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Design and Development of Sustained Release Floating Beads of Metronidazole Using Natural Polymer

[2]Pund Yogesh P, *[1]Mundada Atishkumar S

*[1,2]Department of Pharmaceutics, SNJB's S.S.D.J. College of Pharmacy, Chandwad, Dist. Nashik, Maharashtra

Abstract

The retention of drug delivery system in the stomach for longer time is essential to improve the bioavailability and therapeutic efficacy of the drugs used for the diseases like H. Pylori infection, bacterial and protozoal infection. The objective of the present study was to prepare oil entrapped floating beads of metronidazole using low methoxy pectin obtained from seeds of *Helianthus annuus* and *Passiflora edulis flavicarpa*. The beads were prepared employing ionotropic gelation method and evaluated for various physicochemical properties like size, surface morphology, buoyancy, swelling ratio and index, percent drug content, drug entrapment efficiency and in *vitro drug* release. The average bead size was found to be between 180 ± 8.3 µm. The drug content and drug entrapment efficiency was achieved between 81 to 93%. All batches having the good swelling ability which ensured extended drug release nearly up to 12 hrs in a controlled manner. All the developed formulations exhibited complete and excellent buoyancy over a period of 12 h. It can be concluded from the results of the present investigation that low methoxy pectin obtained from *Helianthus annuus* and *Passiflora edulis flavicarpa* can be used to develop gastroretentive drug delivery system to retain and deliver drug in stomach for a prolonged period of time.

Keywords

Ionotropic gelation technique; Natural polymer; Cross linking agents; Metronidazole; Floating beads; Oil entrapped pectinate beads

Introduction

Oral controlled release drug delivery systems have been developed over few years due to their considerable therapeutic benefits such as ease of administration, patient compliance and flexibility in formulation. However, this approach has suffered with several drawbacks such as inability to retain and locate the controlled release dosage forms within the gastrointestinal tract (GIT) due to variable gastric empting and motility. The relatively brief gastric empting time in humans, which normally averages 2-3 hrs through the major absorption zone i.e., stomach and upper intestinal part, can result in incomplete drug release from dosage form leading to insufficient efficacy of the administered dose [1]. This restriction has led to the development of oral controlled dosage forms with gastroretentive properties. After oral administration, such dosage forms could lengthen the gastric residence time of dosage forms in the upper GIT and gradually release incorporated molecules in sustained release manner to obtain optimal bioavability [2]. Several gastroretentive techniques have been reported such as mucoadhesion, high density system, superporous hydrogel system, expandable drug delivery system, magnetic drug delivery system and floating drug delivery system [3]. Floating drug delivery has been extensively explored amongst all as it can be developed easily using different approaches like as Low density approach, Swelling systems, Ion exchange resins, Osmotic regulated systems, Bio/ Muco-adhesive systems. Low density approach is one of them which can be designed to provide buoyancy to the formulation onto the gastric contents [4]. Thus low density system will be retained in the stomach for several hrs allowing slower drug release at a desired rate [5].

***Corresponding author:** Atishkumar S Mundada, Department of Pharmaceutics, SNJB's S.S.D.J. College of Pharmacy, Chandwad, Dist. Nashik, Maharashtra. E-mail: atishmundada@rediffmail.com

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Over the last few years, naturally occurring polysaccharide such pectin, alginate, chitosan have received much attention in drug delivery system due to their excellent biocompatibility, biodegradability, non-toxicity and their ability to forms gel bead due to their ion binding properties [6]. Pectin with degree of methylation (DM) higher than 50%, named as high methoxy pectin (HMP), have ability to form a gel after heating in sugar solutions at concentration higher than 55%. Pectin with DM lesser than 50%, named as low methoxy pectin (LMP), has ability to form gel in presence of divalent cations like calcium ions [7,8].

