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Original Article

Design and evaluation of pH sensitive multi-particulate systems for chronotherapeutic delivery of pioglitazone hydrochloride

Gowrav M. P*, Shivakumar H. G and Vishal Gupta N

Dept. of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore-570 015, Karnataka, India

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ABSTRACT

The aim of the present study was to develop a pH sensitive gastroretentive drug delivery system for an anti diabetic drug pioglitazone HCl based on gas formation technique using 3^2 factorial design, in order to prolong the gastric residence time and increase the overall bioavailability of the dosage form, since the absorption is erratic in diabetic patients. The system consists of the drug loaded pellets which is coated with two different layers, inner layer of effervescent material (sodium bicarbonate) and an outermost layer of gas-entrapped sustained release polymeric membrane (Chitosan: Eudragit S100). The time to float increased as the coating level of gas-entrapped polymeric membrane increased. The optimum system could float completely within 2 min and maintained the buoyancy for a period of 12 h. Both the rapid floating and the sustained release properties were achieved in the multiparticulate drug delivery system developed in this present study.

Keywords- Pellets, pH sensitive, gastroretentive, pioglitazone HCl, factorial design.

INTRODUCTION

The pH sensitive drug delivery systems are gaining importance as these systems deliver patient therapeutic efficacy and compliance. Diseases wherein pH sensitive drug delivery systems are promising include asthma, peptic ulcer, diabetes, cardiovascular diseases, cancer and hypertension. The specific time that patients take their medication is very important as it has significant impact on treatment success. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. Drug pharmacokinetics can also be pH-sensitive: therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose [1]. An elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and allowed to be released at an appropriate rate. Because most absorption windows are thought to be located in the proximal small intestine, the obvious strategy will be to hold the formulation in stomach (i.e. gastroretention). The Holy Grail remains the retention of a delivery system in the fasting human stomach using a system that will be safe and effective. The intimate contact of the drug delivery system with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities. Most of the floating systems are single unit systems such as tablets and capsules. A major drawback of these systems is their high variability of the GI transit time due to all-or-nothing emptying processes [2-7]. Whereas, the multiple-unit dosage forms are an attractive alternative since they have been shown to decrease the inter and intra subject variabilities in drug absorption as well as to lower possibility of dose dumping [8,9,10]. Use of effervescent compounds and swellable polymers is an novel approach for designing multiple-unit floating drug delivery systems [11]. Pioglitazone Hcl which is chemically 5-[4-[2-(5-Ethyl-2-pyridinyl) ethoxy] benzyl] thiazolidine-2,4-dione, Hydrochloride. It is a thiazolidinedione compound used in the treatment of type II diabetes. It is an insulin sensitizer that acts as agonist of the peroxisome proliferator-activated receptor subtype gamma (PPAR-γ).

***Corresponding Author Address:** Gowrav M.P, Dept. of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore-570 015, Karnataka, India. E-mail: gowravmp@gmail.com*

Activation of PPAR-γ receptors promotes the production of gene products involved in lipid and glucose metabolism. It also improves insulin response to target cells without increasing the pancreatic secretion of insulin. It is poorly soluble in aqueous media and its highly absorbed from stomach. Therefore, dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Pioglitazone hydrochloride has a biological half-life of 3-6 h and is eliminated rapidly.

The aim of the present work is to develop a pH sensitive gastroretentive drug delivery system. Pioglitazone hydrochloride, which is better absorbed in the stomach was selected as the drug of choice. The effect of the various parameters such as type, blend ratio and coating level of the gas-entrapped polymeric membrane, on the floating ability and drug release studies of the pellets were evaluated.

MATERIALS AND METHODS

Materials: Pioglitazone HCl was obtained as gift sample from Wockhardt Ltd, Aurangabad, India. Eudragit S100 was purchased from Degussa India Pvt Ltd, Mumbai, Chitosan was purchased from SRL, Mumbai, India. Hydroxy propyl methyl cellulose (HPMC) and Microcrystalline cellulose (MCC) was purchased Loba chemie, Mumbai, India.

