Research Article

Formulation and Evaluation of Floating Drug Delivery Systems of Propranolol HCl using Modified Pulsincap Technique

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ABSTRACT

Oral controlled release drug delivery systems are one of the promising systems for prolonged duration of action for chronic diseases like hypertension, diabetes etc. Drugs with absorption window in upper GIT (gastro intestinal tract) require special attention for effective therapy. Gastric floating drug delivery systems (GFDDS) are one such suitable delivery system. In our present investigation we attempted to utilize modified pulsincap technique to develop GFDDS of propranolol HCl using PEO WSR 303 polymer. Modified pulsincap technique involve exposing the capsule body to formaldehyde vapors which results in hardening of the shell. The drug- polymer- excipient mixture was filled into the hardened body and covered with untreated cap. All the formulations were evaluated for residual formaldehyde estimation, weight variation, drug content, *in-vitro* buoyancy, drug release pattern, compatibility studies etc. The formulations F1-4 with drug-polymer ratio 1:0.75 of 1 hr formaldehyde vapour exposure and F2-3 with drug: polymer ratio 1:0.5 of 2 hrs formaldehyde vapour exposure were considered as the optimized formulations as they released 99.99% and 100.00% of the drug in 12 hrs respectively with sufficient buoyancy characteristics. Promising results concluded that the modified pulsincap technique can be successfully used for the development of GFDDS of propranolol HCl using PEO WSR 303.

Keywords: Formaldehyde, floating capsules, modified pulsincap, propranolol HCl, PEO WSR 303

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INTRODUCTION

There are different types of dosage forms with prolonged gastric residence time. These include floating drug delivery systems, swelling and expanding systems, gastric floating drug delivery system (GFDDS), polymeric bio-adhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. Compared to these approaches, the GFDDS has several advantages like the buoyancy, safety for clinical use etc [1,2].

Propranolol HCl is a synthetic, non-selective beta-adrenergic receptor-blocking agent widely used in the management of hypertension. It has low bioavailability and shorter elimination half life (2 to 6 hours) due to its narrow absorption window in the upper parts of the gastro intestinal tract [3]. Thus a controlled release dosage form of propranolol HCl is desirable for the improvement of bioavailability, therapeutic efficacy of the drug and possible reduction of dose.

Polyethylene oxide (PEO) is a biocompatible matrix-forming polymer, which is marketed as "POLYOX™" retards the release rate of drug/s. PEO is widely used in pharmaceutical formulations like controlled release dosage forms.

Floating drug delivery system is used for increasing oral bioavailability of drugs with narrow absorption window in the lower G.I. tract or for drugs locally active in the stomach. In the present investigation the modified pulsincap technique is used to prepare the oral controlled release floating

capsules of propranolol HCl. In modified pulsincap technique, empty hard gelatin capsule bodies are hardened and made water insoluble by exposing to formaldehyde (HCHO) vapours where the amino acid molecules of gelatin gets cross linked with the HCHO vapours. The drug, polymer and excipients mixture is filled into the capsule body and covered with the untreated cap. On exposure to the gastric fluids the untreated cap readily gets dissolved in the GI fluids whereas treated body (hardened body) remains intact without any dissolution and holds the swollen polymer. The swollen polymer with air entrapment and mesh like structure formation results in buoyancy characteristic in addition to controlling the drug release efficiently [4]. The rationale of the present investigation is to modify the pulsincap technique by avoiding plug usage and to check its applicability in the design of floating controlled release systems.

MATERIALS AND METHODS

Propranolol HCl and PEO WSR 303 were obtained as gift samples from Sun Pharma and Unichem Labs respectively. Lactose was purchased from Loba Chemie Pvt. Ltd., whereas formaldehyde A.R., magnesium stearate and hydrochloric acid were purchased from Qualigens Fine Chemicals Pvt. Ltd.

Preparation of cross linked empty gelatin capsules [3, 5-7]

Hard gelatin capsules of size-1 were taken and their bodies were separated from the caps.

Formalin (formaldehyde solution) was taken into the bottom of a desiccator and potassium permanganate was added to generate the fumes.

