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Preparation and Evaluation of Effervescent Tablets

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Raghuchandan HS*[1], S. B. Puranik[2], Bhavesh Shah[3]

[1]Research Scholar, OPJS University, Churu, Rajasthan, India

[2]Research Guide, OPJS University, Churu, Rajasthan, India

[3]Research Scholar, OPJS University, Churu, Rajasthan, India

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ABSTRACT

The Effervescent floating tablets of Pioglitazonewere prepared by direct compression technique. For each tablet formulation, drug, Carrageenan gum, Aloe vera gel powder, sodium bicarbonate, and other diluents were blended homogeneously for 15 min followed by addition of magnesium stearate. The total weight of each tablet was 250 mg. The amount of Carrageenan gum used was in the range of 30–40 mg, whereas Aloe vera gel powder was used in the range of 40-80 mg. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a Rimek rotary tablet machine. Totally, nine formulations were prepared by changing the amount of the ingredients. FT-IR spectral study revealed that similar characteristic peaks appear with minor differences, for the pure drug and drug formulation, it was confirmed that no chemical interaction had taken place between the drug and the polymer used. The evaluation of thermograms obtained from DSC revealed no interaction between the drug and the excipients. From the thermograms, it was evident that melting point of Pioglitazone had not changed when it was formulated as a floating matrix tablet.

INTRODUCTION

The primary aim of oral controlled drug delivery system is to achieve better bioavailability and release of drug from the system, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine. This can be overcome by altering the physiological state and designing the formulations, by which gastric emptying process can be extended from few minutes to 12 h. A drug can act locally in the stomach in case of *H. Pylori* (tetracycline) or in the proximal part of the intestine by prolonged contact with absorbing area.[1,2]Prolonged gastric retention increases bioavailability, decreases wastage of drugs, increases solubility of drugs, which are less soluble in alkaline pH.[3]These dosage forms prolongs the gastric residence time enabling an extended absorption phase for the local treatment of drugs and better bioavailability for the drugs that are unstable in intestinal or colonic environment.[4,5]Gastric retention can be achieved by mucoadhesion or bio adhesion systems,[6] expansion systems,[7,8] high density systems,[9,10,11] magnetic systems,[12,13,14,] super porous hydrogels,[15,16] raft forming systems,[17,18,19] low density systems,[20,21,22] and floating ion exchange resins.[23]

Pioglitazone is an effective oral anti diabetic agent that belongs to the thiazolidinedione drug class. Pioglitazone belongs to BCS class II and exhibits low and variable oral bioavailability. It is majorly absorbed from stomach[24]. Pioglitazone has a short biological half-life of 3-5 h and is eliminated rapidly[25]. Hence controlled release floating formulations are needed for pioglitazone to improve its oral bioavailability and also to prolong its duration of action and to improve patient compliance.

The present study envisages the designing and development of pharmaceutical dosage forms with gastric floating property to improve the bioavailability of Pioglitazone.

MATERIALS AND METHODS

Materials

Pioglitazone HCl obtained as a gift samples from Dr. Reddy's Laboratories(Hyderabad, India). Carrageenan gum, Aloevera Gel powder and Magnesium stearate were obtained from Loba Chemie, Mumbai, India. Sodium bicarbonate, PVP K 30 and Lactose. All other reagents used in the present study were of analytical reagent grade.

ANALYTICAL METHODS

Pioglitazone: The method described by Pawan K Basniwa was followed.[26]

Stock solution: Pioglitazonein pH 1.2 hydrochloric acid (HCl) buffer (100 µg/ml).

Scanning: From the stock solution, a suitable concentration (10 µg/ml) was prepared with pH 1.2 Hydrochloric acid buffer solution and UV scan was taken between 200-400 nm. The spectrum is given in figure 1. The absorption maxima of 224 nm was selected and utilized for further studies.