METHODS

Preparation of drug-loaded pioglitazone HCl pellets

Experimental design [12,13,14]: A randomized, 3^2full factorial design with two factors at three levels was employed to systematically study the formulation of pH sensitive gastroretentive pellets. A total of nine experimental trials were performed at all possible combinations. The independent variables, the amount of Chitosan (A) and the amount of Eudragit S100 (B) were selected on the basis of trials taken during optimization of excipient which were varied at three levels (low, medium and high). The levels of the factors studied were chosen so that their relative difference was adequate to have a measurable effect on the response, along with the information that the selected levels are within practical use. The floating lag time (sec) and cumulative drug release were used as dependent variables (responses). Design-Expert 9.0 software (Stat-Ease Inc., USA) was used for generation and evaluation of the statistical experimental design.

Procedure: Pellet formulation consisting of the drug and MCC was prepared using extrusion-spheronization. On the basis of the initial experiments, the composition of cores was determined. The wet mass was extruded using EXT-65/037, R.R. Enterprises, Thane, India. The obtained extrudate underwent spheronization process (SPH-150/010, R.R. Enterprises) for 15 min and at a rotation speed of 1600 rpm. Wet pellets obtained were dried in a hot air oven at 40^{O}C for 12 h and then sieved.

Coating on the drug loaded pellets: The drug loaded pellets were coated with two successive layers; an effervescent substance (sodium bicarbonate) as an inner effervescent layer, and polymer blend layer (Chitosan:Eudragit S100) as an outer gas-entrapped polymeric membrane. An effervescent agent (sodium bi carbonate) was incorporated into HPMC solution plasticized with Poly ethylene glycol 400 (10%, w/w based on the solids content of HPMC) and then layered onto the drug loaded pellets. The coating level of effervescent layer was made up to 10% weight gain was obtained over drug loaded pellets as shown in table no 1.

The coating conditions were: bead charge - 15 g; preheating of pan at - 80^{0}C, preheating time -15 min, inlet temperature, 45 ◦C; outlet temperature, 40-42 ◦C; atomizing air pressure, 2 lb/in.^{2};spray rate, 0.5-1 ml/min and pan speed of 20 rpm. The pellets were further dried in the coating chamber for 1 hr after the coating was finished in order to evaporate the residual solvent in the polymeric coatings prior to storage.

Characterization of the formulation

Micromeritic properties

a) Tap density: Tap densities of the pellets were determined using tap density tester.
b) Angle of repose: Angle of repose was determined by fixed funnel method.
c) Compressibility: The compressibility of the pellets was determined by Carr's compressibility index.

Pellet size: Pellet size was determined using an image analysis system. Photomicrographs were taken with a digital camera (Sony, Cyber-shot, DSC-H300, Japan). The obtained images were processed by image analysis software (AnalySIS®; Soft Imaging System, Munster, Germany) [15].

Fourier transform infra red (FT-IR) spectroscopy: The sample powder of the formulation was dispersed in potassium bromide to make pellets under hydraulic pressure of 600 kg/cm^2 and scanned between 400 and 4,000

cm^{-1}.All studies were carried out using Shimadzu FT-IR 8400S Japan[16].

Differential scanning calorimetry (DSC): All dynamic DSC studies were carried out on DSC 60, Shimadzu, Japan. Calorimetric measurements were made with empty cell (high purity alpha alumina pans) as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating temperature of 10°C /min. The runs were made in triplicate.

Scanning electron microscopy (SEM): The surface morphology of formulations was determined using a scanning electron microscope (Hitachi S3400, Tokyo, Japan). Samples were mounted on aluminum mount, using double-sided adhesive tape and sputtered by gold under vacuum and were scanned at an accelerating voltage of 15 KV before observation.

Evaluation of pellets

Friability: Friability was determined by using the Roche friabilator tester (Electrolab, India). 10 g of pellets were subjected to impact testing at 25 rpm for 4 min.

Floating time: The floating abilities of the coated effervescent-layered pellets, were determined using 250ml beaker containing 100ml 0.1N HCl. Twenty pellets were placed in the medium and the floating time was measured by visual observation.

Percentage yield: The yield of pellets was determined by the whole weight of pellets formed against the combined weights of drug, polymer and other excipients.

Drug loading: Specific amount (300mg) of crushed pellets were suspended in 100 ml of freshly prepared pH 1.2 with constant agitation at room temperature for 24 h and then filtered. The drug content in the resultant solution was determined by measuring the absorbance at λ_{max} 269nm.