A wire mesh was kept above the solution to place capsule bodies on it for exposure. The capsule bodies were allowed to react with formaldehyde vapours for different time intervals of 1 hour and 2 hours. Then they were collected and kept in a hot air oven at 50^0C for 30 min so that complete reaction between formaldehyde and gelatin takes place. Then these capsule bodies were taken out, kept for air drying to remove residual formaldehyde and stored in a polythene bag.

Chromotropic acid method for estimation of residual formaldehyde [8]

As per the method developed by D.A. Mac Fadyen, the residual formaldehyde in exposed capsules was estimated by chromotropic acid method for which the reagents used are formaldehyde solution A.R., sulphuric acid solution and chromotropic acid reagent.

Chromotropic acid reagent was prepared by dissolving 0.2 g of chromotropic acid in 20 ml distilled water, filtering to remove insoluble sulphones and adding 80 ml H_2SO_4 solution to make up the volume up to 100 ml. The reagent was stored in stoppered bottle and protected from light. It was used within a week.

Procedure:

Formaldehyde A.R. was suitably diluted with distilled water to obtain series of dilutions containing 0.76, 1.52, 3.8, 7.6 and 12.66 µg of formaldehyde per ml of dilution. To 1 ml of each dilution in a stopppered test tube, 9 ml of chromotropic acid reagent was added, mixed and heated in a boiling water bath for 30 min. The purple colored solution was cooled and color was measured in UV-Visible spectrophotometer at 570 nm against a reagent blank obtained by heating a mixture of 9 ml of chromotropic acid reagent with 1 ml of distilled water.

The limit for free formaldehyde according to FDA is 0.002% [9,10].

Formulation

Preparation of physical mixture of drug and polymer

All the ingredients sufficient for a batch were weighed according to the formulae representing various ratios of polymer: drug: excipients has given in (**Table 1**) and Table 2. All the ingredients were geometrically mixed.

Filling of capsules

Hard gelatin capsules of size 1 with formaldehyde treated body and untreated cap were taken for filling. Capsules for each formulation were prepared by manual filling method. Finally the cap was locked onto the capsule body and stored in tightly packed container for further studies.

Table 1: Formula of Propranolol HCl modified Pulsincap GFDDS (1 hr exposed)

Ingredients (mg/capsule)	F1-1	F1-2	F1-3	F1-4	F1-5	F1-6
Propranolol HCl	80	80	80	80	80	80
PEO WSR 303	0	20	40	60	80	100
Lactose	118	98	78	58	38	18
Magnesium stearate	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

Table 2: Formula of Propranolol HCl modified Pulsincap GFDDS (2 hrs exposed)

Ingredients (mg/capsule)	F2-1	F2-2	F2-3	F2-4	F2-5	F2-6
Propranolol HCl	80	80	80	80	80	80
PEO WSR 303	0	20	40	60	80	100
Lactose	118	98	78	58	38	18
Magnesium stearate	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

Evaluation tests [11]

Evaluation of empty gelatin capsules

The prepared formulations, both treated and untreated capsules, were evaluated for various physical tests.

Identification attributes and visual defects

HCHO vapor exposed and unexposed capsules were randomly selected and checked for color, shape, lockability, stickiness and odour.

Weight variation of empty capsules

Both the HCHO treated and untreated capsules were checked for weigh variation.

Solubility of empty capsules

The empty gelatin capsules (both HCHO treated and untreated) were tested for solubility using type-2 dissolution rate test apparatus with distilled water and 0.1 N HCl as mediums. The test was conducted at 37 ± 0.5^{o} C for 14 hours at 50 rpm.

Evaluation of propranolol HCl modified pulsincap GFDDS [12,13]

The formulated capsules were evaluated for *in-vitro* buoyancy studies like floating lag time and total floating time, weight variation, estimation of drug content and *in-vitro* dissolution studies. Compatibility studies were conducted using IR spectroscopy of pure samples of formulation ingredients and the whole mixture.

In-vitro buoyancy studies

All the prepared propranolol HCl modified pulsincap GFDDS of both 1 hr and 2 hrs exposed were subjected to *in-vitro* buoyancy test. The time required for the capsule to rise to the surface of the medium and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the floating time. The floating lag time and the floating time were determined in 1 litre glass beaker containing 900 ml of 0.1 N HCl.

