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RESEARCH ARTICLE

Prochlorperazine Maleate Loaded Sustained Release Floating Microspheres Prepared By Ionotropic Gelation Technique: Morphology and Release Characteristics

Pallavi M. Pawashe[1]*, Shitalkumar S. Patil[2], Nilofar S. Naikwade[3]

[1]Research Scholar, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Dist-Kolhapur, MS, India

[2]Principal and Head Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Dist-Kolhapur, MS, India

[3]HOD, Department of Pharmacology, Appasaheb Birnale College of Pharmacy, Sangli, MS, India

*Corresponding Author E-mail: **pallaviapatil2007@gmail.com**

ABSTRACT:

Once a daily oral sustained release microsphere based floating formulation of Prochlorperazine Maleate (PCZM) was prepared with intent of reduction in frequency of administration which will increase the bioavailability and further to enhance the patient compliance thus avoiding treatment failure. For treatment of vommiting and nausea, PCZM is a drug of choice. PCZM, phenothiazine antipsychotic, has low biological half life and required multiple dosing frequency (3-4 times daily). Ionotropic gelation technique was used to prepare a sustained release floating microsphere using calcium chloride as complexing agent, sodium alginate release retarding agent, and sodium bicarbonate as gas generation mediator. Different formulation batches F1 to F7 were prepared &evaluated for percent yield, entrapment efficiency, micrometric properties, floating lag time, total floating time and *In-vitro* dissolution study. Optimized formulation batch F6was subjected for physical characterization and morphological study like DSC, PXRD, FTIR and SEM respectively. Results of *In-vitro* dissolution study of optimized formulation batch F6 showed sustained release property with floating characteristic of PCZM microspheres for more than 24 hrs. Release study of Optimized formulation F6 followed Korsmeyer's Peppas model release kinetics with non-fickian diffusion. SEM study revealed spherical shape of the microspheres with rough and porous surface.

KEYWORDS: Floating microsphere, Prochlorperazine Maleate, Ionotropic gelation, floating time, bioavailability

1. INTRODUCTION:

Oral drug delivery is the most preffered way for the drug aministration however suffers with drawbacks like short gastrointestinal transit time, rapid gastric emptying time, thereby reduce the bioavailability. Oral drug delivery dosage forms developed with the intention to increase the residence time of the dosage forms in the upper gastrointestinal tract (GI) or the stomach until the drug is absorbed completely and thus enhancing the bioavailability[1,2].

Floating drug delivery system (FDDS) has the benefit of specific density lower than gastric fluid, stay buoyant in stomach content and prolonged GI transit time thus improvement in biaoavailability. FDDS has benefit of local and sustained drug delivery to the stomach and proximal small intestine thus releasing the drug in the locality of the absorption window[3-5].

Sodium alginate, natural biopolymer composed of mannuronic acid & glucuronic acid in varying proportions & arrangements. Polymer mainly bind & cross linked with divalent or polyvalent cations like Ca^{2+} & Zn^{2+}, Ca^{2+} is preferred as they mainly bind to glucuronic acid. Sodium alginate acts as sustained release agent by formation of gel containing calcium alginate complex, mainly act on gastric mucosa and

enhance the bioavailability. Moreover bioadhesive property of sodium alginate used for targeting stomach[6].

In FDDS, ionotropic gelation method is used widely for preparation of microsphere droplets by dropwise addition of the sodium alginate-drug solution into a calcium chloride solution. Alginate gelling occurs when the calcium like divalent cations fit into the cavities of G-blocks of glucuronic acid residues giving rise to gel structures like three dimensional network. This interaction proposed as an ‘‘eggbox’’ model[7].

Prochlorperazine Maleate (PCZM) a phenothiazine derivative; is dopamine receptor blocker antipsychotic drug. Moreover PCZM is widely used in avoidance and treating of nausea and vomiting induced by chemotherapy, surgery, radiotherapy and migraine. The chemical structure of PCZM depicted in fig.1.