In Vitro **Dissolution:** USP XXIII dissolution apparatus type II was employed in the present studies. Pellets containing 15mg of Pioglitazone HCl were filled in hard gelatin capsules and transferred to the dissolution medium (900ml of pH 1.2 buffer solution). The dissolution medium was stirred at a rate of 75 rpm for 12 hrs maintaining the temperature at 37 ± 0.5ºC. Aliquots of 10ml were withdrawn periodically at 0, 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0 hrs time intervals and drug concentrations were determined by measuring the absorbance at 269 nm.

RESULTS AND DISCUSSION

Based on experimental design, nine formulations of gastroretentive pellets of pioglitazone HCl were formulated and evaluated.

Characterization:

Micromeritic properties: The pH sensitive gastroretentive pellets were evaluated for micromeritic properties, like average size, angle of repose, tapped density, carr's index, friability and percentage yield. Tap density values was found to be in the range 0.82 ± 0.62 gm/cm^3 - 0.92 ± 1.40 gm/cm^3. The angle of repose and Carr's index were in the range of 19.42 ± 0.26 - 26.43 ± 0.44 θ^0 and 8.77 ± 0.90 - 9.39 ± 0.53% for all formulations. The values for angle of repose, Hausner ratio, compressibility index were found to be in good correlation indicating that all formulation possess excellent flow property which confirmed free flowing nature of the pellets. The average pellet size was in the range of 1049 ± 0.51 -1347 ± 0.16µm indicating uniformity of pellets as shown in table no 4.

FT-IR studies: FT-IR studies are used to determine the possible interaction between the drug and polymers used. The existence of an interaction is detected by the alteration, shift or disappearance of a functional group peak of the drug. The prominent peaks of pioglitazone HCl was observed in the region of 3084 cm^{-1} due to the (C-H stretching), a peak at 2996 cm^{-1} due to the C-H stretching, peak at 1743 cm^{-1} observed due to the C = O stretching, peaks at 1610 cm^{-1} C=C stretching and peak at 1243 cm^{-1} corresponds to C-S stretching. It was observed that there was no disappearance or shift in band position of the drug when combined with polymers in indicating that, the drug and polymers were compatible in the formulation as shown in figure no 1.

Differential scanning calorimetry (DSC): The DSC thermograms shows endothermic peaks for the pure drug as well as for the optimised formulation. The temperature To, Tm and Tc are respectively the onset of melt, the melting point and the completion of melt of the drug. The melting point of the pure drug was found to be 199.89 ºC. The melting point of the drug in the optimized formulation (F2) was found to be 196.52 ºC, which indicates that the drug has no interaction with polymers used as shown in figure no 2.

Scanning electron microscopy (SEM): The scanning electron microscopic photograph of optimized formulation (F2) were obtained to observe the surface morphology. SEM photographs of drug loaded pellets were spherical agglomerates

with a slightly rough surface. The surface of the effervescent-layered pellet was slightly smoother and the smoothest was the surface of effervescent-layered pellet coated with polymeric membrane (Chitosan:Eudragit S100) as shown in figure no 3.

Evaluation of pellets:

One of the major factor affecting the extrusion process is the right amount of wet massing liquid content. The right amount of water and isopropyl alcohol levels needs to be optimized for extrusion mass. It was found that if the moisture content of the extrusion mass was less than the lower limit, the mass do not flow satisfactorily through the extruder. In the process of spheronization speed optimization, it was found that at lower speed, more number of rod and dumbbell shaped particles were obtained, where the extrudates resist to convert into pellets. Further increasing the spheronization speed to 1600 rpm for 15 min, narrow sized spheroids were obtained as shown in table no 2 and 3.