Pectin has a very complex structure which depends on both- its source and the extraction process. Hence, in the present investigation attempt has been made to evaluate the gel beads forming ability of LMP obtained from two unused natural sources viz., *Helianthus annuus* and *Passiflora edulis flavicarpa*. Pectin is capable of reducing interfacial tension between an oil phase and a water phase and can be effective in the preparation of emulsion [9]. Thus floating beads can be obtained by incorporating vegetable oil during the gelation of LMP in the solution of the divalent cations. Metronidazole (MZ), a low molecular weight, water soluble drug used in the treatment of *H pylori* infections [10] was selected as a model drug for the present work.

Materials and Methods

Materials

LMP with %DE of 31 and 28 of *Helianthus annuus* and *Passiflora edulis flavicarpa* respectively were procured from Krishna Pectins (Jalgaon) (Ex Gratis). Metronidazole was gifted by Abott laboratories, Mumbai and Vegetable oil was purchased from local market. All other chemicals used were of analytical grade.

Methods

Preparation of Metronidazole Loaded Calcium Pectinate Beadss

Floating beads were prepared using inotropic gelation method as described by Sriamornsak et al. (2005). In this method, Metronidazole was dispersed in aqueous pectin solution under constant stirring for uniform distribution. In that dispersion vegetable oil obtained from seeds of *Helianthus annuus* was added dropwise. The resultant emulsion was then extruded dropwise through a 23G needle in to 5 %w/v calcium chloride solution under continuous stirring at room temperature. The beads so obtained were allowed to remain in calcium chloride solution for 30 minutes to increase the strength of beads (Ishak et al. 2007). The beads were then filtered and washed with distilled water and dried overnight at 40 ^{0}C in hot air oven. Total eight batches were prepared using *Helianthus annuus* pectin and eight batches using *Passiflora edulis flavicarpa* pectin (Table1 and 2).

Physicochemical Evaluation of the Formulations

1) Bead Sizeand Shape [11]

Beads size and shape is important factor to be determined as spherical beads will exhibit good flow property. Beads size and shape was determined using optical microscopic method. Spherical beads are generally formed as emulsion containing drug, pectin and oil is dropped into calcium chloride solution through the syringe. In this method the randomly selected twenty beads from each formulation were taken on the glass slide and observed on Motic microscope (DMB-1 Motic, India) using 4Xeyepiece.

Table 1: Formulation of Metronidazole Floating Beads with *Helianthus annuus* Pectins

Batch code	Drug concentration. (gm.)	Polymer concentration(%w/v)	Oil concentration. (%v/v)	Water	Calcium chloride solution (ml)
F1			10	(ml)	
F2	1.5	3 %	20	50	
F3			30		
F4			40		
F5			10		150
F6	1.5	4 %	20	50	
F7			30		
F8			40		

Table 2: Formulation of Metronidazole Floating Beads with *Passiflora edulis flavicarpa* pectin

Batch code	Drug concentration. (gm.)	Polymer concentration(%w/v)	Oil concentration. (%v/v)	Water	Calcium chloride solution (ml)
F9			10	(ml)	
F10	1.5	3 %	20	50	
F11			30		
F12			40		
F13			10		150
F14	1.5	4 %	20	50	
F15			30		
F16			40		

2) Buoyancy / floating study

The floating study of all batches was carried out using USP dissolution apparatus type II. Fifty beads were placed in the dissolution vessel containing 500ml of 0.1 N HCl (simulated gastric fluid-pH 1.2) maintained at 37 ± 0.5^{0}C for 10 hrs at 50 rpm. The floating ability of beads was measured by visual observation. The time taken by beads to float on the surface of dissolution medium is noted down as floating lag time and duration of floating were recorded [2].

% floating for the developed beads was calculated according to following formula

% floating = (Number of floating beads /Total number of the beads) ×100

3) Swelling Study [12]

Swelling properties of beads was studied randomly selecting around 10 beads. Beads of known mass were placed in the wire basket of USP type I dissolution apparatus containing 900 ml 0.1 N HCL at 37± 0.5^{0}C and stirred at 50 rpm. The beads were periodically removed at pre-determined time intervals during the study period of 2 hrs, drained on tissue paper for complete removal of surface water and weighed. Swelling ratio and swelling index calculated using following formula.

