR-spectroscopic studies indicate no drug-exicipent interaction in formulation. All batch formulations showed lower floating lag time and more than 12 hrs of total floating time.The in vitro dissolution profile of all the prepared floating beads formulation of Tramadol Hcl were found to extend the drug release over a period of 5 to 12 hrs. In vitro dissolution study showed that as the concentration of polymer increases the drug release decreases. Use of more viscosity grade polymer effectively controlled the release of drug over 12 hrs periods. Comparing all the formulation batch F7 was consider as the ideal formulation which exhibited (99.12%) drug release in 12 hrs and showed lower floating lag time and total floating time over more than 12 hrs. Future details investigation is required to established in vivo efficiency of Tramadol Hcl floating beads and long term stability need to be confirm the stability of floating Tramadol Hcl beads.

REFRENCES

Arora S, Ahuja A. Floating drug delivery system: a review. J AAPS PharmSciTech 2005; 6:372–90.d

Bharat W. Tekade, Umesh T. Jadhao, Pankaj H. Bari, Vijay R Patil.,*A* comprehensive review on gastro-retentive drug delivery system. Innovations in Pharmaceuticals and Pharmacotherapy. 5 (2), 94-102, 2017

Bharat W. Tekade, Vinod M. Thakare, Umesh T. Jadhao, FahimKazi., Optimization and In vitro evaluation of verapamil hydrochloride floating bilayer tablet., The Pharma Innovation Journal 2014; 3(6): 48-56.

Deshpande A, Rhodes C, Shah N, Malick A. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug DevInd Pharm 1996; 22:631-9.

Gunesh N. Dhembre, Vilas N. Deshmukh, Rajeshwar V. Kshirsagar, UmeshT.Jadhao, Sandip T. Thoke., Formulation, characterization and evaluation of Floating hollow Microspheres of Pentoxifylline, J Pharm Adv Res, 2022; 6(1)

Jadhao UT., Dhembre GN, SayyedAsad Ali., Design and Development of Gastro Retentive System Containing CefiximeTrihydrate., Int. J. Pharm. Sci. Rev. Res., 67(2), 94-100.,

Jadhao, U. T., Thakare, V. M., Chaudhari, K. P., Tekade, B. W., Chaudhari, C. S., Patil, V. R. 2013. Design and Evaluation of Famotidine Matrix Tablet Using 3^2 Factorial Designs. Research *Journal of Pharmaceutical, Biological and Chemical Sciences*. July-September RJPBCS 4, 3, 1441-1451.

Liew, K. B., Tan, Y. T. F., Peh, K. K., &Rajendran, A. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. The Scientific World Journal. 2014, 1-12. 2014

Manjanna KM, Shivakumar B and Pramodkumar TM. Diclofenac sodium Microbeads for Oral Sustained Drug Delivery, *International Journal of Pharmaceutical Technology and Research.* 2009; 1(9): 317-327.

MenonThulasi V, SajeethC.I, Formulation And Evaluation Of Sustained Release Sodium Alginate Microbeads of Carvedilol, International Journal of PharmTech Research, 2013, 5(2), 746-753.

Mohammad Abu TaherRasel and MoynulHasan. Formulation and Evaluation of Floating Alginate Beads of Diclofenac Sodium. *Dhaka University of Journal of Pharmaceutical Sciences.* 2012; 11(1): 29-35.

RathodSayali P, JadhaoUmesh T, LokhandeSneha S, PanchalPranita P., Design and Development of Multiparticulate Floating Drug Delivery System Containing Lisinopril., *SchAcad J Pharm,* Mar, 2021; 10(3): 54-59.

Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site specific delivery. *Int J Pharm.* 1996; 136:117-139.

SantanuChakraborty, Subas Chandra Dinda, Ch. NiranjanPatra, MadhusmrutiKhandai fabrication and characterization of alginate Carbopolmicroparticulate system of Aceclofenac for oral sustained drug delivery, *International Journal of Pharmaceutical Sciences Review and Research*. 2010; 4(2): 192-199.

SwarnkarKedar Prasad, TanwarMukesh, Sharma Ashok, SinghalMonit Sharma Ashish KR. Preparation and optimization of oral floating alginate gel beads of Famotidine. *International Journal of Pharmaceutical Studies and Research.* 2012; 3(2): 4-8.

SwarnkarKedar Prasad, TanwarMukesh, SharmaAshok, SinghalMonit, SharmaAshish, Preparation and Optimization of Oral Floating Alginate Gel Beads of Famotidine, *International Journal of Pharmaceutical Studies and Research,* 2012, 3(2), 4-8.

Tekade B. W, Jadhao U. T, Patilpooja,Patil V.R., Formulation and In-vitro evaluation of Capecitabine floating tablet., *The Pharma Innovation Journal* 2017; 6(8): 171-175.

Tekade B. W., Jadhao U. T., Thakare V. M., Yogita A. Chaudhari., Vaishali D. Patil, Chaudhari C. S. Design and In-vitro Evaluation of Ethyl Cellulose Based Floating Microspheres Containing Antidiabetic Drug. *Asian Journal of Biomedical and Pharmaceutical Sciences;* 3(23) 2013, 33-37.

Yadav M, Choudhary D, Shrivastava B. Formulation and Evaluation of Sustain Release Floating Beads of AntiHypertensive Drug Ramipril. *International Journal of Pharmaceutical Sciences.* 2014; 3(5): 114-131.

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