The system consisted drug loaded pellet, effervescent layer and gas-entrapped polymeric membrane, respectively. Since sodium bicarbonate alone shall not adhere onto the drug loaded pellets, hydroxyl propyl methyl cellulose was used as a binder in coating of the inner effervescent layer. An ideal coating polymer for a gastroretentive floating system should be water permeable to initiate the effervescent reaction and the floating process rapidly. Therefore, the hydrated coatings should also be impermeable to the generated CO_2 in order to maintain floatation. Regarding the mechanical properties, the polymeric coatings should be flexible in hydrated state to withstand the pressure of the generated gas and to avoid rupturing. According to these reasons, the higher flexible polymer, polymer blend (Chitosan : Eudragit S100), was selected and investigated as a gas entrapped polymeric membrane in this study. Upon contact with the simulated gastric fluid, the fluid penetrates into the effervescent coated layer through the outer coated polymeric membrane. Carbon dioxide was liberated through neutralization reaction and was entrapped in the polymeric membrane.

Friability: The friability of the all formulations ranged from0.43 ± 0.91-0.63 ± 0.45%. This indicated that the coated pellets were quite hard and able to withstand the mechanical stresses of the subsequent coating process. Regarding their mechanical properties, the polymeric coatings
Should be sufficiently flexible in wet state to be able to withstand the pressure of the generated
gas and to avoid rupturing. Due to these reasons, the higher flexibility polymer, an non aqueous polymer blend (Eudragit S100), was chosen and investigated as a gasentrapped polymeric membrane.

Floating lag time: The floating ability of the effervescent-layered pellets coated with polymeric membrane was investigated in respect to ratio of the polymeric coating. Floating of pellets occurred due to generation of CO_2via neutralization reaction. The system should float in a few minutes after contact with gastric fluid to prevent the dosage form from transiting into the small intestine together with food. The floating time of pH sensitive gastroretentive pellets were found to be in a range of 113±1 - 168±1 seconds as shown in table no 5.

Percentage yield: The % yield of pH sensitive gastroretentive pellets were in the range of 77.9 ± 1.7 – 82.6 ± 2.2 % respectively. This indicated that the percentage yield was satisfactorily good.

***In vitro* drug release studies**

The *in vitro* drug release studies were carried in order to ensure the release of the drug to the dissolution medium. The amount of drug released at the end of 12 h for the optimized formulation (F2) was found to be 99.12 ± 0.91 %.

Experimental design

The application of factorial design yielded the following regression equations.

Final equation in terms of Actual Factors

Floating lag time = +136.67 + 23.00*Chitosan[1] -2.67*Chitosan[2] -6.33 * EudragitS100[1] + 0.33 * EudragitS100[2]

%Drug release = +95.07-3.70*Chitosan [1]+0.60*Chitosan [2]+1.03* EudragitS100 [1] + 0.30 *EudragitS100[2]

From the experimental results, the effects of all studied variables and the variable interactions were graphically and statistically interpreted for all responses. The results of ANOVA indicated that all models were significant ($p < 0.05$) for all response parameters investigated. Model simplification was carried out by eliminating non-significant terms ($p > 0.05$) in polynomial equations.

From the results of floating lag time (sec) as shown in 3D graphs(figure 6), it clearly shows that higher concentration of chitosan decreased floating lag time because chitosan is soluble in gastric pH which swells and releases CO_2 via neutralization reaction from inner effervescent coated layer whereas increased amount of eudragitS100 increased floating lag time because eudragit S100 is impermeable in gastric pH.

From the results of *in vitro* drug release as shown in 3D graphs(figure 7), it shows that, lower concentration of chitosan and higher concentration of eudragit S100 was inversely proportional to drug release which retarded drug release whereas higher amounts of chitosan and lower amounts of eudragit S100 increased drug release, since chitosan swells rapidly in gastric pH.

CONCLUSION

pH sensitive gastroretentive pellets based on gas formation technique was successfully optimized using 3^2 factorial design of experimentation to prolong the gastric residence time and increase the overall bioavailability of the drug from dosage form. The system consists of drug loaded pellets, effervescent layer and polymeric membrane. The time to float increased as concentration of eudragitS100 coating level of gas-entrapped polymeric membrane increased. The optimized formulation (F2) could float completely within 113 sec and maintained the buoyancy over a period of 12 h. The *in vitro* release shows that, lower amounts of chitosan and higher amounts of eudragit S100 was inversely proportional to drug release. Both the rapid floating and the sustained release properties were achieved. From the study, it can be concluded that the pellets of pioglitazone HCl prepared by using chitosan and eudragit S100 possess pH sensitive gastroretentive properties and can be used in the treatment of type II diabetes mellitus.