Weight variation test

According to I.P., an intact capsule was weighed and then it was opened without losing any part of the shell. The contents were removed as completely as possible and shell was reweighed. The difference between the weighings gave the weight of the contents. This procedure was repeated for another 19 capsules. The average weight and % deviation of individual capsules from average weight was determined.

Estimation of drug content

From each batch, 5 capsules were randomly collected and the formulation mixture was separated. The powder mixture equivalent to 100 mg of propranolol HCl was weighed and transferred to 100 ml volumetric flask. It was dissolved in small quantity of methanol with vigorous shaking on a mechanical shaker and filtered into a 50 ml volumetric flask through 0.45 μm millipore nylon filter disc and the filtrate was made up to the mark with 0.1N HCl. Further appropriate dilutions were made and the absorbance was measured at 319 nm against blank (0.1N HCl).

In-vitro dissolution studies

In-vitro release of propranolol HCl from the prepared floating capsules was studied using type-2 USP XXIV dissolution rate test apparatus (Model: DISSO 2000, M/s. LABINDIA) employing the paddle stirrer. The dissolution medium used was 900 ml of 0.1N HCl maintained at a temperature of 37±0.5º C and the paddle was rotated at 50 rpm for 12 hrs. At each interval of 1 hour, 5 ml samples were withdrawn by means of a syringe fitted with a prefilter and immediately replaced with 5 ml of fresh medium. The absorbance of the samples was measured at 319 nm after suitable dilution with the medium using Elico SL-159 UV Spectrophotometer.

Drug release kinetics [14-18]

As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, Higuchi and Hixson-Crowell erosion and Korsmeyer-Peppas equations. The order of drug release from matrix systems was described by using zero-order or first-orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi diffusion, Hixson-Crowell erosion and Korsmeyer-Peppas equations.

Drug-polymer interaction studies by Fourier transform infrared spectroscopy

Infrared spectral analysis of pure samples of propranolol HCl, PEO WSR 303, lactose, magnesium stearate and optimized formulation were done using Fourier transform infrared spectrophotometer (Shimadzu model 8300). The IR spectra were done against KBr background.

RESULTS AND DISCUSSION

Estimation of free formaldehyde content

The limit for residual formaldehyde according to FDA is 0.002% and the formaldehyde exposed hard gelatin capsule bodies passed the chromotropic acid test as the value obtained is less than the standard limit.

Evaluation tests for empty gelatin capsules

All the empty capsules were lockable type, odourless, soft and sticky when touched with finger. After formaldehyde vapour treatment, there were no significant changes in the capsules except for the slight stickiness. There was no significant change in colour and shape after formaldehyde vapour treatment. The individual weights of each capsule were quite uniform and cross linking did not show any significant change in weight. Untreated bodies dissolved in 15 min where as treated bodies remained intact even after 14 hrs. However untreated cap was dissolved in 15 min.

Evaluation of propranolol HCl modified pulsincap GFDDS

In-vitro buoyancy studies

The polymer present in the formulation swollen in the presence of fluid and formed mesh like structure entrapping the drug enabling its slow release. This also provided buoyancy to the capsule.

All the prepared pulsincaps floated on the surface immediately upon their addition to the 0.1N HCl indicating no floating lag time. The floating time of the prepared modified pulsincaps was found to be in the range of 6-14 hrs (**Table 3**). The results indicated that floating time was increased with increase in the polymer concentration. Except formulations F1-1 and F2-1 all other formulations resulted in floating times >14 hrs.

Weight variation test

All the prepared modified pulsincap GFDDS formulations complied with the compendial standards for uniformity of weight.

Estimation of drug content

The drug content estimated was found to be in the range of 98% to 102% of the stated amount of propranolol HCl and was within the standard limit of ±5 % variation (**Table 4**).

Thus, the propranolol HCl gastric floating modified pulsincap formulations prepared with PEO WSR 303 were found to be of good quality fulfilling all the official and other requirements.