Swelling ratio =Weight of wet beads / Weights of dried beads.

Swelling index = (wet weight – dried weight) /dried wet ×100

4) Drug Content and Entrapment Efficiency [13]

Accurately weighed 100 mg of formulated beads from each batch were taken and crushed. Crushed material was dissolved in 100 ml water in 100 ml volumetric flask and volume was made up to 100 ml. The solution was sonicated for 2 hrs using ultrasonicator (D compact, Labhosp, India) to ensure complete release of the drug into the water. The solution was then filtered and the drug content in the filtrate was determined spectrophotometrically using a UV-visible Spectrophotometer (V630 Jasco, Japan) at 320 nm. The percent drug entrapment efficiency of bead was calculated using following formula.

%DEE= (Actual drug content in beads/ Theoretical drug content in beads) × 100

5) In Vitro Dissolution Studies [14]

The drug release profile from the calcium pectinate beads was carried out using the USP type II dissolution test apparatus using 900 ml 0.1 N HCL maintained at 37 ± 0.5^{0}C and stirred at 50 rpm. Sample were collected periodically and replaced with fresh dissolution medium to maintain sink condition. Drug release was determined using UV spectrophotometer at 277 nm. Data analysis was done using PCP Disso software (Version 2, developed by BVDU's College of Pharmacy Poona).

Optimization

The formulation meeting the set objective was selected after screening the results of all evaluation parameters for the developed formulations [15]. The surface morphology of the optimized drug loaded calcium pectinate beads was carried out using scanning electron microscope (SEM). The cross sections of randomly selected beads from optimized batch were coated with gold to a thickness of about 30 nm in vacuum evaporator. Morphological examination of the surface, external and internal structure of the dried beads was then carried out. The SEM images for the optimized formulation have been depicted in Figure 1.

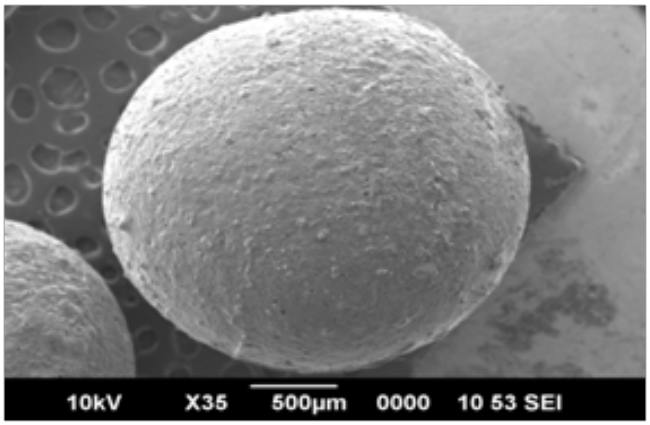


Image A

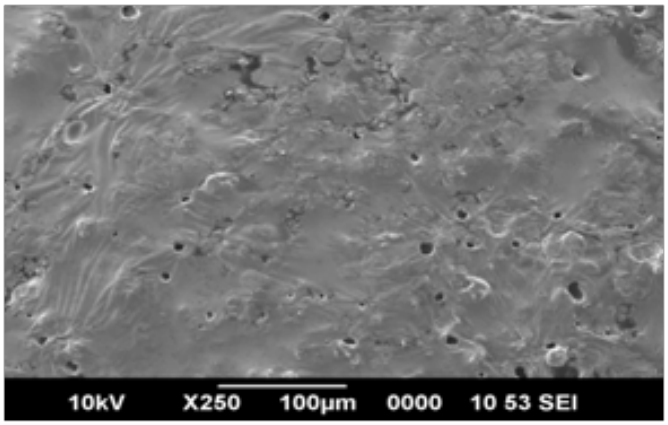
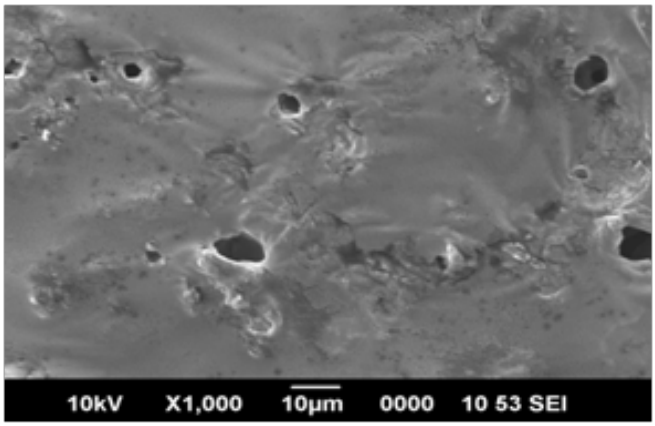