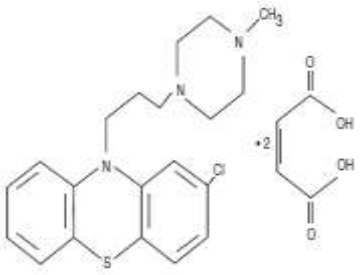


Fig. 1. Chemical structure of PCZM

PCZM has bioavailability of 12.5%. It has shorter half life of 5 to 8 hrs owing to multiple dosing of drug. PCZM has good solubility in acidic pH with absorption in stomach. Therefore FDDS formulation of PCZM can be absorbed and retained in stomach for longer period of time to maintain therapeutic level[8-10].

However previously reported floating tablets of PCZM as a single unit floating systems has certain drawbacks like variability in gastric retention time owing to their ‘all-or-none’ emptying process. This may result in local irritation, high variability and decreased bioavailability. In contrast, microparticulate multiple-unit dosage systems like microsphers have the advantages of an adjustable release, reduced variability, increased bioavailability, decreased risk of local irritation and possibility of dose dumping[11-13].

The aim of present study was to prepare sustained release prochlorperazine maleate (PCZM) floating microspheres using sodium alginate polymer and sodium bicarbonateas gas forming agent by ionotrophic gelation method to enhance bioavailability and to improve patient compliance.

2. MATERIALS AND METHODS:

2.1 Chemicals:

Prochlorperazine Maleate (PCZM) was obtained from Abbott healthcare Pvt. Ltd., Mumbai, India. Sodium alginate (low viscosity) was purchased form Unique biological and chemicals, Kolhapur, India. Calcium chloride and Sodium bicarbonate were obtained from Kronox lab sciences Pvt Ltd, Mumbai. All the other reagents and chemicals used in the research work were of analytical grade.

2.2 Preparation of floating microspheres:

Floating microspheres were prepared with ionotrophic gelation method[14]. To the homogenous sodium alginate solution, PCZM and sodium bicarbonate was added. A calcium chloride solution was prepared and placed on magnetic stirrer. The microspheres were formed by dropping 10 ml homogenous alginate solution using a 21 G syringe needle into calcium chloride solution with falling distance 10 cm. The prepared floating microspheres were allowed to stir for 30 minutes in the solution at room temperature to be cured. Finally microspheres were filtered, collected and oven-dried at 50^0C.

Table 1. enlisted the list of different formulations batches prepared by using different concentrations of the sodium alginate, sodium bicarbonate & calcium chloride. Total seven formulations batches were prepared F1 to F7 and evaluated for percent yield, entrapment efficiency, floating lag time and total floating time.

Table 1. Formulation design of PCZM floating microspheres

Formulations	PCZM (mg)	Sodium Alginate (%)	Sodium Bicarbonate (mg)	Calcium Chloride (%)
F1	200	3	100	8
F2	200	4	100	8
F3	200	5	100	8
F4	200	4	200	8
F5	200	4	400	8
F6	200	4	100	10
F7	200	4	100	12

3 CHARACTERIZATION OF MICROSPHERES

3.1 Percent yield:

The percent yield of beads was calculated according to following formula:

$$\% \text{ yield} = \left\{\frac{\text{mass of beads}}{\text{mass of drug} + \text{mass of polymer)}}\right\} \times 100$$

3.2 Entrapment efficiency:

Accurately weighed amount of floating microspheres were crushed & transferred to volumetric flask containing methanol and volume was made using methanol. The solution was filtered & absorbance was measured by UV spectrophotometer (Shimadzu UV 1700) at 254 nm. Entrapment efficiency was estimated using following formula:

$$\% \text{ Entrapment efficiency} = \left\{\frac{\text{Amount of drug actually present}}{\text{Theoretical drug content}}\right\} \times 100$$

3.3 Evaluation of micromeritic properties:

Microspheres were characterized for determination of bulk density & tapped density. On the basis of density calculation, Hausner's ratio and Compressibility Index was determined. Angle of repose measurements were determined for assessment of flow property of microspheres.