In-vitro dissolution studies

Effect of polymer concentration

The release profiles of propranolol HCl from 1 hr exposed modified pulsincaps were shown in Fig. 1. More than 99.9% of the drug was released from F1-1, F1-2, F1-3, F1-4 and F1-5 in 2, 5, 7, 12 and 14 hrs respectively.

The release profiles of propranolol HCl from 2 hrs exposed modified pulsincaps were shown in (**Figure 2**). More than 99.9% of the drug was released from F2-1, F2-2 and

F2-3 in 4, 9 and 12 hrs respectively. In both the cases the drug release was decreased with increasing concentrations of polymer PEO WSR 303.

Table 3: Floating time of Propranolol HCl modified Pulsincap GFDDS

Formulation	Floating time (hrs)
F1-1	6
F1-2	>14
F1-3	>14
F1-4	>14
F1-5	>14
F1-6	>14
F2-1	8
F2-2	>14
F2-3	>14
F2-4	>14
F2-5	>14
F2-6	>14

Table 4: Drug content of Propranolol HCl in Formulations

Formulation	Drug content# (%)
F1-1	99.57±0.61
F1-2	98.73±0.85
F1-3	100.70±0.4
F1-4	100.23±1.35
F1-5	99.66±0.31
F1-6	100.47±1.05
F2-1	101.13±1.19
F2-2	100.37±0.76
F2-3	99.33±0.81
F2-4	99.73±1.66
F2-5	100.90±1.48
F2-6	99.56±0.99

#mean ± s.d., n=3

Effect of exposure time of formaldehyde vapours on drug release

The studies indicated that 2 hrs exposed capsules retarded and extended the drug release more compared to 1 hr exposed capsules which may be due to excessive cross-linkage of the gelatin molecules initiated by the formaldehyde.

Among the formulations tested, F1-4 and F2-3 released the drug over a period of 12 hrs with sufficient buoyancy characteristics. The objective of the present investigation is to extend the release of the drug over a period of 12 hrs and hence these two formulations satisfied the objectives.

Drug release kinetics

The formulation F1-4 with drug-polymer ratio 1:0.75 of 1 hr formaldehyde vapour exposed and F2-3 with drug: polymer ratio 1:0.5 of 2 hrs formaldehyde vapour exposed were considered as the optimized formulations as they released 99.99% and 100.00% drug in 12 hrs respectively with sufficient buoyancy characteristics. Both the optimized formulations followed zero order release with non-Fickian diffusion mechanism. Among the two, F2-3 was confirmed as the best formulation as it utilized less amount of polymer compared to F1-4 and released 100.00% drug in 12 hrs.

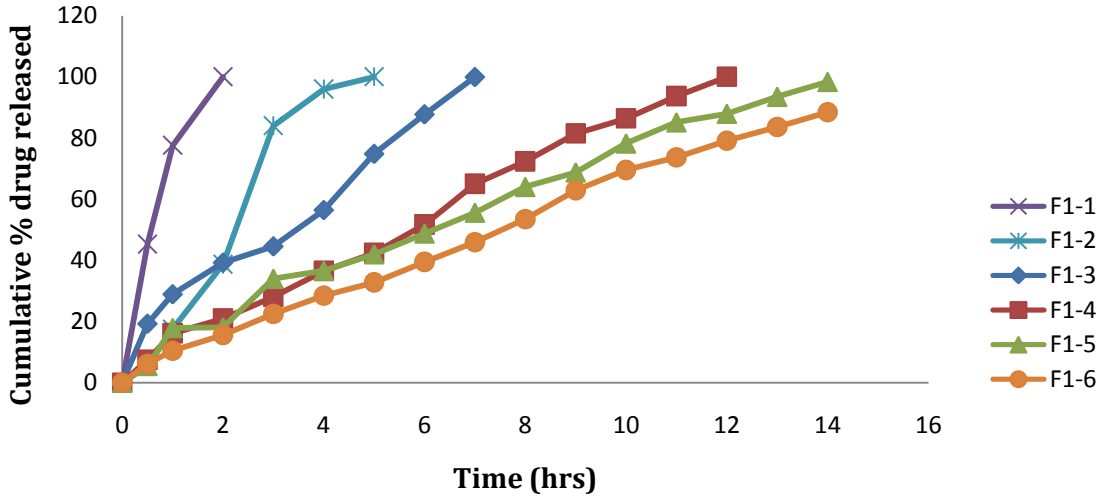


Figure 1: Dissolution Profile plots of Propranolol HCl modified Pulsincap GFDDS (1 hr exposed): F1-1 to F1-6