Table No 1: Blend ratio for preparation of coating solution for Chitosan: Eudragit S100 based on factorial design.

Sl.No	Coating weight gain	Polymer blend ratio gm (%)		Chloroform:Propen-2-nol 60:40(ml)
		Chitosan	Eudragit S100	
1	10%	4	15	100ml
2	10%	8	10	100ml
3	10%	8	15	100ml
4	10%	8	20	100ml
5	10%	4	20	100ml
6	10%	6	20	100ml
7	10%	4	10	100ml
8	10%	6	10	100ml
9	10%	6	15	100ml

Table No 2: Optimization of drug loaded pellets on spheronization speed

Spheronization speed (rpm)	Spheroid description
400	Dumbbell shape
800	Dumbbell shape
1400	Dumbbell shape
1600	Spheroids with narrow size range

Table No 3: Optimization of drug loaded pellets on spheronization time

Spheronization speed (rpm)	Spheronization time (min)	Spheroid description
1600	5	Spheroids not formed
	10	Spheroids formed
	15	Spheroids formed

Table No 4: Characterization of pH sensitive gastroretentive pellets

Formulation code	Average size (μm)	Angle of repose θ^0	Tapped density (g/cm^3)	Carr's index (%)	Friability (%)	Drug loading (%)
F-1	1049±0.51	23.13±0.22	0.83±0.64	9.11±0.32	0.55±0.78	23.22±0.45
F-2	1104±0.25	21.41±0.15	0.85±0.92	8.77±0.90	0.62±0.45	19.33±0.63
F-3	1125±0.23	19.42±0.26	0.92±1.40	9.40±0.53	0.56±0.82	21.52±0.43
F-4	1285±0.35	23.22±0.35	0.83±1.01	8.91±0.98	0.43±0.36	19.24±0.92
F-5	1223±0.10	24.22±0.30	0.85±0.55	8.73±1.76	0.51±0.78	20.46±0.41
F-6	1245±0.32	26.43±0.44	0.82±0.82	8.70±2.01	0.62±0.22	21.35±0.87
F-7	1347±0.16	25.16±0.15	0.82±0.62	8.83±1.11	0.42±0.91	22.64±0.32
F-8	1135±0.21	23.42±0.88	0.91±1.43	9.32±0.53	0.55±0.82	21.12±0.81
F-9	1238±0.31	22.11±0.81	0.84±1.41	9.15±0.53	0.48±0.82	20.42±0.65

Standard deviation n=3

Table No 5: Floating lag time of pH sensitive gastroretentive pellets

FORMULATION CODE	FLOATING LAG TIME (sec)
F-1	161±1
F-2	113±1
F-3	116±1
F-4	120±2
F-5	168±2
F-6	140±1
F-7	150±1
F-8	128±1
F-9	134±2