3.4 Floating lag time & total floating time:

Floating microspheres were placed in 500 ml 0.1N HCl (pH 1.2) maintained at 37^0C and examined for duration of time till they float which is total floating time. Floating lag time was evaluated by measuring time between introduction of microspheres into the dissolution medium & its uprise to one third of vessel.

3.5 Morphological characterization of microspheres:

Morphological evaluation of the optimized formulation F6 was carried out by JSM-6400 scanning electron microscope (SEM) (JEOL, Tokyo, Japan). The samples were fixed on aluminum stubs with conductive double sided adhesive tape and coated with the gold by sputter coater at 50mA for 50s (JEC 550 Twin Coater).

3.6 Fourier transform infra-red spectroscopy (FTIR):

FTIR spectra of PCZM, sodium alginate, physical mixture & optimized formulation F6 were recorded with anFTIR spectrometer (Agilent technologies Cary 630) to evaluate drug-polymer interactions. The sample was analyzed in the region of 400-4000cm^{-1}.

3.7 Differential scanning calorimetry (DSC):

Thermal properties of PCZM, sodium alginate, physical mixture and optimized formulation F6 were analyzed by DSC (SDT Q600 V20.9 Build 20) calibrated with indium and zinc. Exactly weighed quantity of sample was placed in aluminum pan and nitrogen was used as atmosphere with flow rate 10 ml/min and scanning rate at 10^0C/min for the range of 0-300^0C.

3.8 Powder X-ray diffraction study (PXRD):

XRD pattern of PCZM, sodium alginate, physical mixture and optimized formulation F6 were determined by Philips Analytical X-RD (PW 1729, Philips, Netherland) with copper target. The measurements were performed at 40kV voltage, 30mA current. The scanning angle ranged from 5 to $60^0$of 2θ, steps were 0.02^0 and counting rate was 0.4s/step.

3.9 *In-vitro* dissolution study:

In-vitro dissolution study was carried out on an equivalent of 10 mg of the PCZM using dissolution test apparatus USP type II (Lab India 2000, Mumbai) at temperature of 37±0.5^{O}C, stirring speed of 50 rpm employing 900mL of 0.1N hydrochloric acid as the dissolution medium. Aliquots 5 ml were withdrawn at predetermined time intervals 1,2,3,4,5,6,8,12,16,20 and 24 hrs and the volume withdrawn was immediately replaced with fresh dissolution medium to maintain a proper sink condition. The samples withdrawn and concentration of PCZM were determined at 254 nm using UV spectrophotometer (Shimadzu UV 1700).

3.10 Release kinetics:

The release rate kinetics & mechanism of drug release were studied by fitting the *In-vitro*dissolution data with different kinetic models (Zero order, First order, Higuchi matrix and Korsmeyer'sPeppas model).

4 RESULTS AND DISCUSSION:

4.1 Percent yield:

Percent yield of prepared formulation batches were depicted in table 2. All the prepared formulations F1 to F7 showed percent yield in the range 66.21% to 93.07%. with increment in sodium alginate concentration F1 to F3, the percent yield was increased from 71.65% to 83.46%. Increasing the concentration of sodium bicarbonate (F2, F4 and F5) showed low percent yield, as at high dense structure can retain more PCZM drug effectively. The effect of increasing calcium chloride concentration in (F2, F6 and F7) appear on the degree of cross-linking that was increased, and so the percent yield increased.[15]