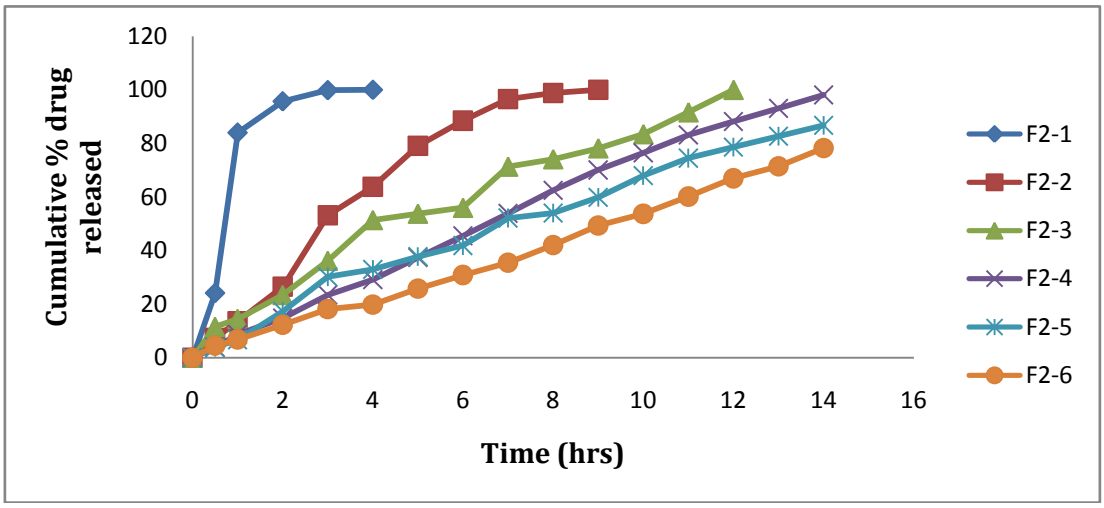


Figure 2: Dissolution profile plots of propranolol HCl modified pulsincap GFDDS (2 hrs exposed): F2-1 to F2-6

Table 5: Correlation coefficient (r) values and release kinetics of propranolol HCl modified pulsincap GFDDS

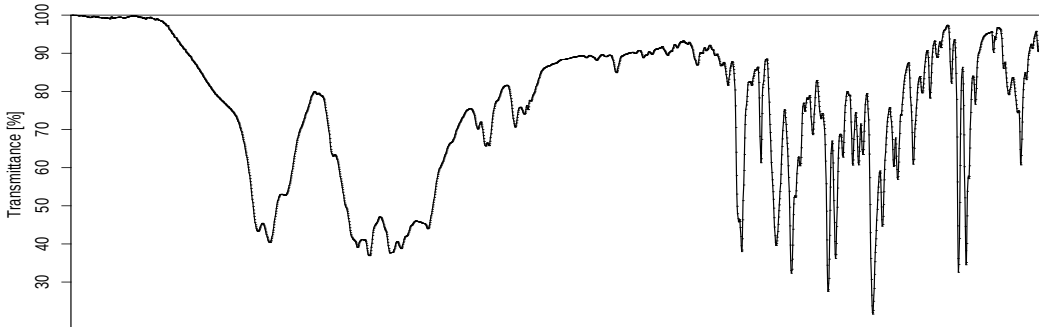
Formulation	r-value				n-value
	Zero order	First order	Higuchi	Erosion	Peppas
F1-1	0.6292	0.3130	0.7758	0.7113	0.5805
F1-2	0.8258	0.8809	0.9165	0.9224	0.6882
F1-3	0.9492	0.7835	0.9792	0.9513	0.6447
F1-4	0.9969	0.7071	0.9705	0.9289	0.5945
F1-5	0.9934	0.9700	0.9787	0.9741	0.5843
F1-6	0.9979	0.9772	0.9659	0.9884	0.5752
F2-1	0.6236	0.6253	0.7891	0.7772	0.4675
F2-2	0.9279	0.8992	0.9695	0.9853	0.6782
F2-3	0.9864	0.6715	0.9864	0.9214	0.5320
F2-4	0.9989	0.9695	0.9664	0.9876	0.7202
F2-5	0.9934	0.9843	0.9767	0.9929	0.6831
F2-6	0.9974	0.9787	0.9570	0.9874	0.5865