Image B



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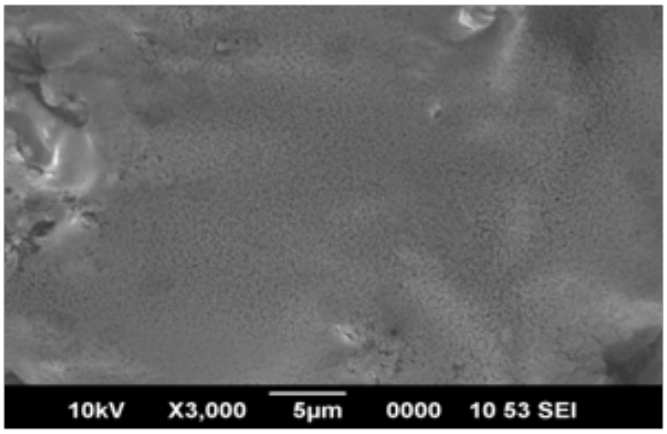
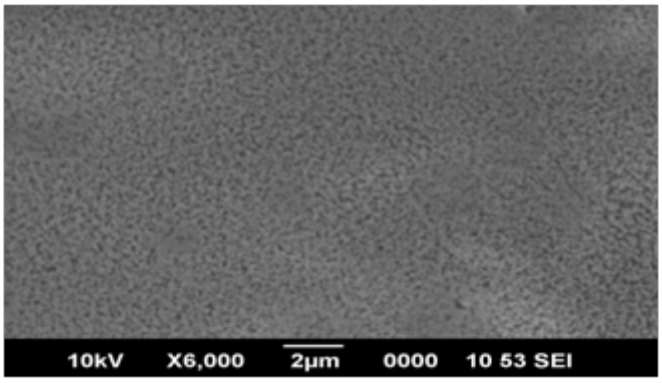


Image D



Images E

Figure 1: Scanning Electron Microscopy (SEM) images

Stability Study for Optimized Formulation

The stability study for the optimized formulation was carried out as per ICH guidelines by keeping formulated beads at, 40 ± 2 0C/ 75 %RH for the period of three months. The evaluation was performed for physico-chemical parameter like drug contain, floating time and in Vitro drug release at day 0, 30, 60 and 90.

Result and Discussion

There has been considerable research over the last decade on the possibility of controlled and site-specific delivery to the GIT by controlling the GI transit of orally administered dosage forms. Numerous polysaccharides have been tried as an excipient into pharmaceuticals due to their biocompatible, biodegradable, inexpensive and non-toxic nature. These materials

undergoes simple ionotropic gelation to form multiparticulate system which can provide various desired drug release patterns. In low-density approach, the spherical beads apparently having lower density than that of gastric fluid can be used as a carrier for controlling the release of a drug in the upper part of the GIT.