Table 2. Percent (%) yield and entrapment efficiency for formulation batches

Formulation code	Percent (%) yield	Entrapment efficiency(%)
F1	71.65±0.95	87.36±1.23
F2	76.43±0.96	91.12±1.037
F3	83.46±1.04	94.02±1.64
F4	69.28±2.49	79.59±1.27
F5	66.21±1.34	74.38±0.70
F6	89.74±0.68	88.47±0.91
F7	93.07±1.18	76.48±0.67

mean ± SD n=3

4.2 Entrapment efficiency:

All the prepared formulation batches F1 to F7 mentioned in Table 2 showed entrapment efficiency in between 74.38% to 94.02%. Increased entrapment efficiency observed with high level of sodium alginate (F1 to F3). This may be attributed to increasing concentration of sodium alginate, more calcium binding sites available on polymeric chain causing more cross linking[16]. Entrapment efficiency (F2, F4 and F5) decreased with increased concentration of Sodium bicarbonate. This may be due to at high concentration of sodium bicarbonate, there could be increased pores on surface of microspheres. Decreased entrapment efficiency (F2, F6 and F7) observed with high

concentration calcium chloride. This may be due to at high concentration of calcium chloride, gelling between the sodium alginate and calcium chloride occurs instantaneously which results in squeezing out of aquous phase from gel[6].

4.3 Micromeritic studies:

Micromeritic properties were determined for formulation batches (F1-F7). Results showed angle of repose in acceptable limit, compressibility index below 15, Hausner's ratio below 1.25. The values specified in Table 3indicate that all the formulations showed good flow properties and compressibility may due to uniform and spherical shape of the microspheres.

Table 3. Micromeritic studies for formulations batches

Formulation code	Angle of repose (^{0})	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Compressibility Index
F1	32.89 ± 0.56	0.408±0.005	0.466±0.002	1.14±0.014	12.56±1.283
F2	31.88 ± 0.34	0.432±0.007	0.487±0.008	1.12±0.012	11.28±0.996
F3	32.49±0.41	0.364±0.013	0.408±0.004	1.11±0.040	10.76±3.120
F4	31.41 ± 0.96	0.412±0.006	0.471±0.003	1.14±0.020	12.94±1.635
F5	33.23 ± 1.60	0.438±0.019	0.504±0.029	1.13±0.009	12.38±0.909
F6	28.55±0.68	0.405±0.001	0.472±0.010	1.16±0.028	14.12±1.962
F7	26.65 ± 0.61	0.453±0.007	0.527±0.005	1.14±0.035	12.48±2.831

mean ± SD n=3

4.4 Floating lag time and floating time:

Floating lag time & total floating time are fundamental parameters for efficient application of FDDS formulation. The result for formulation batches F1 to F7 were depicted in Table 4. All formulation batches showed total floating time above 24 hrs. The effect of concentration of sodium alginate has an immense effect on these floating parameters. Floating lag time& total floating time increased with increasing sodium alginate (F1 to F3) concentration may be due to increase in viscosity, thus more time required for penetration of water into microspheres, therby microspheres can retain carbon dioxide for a longer period of time thus shows longer floating time. An increment in concentration of sodium bicarbonate (F2, F4 and F5), the floating lag time & total floating time decreased this behavior may be due to the fact that as amount of sodium bicarbonate increases the result of effervescence amount increases too, which in turn causes porous formation. This lead to rapid hydration of polymer matrix and therefore cause decrease in total floating time which exhibits excellent buoyancy.

Increasing calcium chloride concentration (F2, F6 and F7) has significant decrease in floating lag time and the floating duration augmented due to the formation compact complex of sodium alginate with Ca^{2+} ions[17,18].

Table 4. Floating lag time & total floating time of formulation batches

Formulation code	Floating lag time (Sec)	Total floating time (hrs)
F1	44±3.29	27±1.24
F2	68±2.94	31±2.05
F3	112±3.85	41±2.44
F4	30±1.63	27±1.41
F5	13±2.05	25±1.69
F6	46±1.24	34± 0.47
F7	35±3.85	36±1.24

mean + SD n=3

4.5 Morphological characterization of microspheres:

Optimised batch F6 was studied for Scanning Elelctron Microscopy (SEM) to study morphological characters of the microsphere and the photograph depicted in fig. 2.