FTIR analysis

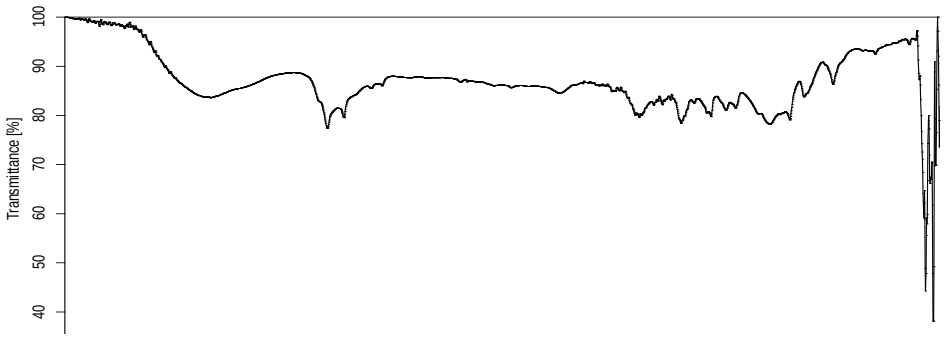
FTIR of Propranolol HCl showed a characteristic secondary amine –N-H stretch at 3280 cm^{-1}, C-H stretch at 2964cm^{-1}, Aryl C=C stretch at 1579cm^{-1}, Aryl O-CH_2 asymmetric stretch at 1240cm^{-1}, Aryl O-CH_2 symmetric stretch at 1030 cm^{-1} and peak at 798cm^{-1} due to alpha –substituted naphthalene.

PEO WSR 303 showed a characteristic alcoholic –OH stretch at 3433cm^{-1}, -C-O-C- asymmetric stretch at 1260cm^{-1} and –C-O-C- symmetric stretch at 1060cm^{-1}.

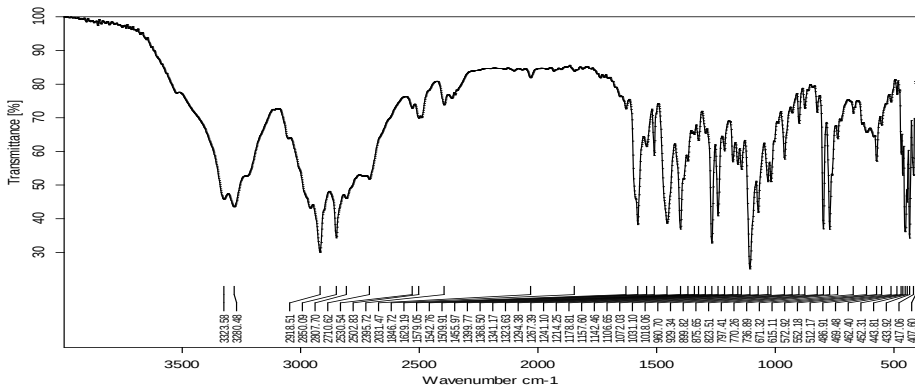
The major peaks for the pure drug and the polymers were well in support with the theoretical prediction with respect to the functional groups as given above. Presence of PEO WSR 303 and other excipients did not produce any major shift in principal peaks of propranolol HCl and also the presence of one ingredient did not produce shift in the peaks of other ingredients. This indicated that there is no interaction among drug, polymer and the excipients used in the study. Hence FTIR spectral analysis proved the compatibility of the drug and polymer/ excipients used in the study.