Standard deviation n=3

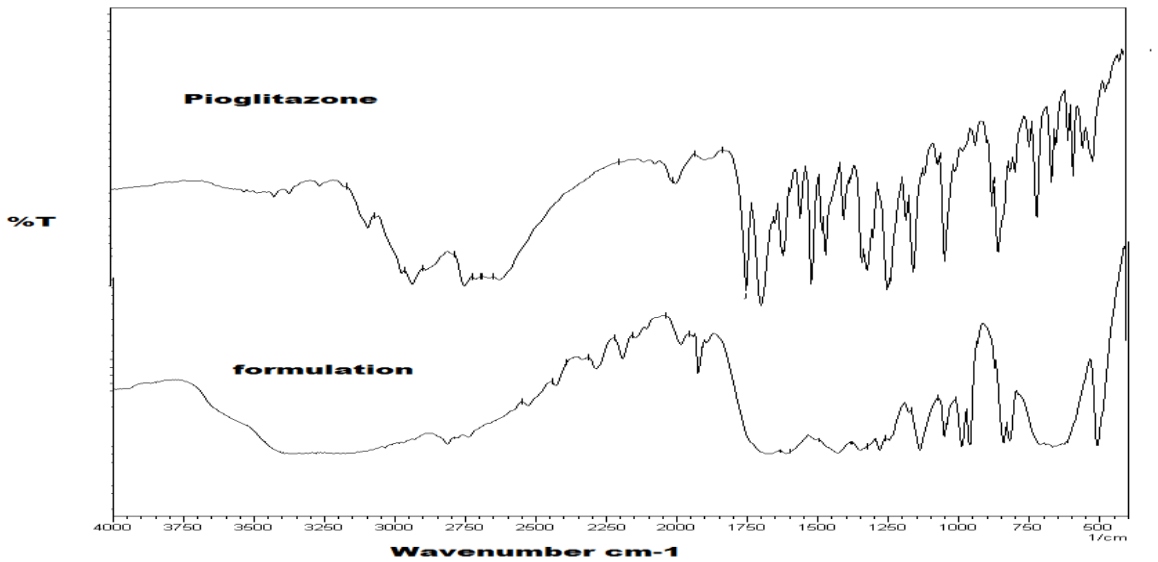

Figure 1: FT-IR spectra of pure drug pioglitazone HCl and formulation (F2)

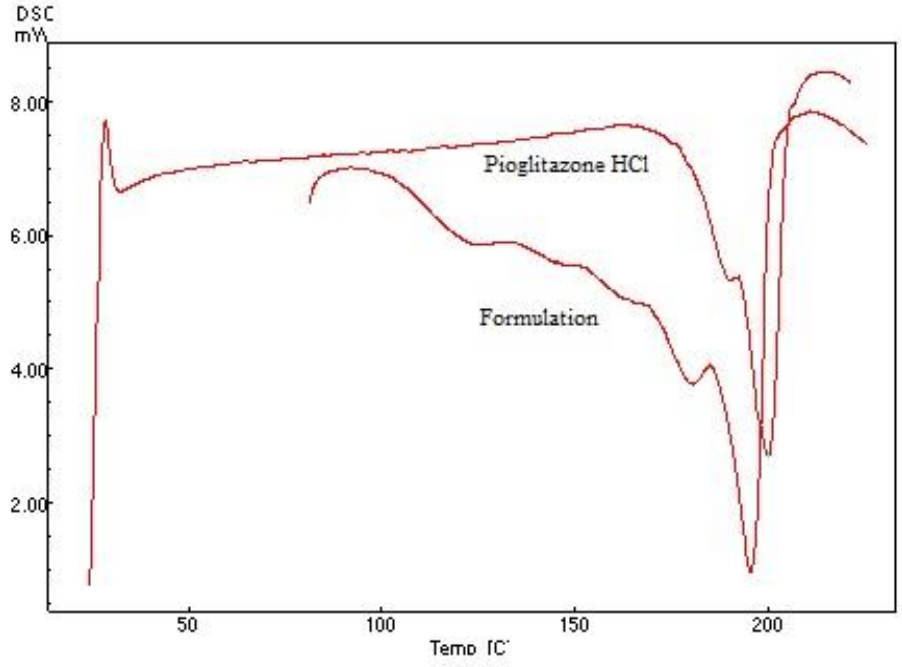

Figure 2: DSC thermograms of pure drug pioglitazone HCl and formulation (F2)