Drug - Excipients compatibility study

Physical mixtures of the drug and LMP that were placed at 55 ^{0}C in dry and 75 %RH environment were observed for caking, discoloration, liquefaction and other physical changes after 15 days. It was observed that there was no caking, discoloration and liquefaction. The presence of any physical incompatibility would have led to caking, discoloration and liquefaction and in absence of that it can be concluded that the drug and polymer were compatible with each other.

The physicochemical interaction between drug and polymer was confirmed by using FTIR spectroscopy. IR Spectra of physical mixture of the drug and LMP before keeping it for compatibility study were recorded. Spectra of the physical mixture showed all characteristic peaks of the drug as well as the LMP intact. Hence it can be said that there is no interaction between drug and LMP. DSC is one of the tools to investigate the possible physical and chemical interaction between drug and polymer.DSC spectra of metronidazole shows sharp endothermic peak at 160.10 ^{0}C that corresponds to the melting point of the drug which confirms the purity of metronidazole. DSC Spectra of physical mixture of the drug and LMP before compatibility study revealed thermal transition at 253.00 ^{0}C which corresponds to the melting point of the LMP and sharp endothermic peak at 158.20 ^{0}C corresponding to the melting point of the drug. The values were congruent with the melting point of the drug and polymer confirming the compatibility between drug and the polymer.

Beads Size and Shape

Size and shape was determined by using optical microscopic method. The oil concentration and polymer concentration is an important parameter which affected the size and shape of the beads. When the concentration of the oil was increased in the formulation the size of the beads was also found to be increased. Formulation F1 containing 10 %v/v oil exhibited average beads size around 1.78 ± 0.06 mm and batch F4 containing 40 %v/v oil having beads size of 2.22 ± 0.12 mm.

Polymer concentration also affected the size and shape of the beads. It was observed that as the LMP concentration goes below 3%w/v then beads became elongated whereas for more than 4 %w/v concentration, beads shape was changed from spherical to disc like and irregular. Beads of formulation F5 to F8 (4 %w/v polymer) were spherical and size was larger than formulation F1 to F4 (3 %w/v polymer).

Buoyancy Behavior

The floating behavior of all the beads was studied using USP dissolution apparatus type II (Electrolab TDT 08L). The oil containing calcium pectinate beads floats immediately and remained buoyant for more than 12 hrs. However the amount of oil used in the formulation has a significant impact on the buoyancy of the formulations as concentration of oil below 10%w/w did not exhibit any floating. The different floating lag time was observed for formulation F1-F8 due to varying oil concentration. Floating lag time was found to decrease with increasing the oil concentration in formulation. Batches F1 to F4 having varying oil concentration exhibited different floating lag time. Batch F1&F9 (10% oil) has a floating lag time 12-13 minutes, batch F2& F10 (20% oil) has floating lag time 5-6 minutes, batch F3& F11 (30% oil) has floating lag time 2-3 minutes whereas formulation F4& F12 containing (40% oil) has floating time 10-20 second. The floating behavior of the *Helianthus annuus* pectin beads was similar to that of *Passiflora edulis flavicarpa* pectin beads. Hence it can be said that the type of pectin and degree of esterification did not affect the buoyancy behavior of beads.

Swelling Study

Swelling properties were studied by measuring the % water uptake after 2 hrs in 0.1 N HCL (1.2 pH) maintained at physiological temperature of 37 0C. The maximum % swelling was observed within 20-40 min followed by sudden reduction in weight in the next 20- 30 min. This effect might be due to the solubility of drug and polymer that could have influenced the swelling behavior of the beads. Batches having low concentration of polymer (less than3%) exhibited faster erosion due to weak gel strength. Batches prepared using high polymer concentration (more than 4%) showed maximum swelling ratio and swelling index and no erosion till 120 min.

Cross linking agent concentration also had significant impact on the swelling as it was observed that high amount of cross linker exhibited less erosion of beads. Curing time is also one of the major factors affecting swelling ratio and swelling index. Curing time less than 15 min showed faster erosion of beads with minimum swelling ratio and swelling index due to incomplete cross-linking of pectin in the formulation. The source of LMP did not exhibit any influence on swelling behavior as beads obtained from pectin of both seeds showed similar swelling.