Propranolol HCl



PEO WSR 303



Optimised formulation (F2-3)

Figure 3: FTIR Spectra of Propranolol HCl modified Pulsincap GFDDS (F2-3)

CONCLUSION

The present investigation revealed that PEO WSR 303 can be successfully used in the preparation of oral controlled release gastric floating drug delivery systems of propranolol HCl using modified pulsincap technique. It was also proved that 1 hr and 2 hr exposure to formaldehyde vapours is able to control the drug release for 12 hours. No work has been reported till date on the design of floating modified pulsincaps of propranolol HCl using the said polymer. Hence this makes a significant contribution for the development of propranolol HCl modified pulsincap GFDDS.

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REFERENCES

1. Bhalla Neetika, Goswami Manish. Floating Drug Delivery System. Int J Pharm Res Allied Sci. *2012;* 1(4):20-28.
2. Tomar Preeti, Shukla Vaibhav, Kharia Ankit Anand, Chatterjee D. P. Floating drug delivery system: an updated review. J Med Pharm Allied Sci. 2013; 4:31-42.
3. Huang YB, Tsai YH, Yang WC, Chang JS, Wu PC, Takayama K. Once-daily propranolol extended-release tablet dosage form: formulation design and *in-vitro/in-vivo* investigation. Eur J Pharm Biopharm. 2004; 58:607–614.
4. L. Srinivas, D. Lohithasu, D. Madhupriya, N. Siddhartha, N. Tejaswi. Formulation and evaluation of ibuprofen pulsincap technique for controlled release. Der Pharmacia Lettre. 2013; 5(1):60-68.
5. Sindhu Abraham, MS Srinath. Development of modified pulsincap drug delivery system of metronidazole for drug targeting. Indian J Pharm Sci. 2007; 69(1):24-27.
6. Swati C Jagdale, Pravin S Phule, Gajanan J Chavan. Formulation and evaluation of modified pulsincap drug delivery system of rizatriptan benzoate. Int J Pharm Pharm Sci. 2014; 6(5):48-52.
7. Sharma GS, Srikanth MV, Sunil S, Ramana Murthy KV. Application of modified pulsincap technique for oral controlled drug delivery of gliclazide. Int J Pharm Pharm Sci. 2012; 4(3):618-624.
8. D. A. MacFadyen. Estimation of formaldehyde in biological mixtures. J Bio Chem. 1945; 158(1):107–133.
9. Nagaraja G, Sunil Agarwal, Dinesh Shenoy, Paramjeet Singh Minhas, Yogesh D. B., Fazil Baig. Design and evaluation of time programmed pulsincap system for chronotherapeutic delivery of losartan potassium. J Chem Pharm Res. 2013; 5(6):76-87.
10. V.S. Mastiholimath, P.M. Dandagi, S. Samata Jain, A.P. Gadad, A.R. Kulkarni. Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma. Int J Pharm. 2007; 328(1):49-56.
11. Khan Abdul Waris, Ahmed Mohammed Gulzar, B Ramesh. Formulation and evaluation of novel sustained relese capsules of terbutaline sulphate. Int Res J Pharm. 2011; 2(1): 249-255.
12. Rosa M, Zia H, Rhodes T. Dosing and testing *in-vitro* of a bioadhesive and floating drug delivery system for oral application. Int J Pharm. 1994; 105:65-70.
13. Indian Pharmacopoeia, Govt. of India, Ministry of Health and Family Welfare, The Indian Pharmacopoeia Commission, Ghaziabad, India, 182, 2007.
14. Lazarus J, Cooper J. Absorption, testing and clinical evaluation of oral prolonged-action drugs. J Pharm Sci. 1961; 50:715-732.
15. Wagner JG. Interpretation of percent dissolved-time plots derived from i*n-vitro* testing of conventional tablets and capsules. J Pharm Sci. 1967; 58:1253-1257.
16. Higuchi T. Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52:1145-1149.
17. Korsmeyer RW, Gurney R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymer. J Pharm Sci. 1983; 15:25-35.
18. Ritger P L, Peppas N A. A simple equation for description of solute release II. fickian and anomalous release from swellable devices. J Cont. Rel.1987;5:37-42.