Figure 3: SEM images of formulation F2

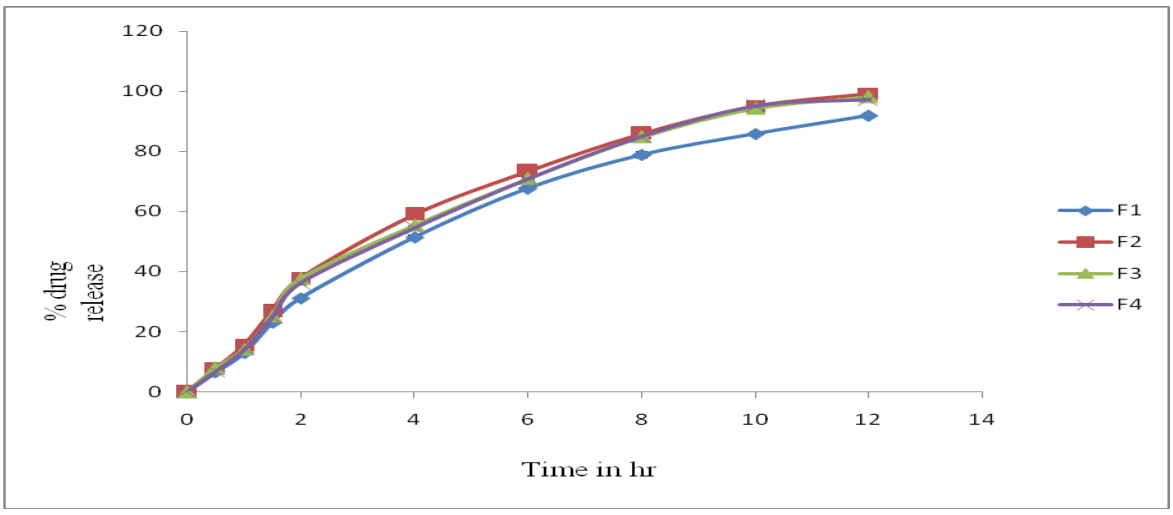

Figure 4: *In vitro* drug release studies of formulations F1-F4

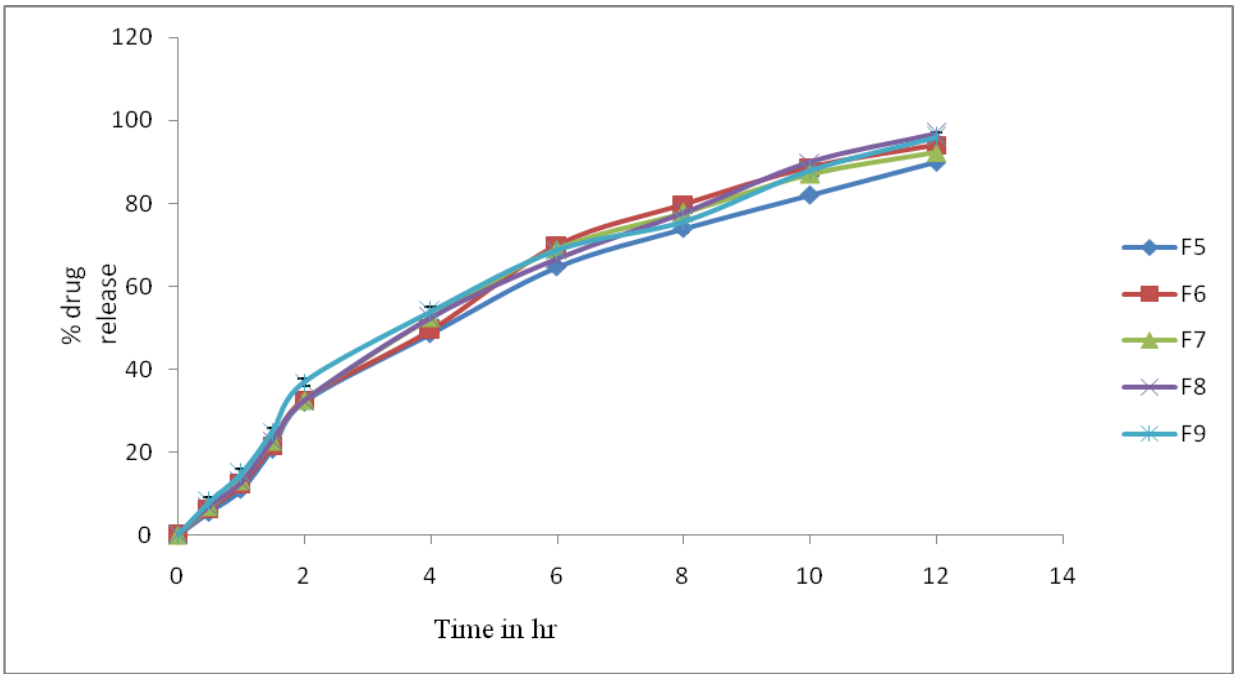

Figure 5: *In vitro* drug release studies of formulations F5-F9

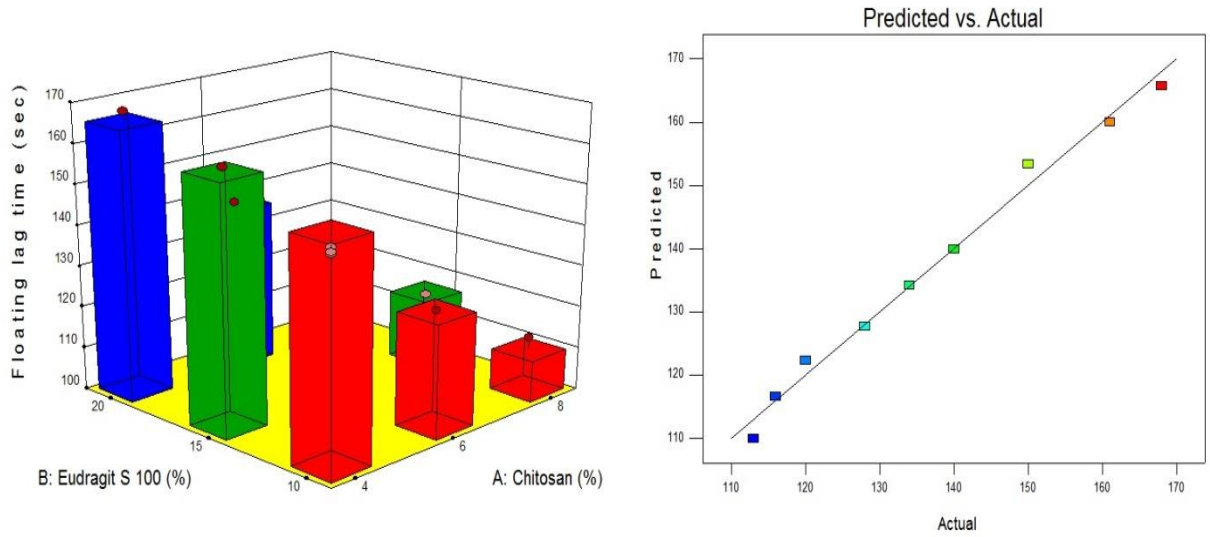