Drug Content and Drug Entrapment Efficiency

Drug content and drug entrapment efficiency of formulated oil-entrapped calcium pectinate beads containing metronidazole ranged from 75.94 ± 1.16 to 92.06 ± 2.08 and 75.90 ± 1.09 to 91.98 ± 2.02 respectively. It was found that drug content and entrapment efficiency of oil entrapped calcium pectinate beads was increased with increase in oil concentration.

The phenomenon of increasing drug content and entrapment efficiency may be due to either partitioning of some amount of drug in the oil phase or formation of oil barrier that could have obstructed the passage of molecule to external media during preparation.

The concentration of the polymer also had influence on the drug content and entrapment efficiency. The increased in polymer concentration resulted in the increase in the drug content and entrapment efficiency. This could have happened due to increased viscosity of the emulsion which might have prevented drug leaching into the cross linking solution. This means increased in polymer ratio in the formulation has helped in higher drug entrapment. Results of this study have been depicted in table 3 and 4.Curing time is also one of factors that affected the drug content and drug entrapment efficiency. With increasing the cross-linking (curing) time increase in the % drug entrapment efficiency of calcium pectinate beads was observed.

Table 3: Characterization of floating beads of metronidazole from batches F1 to F8

Batch Code	Particle Size of Beads (mm)	Floating Lag Time (min.)	Floating Time (hrs.)	Welling Study		Drug Content (%)	Drug Entrapment Efficiency (%)
				S. Ratio	S. Index		
F01	1.78 ± 0.06	8 ±2min	>12	1.73± 0.09	73.17± 1.04	75.94± 1.16	75.90± 1.09
F02	1.92 ± 0.08	3 ± 1min	>12	1.73± 0.10	73.91± 1.06	83.53± 1.52	83.52± 1.45
F03	2.12 ± 0.11	1 ±0.5min	>12	2.04± 0.12	95.83± 1.26	89.60± 1.89	89.55± 1.81
F04	2.22 ± 0.12	0.5 ±0.5 min	>12	1.85± 0.08	85.83± 0.96	90.38± 1.55	89.32± 1.51
F05	1.76 ± 0.07	8.5 ±3min	>12	1.77± 0.12	77.27± 1.27	87.47± 1.59	87.40± 1.56
F06	1.89 ± 0.09	3 ± 1min	>12	1.72± 0.10	72.91± 1.09	86.58± 1.48	86.51± 1.44
F07	2.09 ± 0.13	1 ± 0.5min	>12	1.83± 0.11	83.33± 1.22	92.05± 1.86	92.21± 1.84
F08	2.21 ± 0.12	0.5 ± 0.5 min	>12	1.76± 0.10	76.26± 1.11	89.30± 1.65	90.01± 1.61

Table 4: Characterization of floating beads of metronidazole from batches F9 to F16

Batch Code	Particle Size of Beads (mm)	Floating Lag Time (min.)	Floating Time (hrs.)	Welling Study		Drug Content (%)	Drug Entrapment Efficiency (%)
				S. Ratio	S. Index		
F09	1.84 ± 0.07	7 ±2.5 min	>12	1.73± 0.14	73.80±1.32	84.03± 1.54	83.90± 1.50
F10	1.93 ± 0.09	4± 1.5 min	>12	1.79± 0.12	79.59± 1.29	84.27± 1.78	84.21± 1.71
F11	2.12 ± 0.12	1 ±0.5min	>12	1.92± 0.12	92.59± 1.28	91.59± 2.01	91.34± 1.98
F12	2.21 ± 0.13	0.5 ± 0.5min	>12	1.71± 0.13	77.04± 1.39	88.90± 1.38	88.80± 1.29
F13	1.80 ± 0.06	9 ± 3 min	>12	1.69± 0.11	69.23± 1.12	88.91± 1.45	88.83± 1.38
F14	1.91 ± 0.08	5 ±1.5min	>12	1.78± 0.12	78.72± 1.21	89.04± 1.51	89.00± 1.47
F15	2.10 ± 0.11	1 ± 0.5min	>12	1.82± 0.10	82.05± 1. 12	92.06± 2.08	91.98± 2.02
F16	2.19 ± 0.12	0.5 ± 0.5 min	>12	1.76 ± 0.12	76.27 ±1.24s	91.82 ±1.96	91.97 ± 1.69