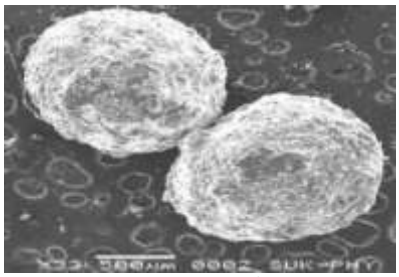


Fig. 2. Scanning Electron Microscopy of Formulation F6

Result highlighted that particles were spherical and descrete. Microspheres surface were rough, irregular and porous this may be due to uniform dispersion of the drug in molecular level in the alginate polymer matrix and presence of gas forming agent changes dense compact structure in porous nature[15,19].

4.6 Fourier transform infrared spectroscopy (FTIR):

Fig. 3 showed FTIR data for PCZM (A), Sodium alginate (B), physical mixture (C) and formulation F6 (D).

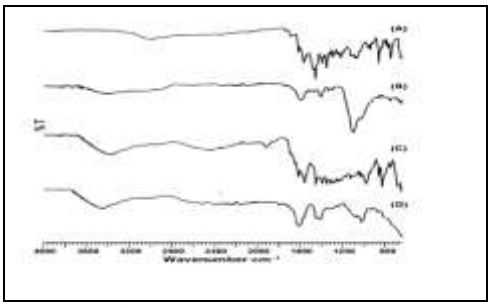


Fig. 3 FTIR study for PCZM (A), Sodium alginate (B), Physical mixture (C), Formulation F6 (D)

FTIR spectrum for the pure PCZM displayed band at 3010.30cm^{-1}assign to the (C-H) aromatic rings of drug. The band appeared at 1683.88 cm^{-1} corrosponds to stretching of C=O of carboxylate group of maleate structure[20]. The band appeared at 1562.98 cm^{-1} attributed to (C=C) of the aromatic ring. The band appeared at 1086.33 cm^{-1} correspondsn to (C-Cl) stretching in the benzene ring. All the major absorption peaks observed in physical mixture and optimized formulation F6 with little shifting of absorption values indicating no chemical interaction.

4.7 Differential scanning calorimetry (DSC):

Fig. 4 showed DSC study for PCZM (A), sodium alginate (B), physical mixture (C) and optimized formulation F6(D). Pure drug PCZMshowed sharp endothermic peak at 214.31^{0}C indicating crystalline nature of the drug while the physical mixture showed sifting of drug peak to lower value at 199.38^{0}C and further the optimized formulation F6 showed drugpeak sifted to 195.47^{0}C with significant decrease in intensity of peak suggesting drug is molecularly dispersed in the polymer and transferred to amorphous phase.

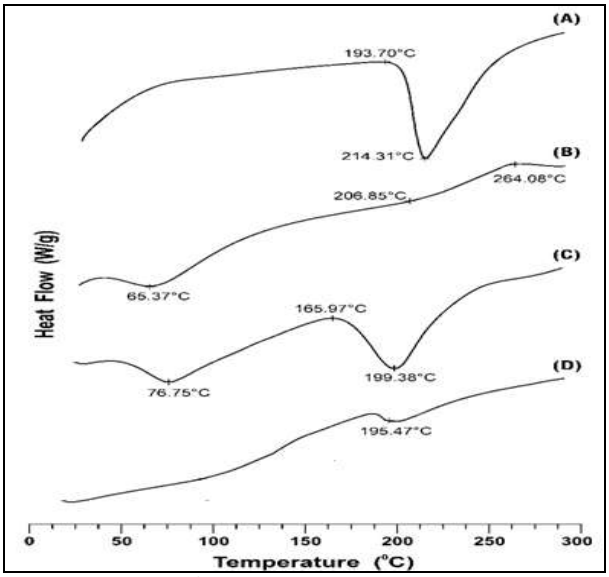


Fig. 4 DSC study of PCZM (A), Sodium alginate (B), Physical mixture (C), Formulation F6 (D)