Figure 6: Influence of chitosan and Eudragit S100 on floating lag time (sec)of pH sensitive pellets

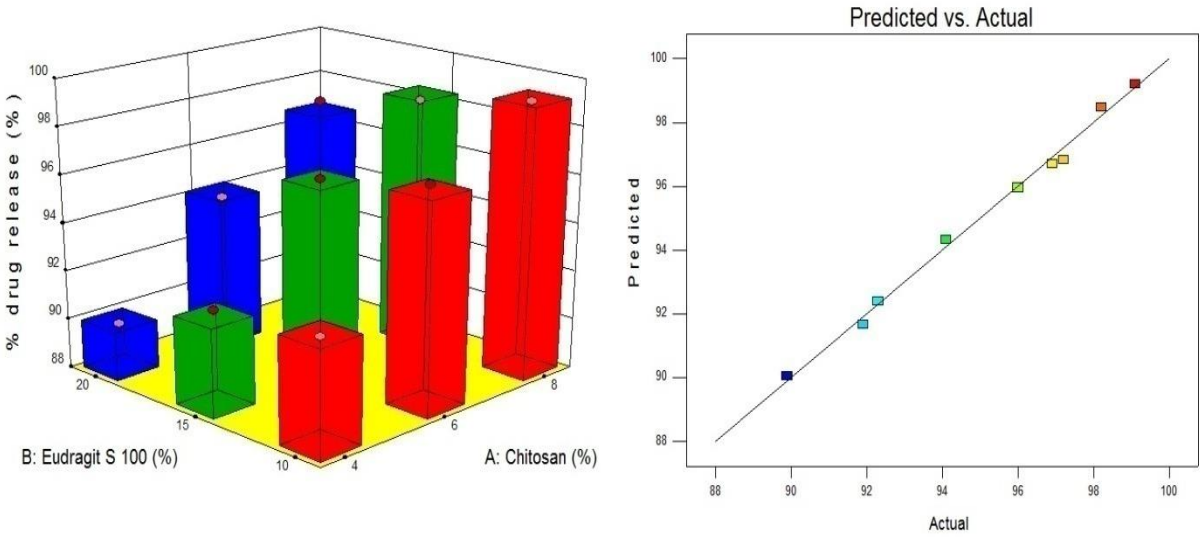

Figure 7: Influence of chitosan and Eudragit S100 on % drug release of pH sensitive pellets.

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