In Vitro Drug Release

In vitro drug release study to examine the suitability of the calcium pectinate beads as a gastroretentive drug delivery system was performed in 0.1 N HCL (simulated gastric fluid pH1.2) using USP type II dissolution apparatus. Formulations prepared from two different polymers (LMP) with varying concentration showed the different release patterns. Formulations F1 to F4 having polymer concentration 3 %w/v exhibited the release up to 10 hrs. Formulations F5 to F8 having polymer concentration 4 %w/v could prolong the release upto12 hrs. Thus it can be said that increase in polymer concentration resulted in control over the drug release. This release profile could have been due to the higher concentration of pectin in beads resulted in more hydrophilic property to beads that could binds better with aqueous medium to form viscous gel structure and which may block pore on the surface of beads.

The significant increase in drug release from the pectin beads containing metronidazole was observed with increasing oil to water ratio. The mechanism involved into slow and sustained drug release from pectinate floating beads containing high amount of entrapped oil must be the saturation of the drug. Actually, drug transportation from beads to the dissolution medium may undergo two steps. 1) The drug may diffuse out of oil pockets into bead-matrix. 2) It may diffuse out of the matrix into the dissolution medium. However in beads with high concentration of oil most of the drug remained saturated and dispersed in the oil pockets of the beads to from a drug-oil dispersed matrix. The beads obtained from *Helianthus annuus* pectin exhibited better control over the drug release than the LMP obtained from *Passiflora edulis flavicarpa* although not very significant.

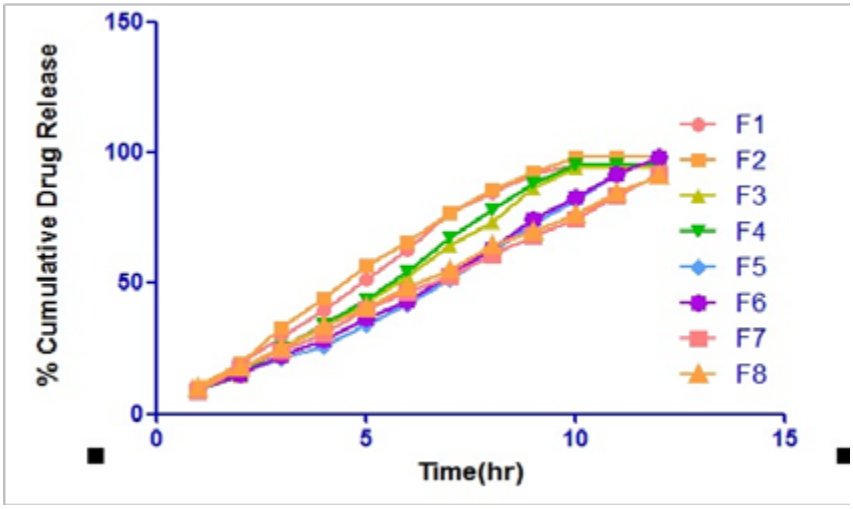


Figure 2: Drug release profile for batch F1 to F8 (*Helianthus annuus* pectin)