4.8 Powder X-ray diffraction study (PXRD):

Fig. 5 showed XRD pattern forPCZM (A), sodium alginate (B), physical mixture (C) and optimized formulation F6(D). PXRD data of pure drug showed intense and sharp peak at 2θ of 25.43^{0}and 17.60^0 with peak intensities of 2043 and 836 respectively. Formulation F6 showed peak at 2θ of 25.43^0 and 17.59^0 with decrease in peak intensities 34 and 56 respectively. Crystallinity was measured by comparing some characteristic peak heights in the diffraction pattern of formulation with reference pure drug. The peak height at 2θ of 25.43° was used for calculating the relative decrease in crystallinity (RDC) of formulation. The RDC value for formulation F6 was 0.0166. No distinctive XRD pattern was observed for formulation F6 and thus it can be stated that the drug was present in amorphous state. This clearly indicated in formulation of PCZM microspheres crystalline state of drug was changed.

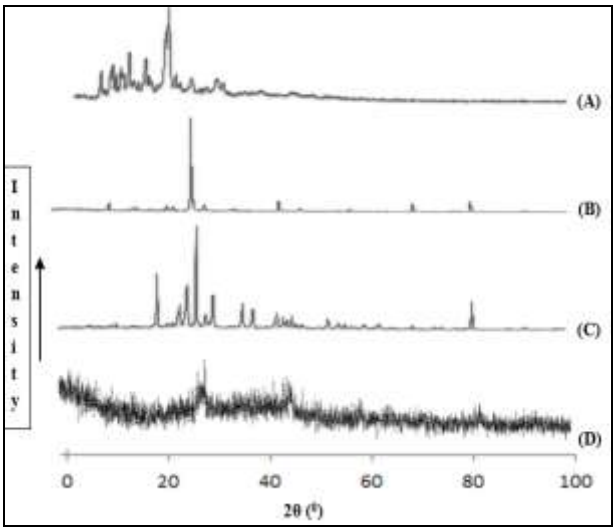
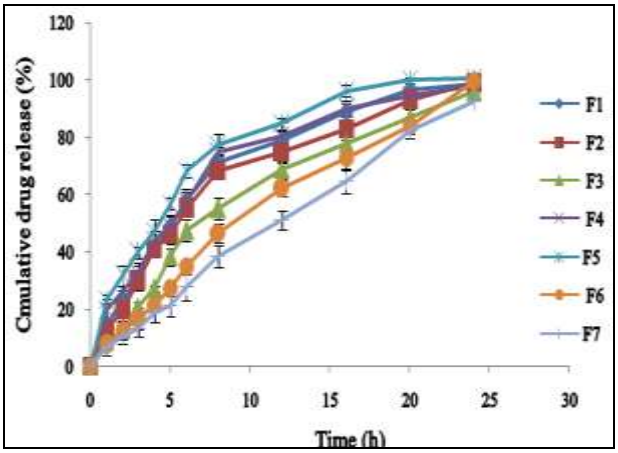


Fig 5. PXRD pattern for PCZM(A), Sodium alginate (B), Physical mixture (C), FormulationF6 (D)

4.9 *In-vitro* dissolution study:

The results of *In-vitro* dissolution study were depicted in fig. 6. Prepared formulation batches showed differnce in drug released due to change in concentartions of polymer used for the batches. *In-vitro* study of alginate microspheres of PCZM showed changed and sustained release of drug. The perecent (%) of drug release decreases with an rise in the polymer concentration (F1-F3). This can be explained by principle of gelation as number of cross linking points between sodium alginate & calcium chloride increases (F2, F6 and F7) with increase in alginate concentration[21]. Microspheres prepared with 12% concentration of calcium chloride (F7) due to more cross linking between alginate with calcium ions resulting in rigid gel network showed retarding sustained release effect more slowly with 92.63% drug release[22]. Although 10% concentration of calcium chloride containing F6 batch showed 99.73% drug release in a sustained manner. At low concentration of sodium bicarbonate, more dense structure of alginate was maintained which leads to lower amount of drug release, but increasing concentrations of sodium bicarbonate (F2, F4 and F5), the drug release was increased because of enhanced porous nature of formulations.[23] This relationship was due to high concentration of sodium bicarbonate increases the pore size of polymer network and thereby created channels for PCZM release.[12]



mean + SD n=3

Fig. 6 Comparative *In-vitro* dissolution study of formulation batches

4.10 Release kinetics data of optimized formulation:

The drug release parameters for the optimized formulation i.e. F6 were fitted to various release models. After that we found that the kinetics of drug release optimized formulation batch F6 follows Korsmeyer–Peppas model as represented in fig7.

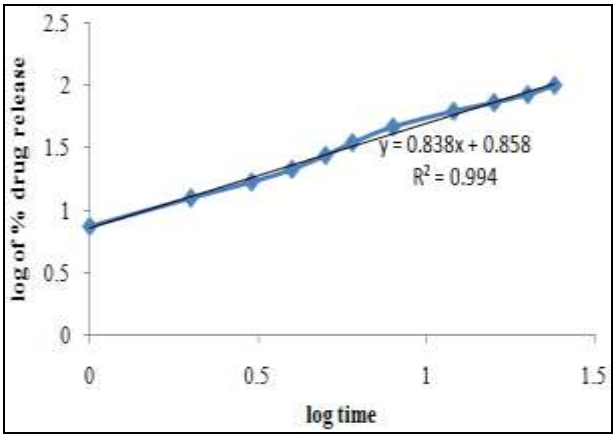


Fig. 7.Korsmeyer peppas model for optimized batch F6

Table 5. Regression coefficients (r^2) derived from release data for Formulation (F6) using different drug release models.

Formulation batch	Zero order r^2	First order r^2	Higuchi matrix r^2	Korsmeyer Peppas	
				r^2	n
F6	0.981	0.849	0.961	0.994	0.833

Based on results mentioned in table 5, data after fitting into various models for formulation batch F6 follows Korsmeyer's Peppas model (r^2=0.994), indicating erosion of polymeric chain. To explain mechanism of drug release, drug release exponent (n) was calculated and found to be 0.833 indicates non-fickian diffusion. Thus erosion as well as diffusion were two processes by which drug release was sustained[24].

5 CONCLUSION:

Based on data, formulation batch F6 showed optimum results with floating lag time 46sec, total floating time more than 24 hrs, entrapment efficiency 88.47% and drug release 99.73% compared to other formulations batch F6 showed more sustained release effect in desired manner. The microsphere based sustained release floating microspheres of PCZM was successfully prepared by ionotropic gelation method which can be taken once a daily having advantage over immediate release dosage form which required 3-4 times administration daily. Thus once a day formulation results in improvement bioavailaility and therby patient compliance.

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7 CONFLICT OF INTEREST:

The authors declare no conflict of interest.

8 REFERENCES:

1. Borg TM, El-Dahan MS, Hammoodi HA. Bioavailability Improvement of Diltiazem Hydrochloride Gastro retentive Sustained Release Tablets. Journal of Pharmacy and Biological Sciences. 2016;11(6):44-52.
2. Narang N. An updated review on: floating drug delivery system (FDDS). International journal of applied pharmaceutics. 2010;3(1):1-7.
3. Bhosale UV, Devi K, Choudhary S. Multiunit floating drug delivery system of acyclovir: development, characterization and in vitro-in vivo evaluation of spray-dried hollow microspheres. Journal of Drug Delivery Science and Technology. 2012;22(6):548-554.
4. Satish D, S Himabindu ,YS Kumar. Floating Drug Delivery Systems for Prolonging Gastric Residence Time: A Review. Current Drug Delivery. 2011;8:494-510.
5. Tripathi P, Ubaidulla U, Khar RK, et. al. Floating Drug Delivery System. International journal of research and development in pharmacy & life sciences. 2012;1(1):1-10.
6. Rastogi R, Sultana Y, Aqil M, et. al. Alginate microspheres of isoniazid for oral sustained drug delivery. International Journal of Pharmaceutics. 2007;334,71-77.
7. Cho AR, Chun YG, Kim BK, et al. Preparation of alginate–CaCl2 microspheres as resveratrol carriers. Jornal of Material Science. 2014;49:4612-4619.
8. Jagdale SC, Randhave AB. Hydroxyl Ethyl Cellulose HHX and Polymethyl Methacrylate Based Site Specific Floating Delivery of Prochlorperazine Maleate. Open Pharmaceutical Sciences Journal. 2016;3:149-163.
9. Ngarsenkar MS, Garad SD, Physical characterization and optimisation of dissolution parameters of prochlorperazine maleate coevaporates. International Journal of Pharmaceutics. 1998;160:251–255.
10. Nishimura M, Matsuura K, Tsukioka T, et. al. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. International Journal of Pharmaceutics. 2009;368:98–102.
11. Ma L, Xu L, Wang Q, et. al. Development and evaluation of new sustained-release floating microspheres. International Journal of Pharmaceutics. 2008;358:82–90.
12. Albadry AA, ALI WK, AL-SAADY FA. Formulation and evaluation of prochlorperazine maleate sustained release floating