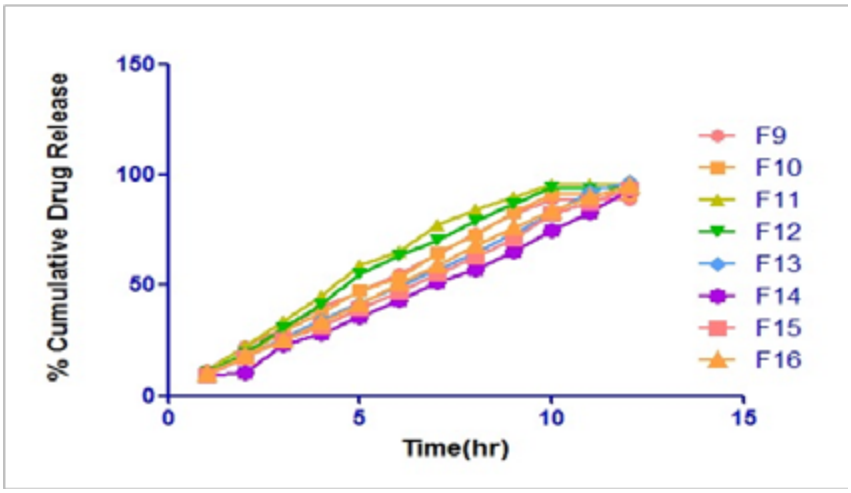


Figure 3: Drug release profile for batch F9 to F10 (*Passiflora edulis flavicarpa pectin*)

Selection and Morphological Examination of the Optimized Formulation

Formulation F7 prepared from *Helianthus annuus* pectin was selected as optimized formulation based on the results of the physicochemical evaluation. Morphological examination of the optimized formulation beads was carried out using scanning electron microscope. Upon air drying, the optimized calcium pectinate beads became small, dense and flattened with wrinkled circumferences due to water diffusing gradually from the sphere under drying process. (Sriamornsak et al. 2004). The oil entrapped calcium pectinate beads were more spherical without hollowness in the middle. The oil entrapped calcium pectinate beads were like a sponge. The pores on the surface of beads represented the oil droplets and their size influenced by the concentration of the oil. Figure 1shows the internal and external morphology of oil entrapped calcium pectinate beads containing 30% sunflower oil. The surface of oil entrapped calcium pectinate beads showed small pores of around 10-40 µm containing oil droplets dispersed all over the surface. The pore size was observed to be small due to the homogenous dispersion of the small fraction of oil phase in pectin solution.

Stability Study

The accelerated stability study was conducted onto the optimized formulation for three month. The visual observation showed that there was no change in physico-chemical properties of formulation as well as no change in the floating time at the end of three months. The results of stability study are depicted in table no.5. Value of drug content shows no significant changes during time of stability study thus it can be suggested that said formulation was stable. In vitro drug release also does not have any significant changes in drug release pattern at the day 0, 30, 60 and 90 days and follows peppas model for drug release.

Table 5: Evaluation of stability study

Time (months)	Floating time(hr.)	Drug content(%)	In vitro drug release study at 12(hr.)
0	>12	92.20	92.36 ± 0.56
1	>12	91.81	91.96 ± 0.65
2	>12	91.77	92.01 ± 0.95
3	>12	91.68	91.55 ± 0.84

Conclusion

The use of naturally occurring polysaccharides functioning as biopolymers has increased in the area of novel sustained release formulation (Badve et al., 2007). These biopolymers are having a unique nature of forming hydrogel beads when they are cross linked with suitable polyvalent cations. These polyanions gained more importance in the development of biocompatible novel sustained and targeted drug delivery product as they are capable to encapsulate large number of micro and macro therapeutic molecules in their hydrogel meshwork structure.

We made an attempt to evaluate LMP obtained from two different sources-seeds of *Helianthus annuus* and seeds of *Passiflora edulis flavicarpa*. The floating beads formulation containing metronidazole using LMP for sustained gastroretentive delivery was successfully developed. The developed pectinate beads had excellent drug entrapment efficiency, appropriate floating ability in gastric fluid with a minimum floating lag-time, suitable controlled release pattern. There was no significant variation in the properties and behavior of beads prepared using LMP from two different sources. Optimized formulation showed good stability over 90 days with respect to drug content, floating lag time and drug release.

Acknowledgment

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