tablet. International journal of pharmacy and pharmaceutical sciences. 2017; 9(2) :89-98.
13. Vedha HB, Brahma RA, Samyuktha RB, Floating Drug Delivery of Nevirapine as a Gastroretentive System. Journal of Young Pharmacists. 2010;2(4):350-355.
14. Gadad AP, Naik SS, Dandagi PM,et. al. Formulation and Evaluation of Gastroretentive Floating Microspheres of Lafutidine Indian Journal of Pharmaceutical Education and Research. 2016;50(2):S76-S81.
15. Abbas AK, Alhamdany AT, et. al.Floating Microspheres of Enalapril Maleate as a Developed Controlled Release Dosage Form: Investigation the Effect of Ionotropic Gelation Technique. Turkish Journal of Pharmaceutical Science. 2018;1-39.
16. Das MK, Senapati PC.Furosemide-loaded Alginate Microspheres Prepared by Ionic Cross-linking Technique: Morphology and Release Characteristics.Indian Journal of Pharmaceutical Science. 2008;70(1):77-84.
17. Alhamdany AT,Maraie NK, Msheimsh BAR. Development and In Vitro/In Vivo Evaluation of Floating In Situ Gelling Oral Liquid Extended Release Formulation of Furosemide. UK Journal of Pharmaceutical and Biosciences 2014;2(5):01-11.
18. Taranalli SS, Dandagi PM, Mastiholimath VS. Development of hollow/porous floating beads of metoprolol for pulsatile drug delivery. Eur J Drug Metab Pharmacokinet 2015;40(2):225-33.
19. Prezotti FG, Cury BS, Evangelista RC. Mucoadhesive beads of gellan gum/pectin intended to controlled delivery of drugs. Carbohydrate Polymers. 2014;113:286-295.
20. Shirsand SB, Suresh, Para MS. Design of Fast Disintegrating Tablets of Prochlorperazine Maleate by Effervescence Method. Indian Journal of Pharmaceutical Sciences.2009;71:447-51.
21. Sanchita M, Kumar S, Krishnamoorthy B, et..al. Development and evaluation of calcium alginate beads prepared by sequential and simultaneous methods. Brazilian Journal of Pharmaceutical Sciences. 2010; 46(4),785-793.
22. Sahare M Dahima R. Formulation and Optimization of Preparative Variables of Gastroretentive Floating Beads of Famotidine by Ionotropic Gelation Technique. Journal of Pharmacy Research 2012;5(10):5001-5006.
23. Sindhumol PG, Nair SCR, Harindran J, et. al. Formulation and evaluation of alginate-cellulose floating microspheres of cefixime trihydrate G International Research Journal of Pharmacy. 2018,9(3):67-74.
24. Akram F, Kabir MT. Characterization of Gliclazide-Loaded Combination of Polymer Microspheres Prepared by Emulsification Solvent Evaporation Method. Scholars Academic Journal of Pharmacy.2016;5(8):309-316.