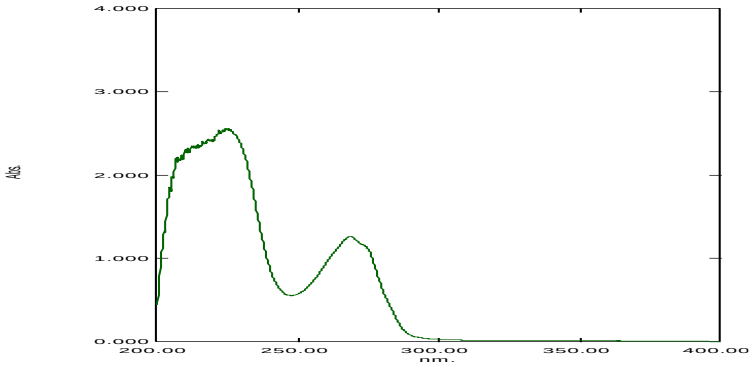

Figure No. 1: UV-Spectra of Pioglitazonein pH 1.2 hydrochloric acid buffer

Standard Plot: From the stock solution, 05,10, 15, 20, and 25 µg/ml solutions of Pioglitazonewere prepared in pH 1.2 hydrochloric acid buffer solution. The absorbance was measured at 224 nm and a graph of concentration versus absorbance was plotted. Standard plot data of Pioglitazonein pH 1.2 hydrochloric acid buffer solution is reported in table 1 and graph in figure 2.

Table No. 1: Standard plot data for Pioglitazonein pH 1.2 hydrochloric acid buffer

Concentration (µg/ml)	Absorbance at 224 nm (mean ± SD*)
0	0
05	0.171± 0.000
10	0.342±0.070
15	0.508± 0.038
20	0.671± 0.102
25	0.837± 0.102

*Standard deviation, n = 3

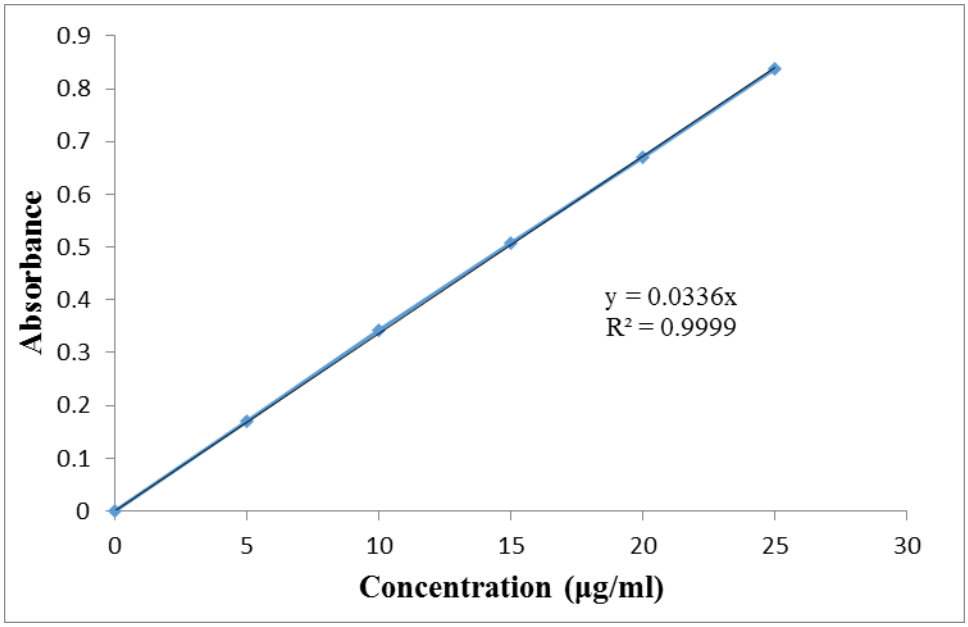

Figure No. 2: Standard plot for Pioglitazonein pH 1.2 hydrochloric acid buffer

Formulation of Effervescent floating tablets[27, 28]

The Effervescent floating tablets of Pioglitazonewere prepared by direct compression technique. For each tablet formulation, drug, Carrageenan gum, Aloe vera gel powder, sodium bicarbonate, and other diluents were blended homogeneously for 15 min followed by addition of magnesium stearate. The total weight of each tablet was 250 mg. The amount of Carrageenan gum used was in the range of 30–40 mg, whereas Aloe vera gel powder was used in the range of 40-80 mg. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a Rimek rotary tablet machine. Totally, nine formulations were prepared by changing the amount of the ingredients as shown in table.

Table No. 2: Formulation chart of effervescent floating Pioglitazone tablets

Ingredients (mg)	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8	EF9
Pioglitazone	15	15	15	15	15	15	15	15	15
Aloevera gel powder	40	40	40	60	60	60	80	80	80
Carrageenan gum	30	35	40	30	35	40	30	35	40
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Lactose	130	125	120	110	105	100	90	85	55
Total weight	250	250	250	250	250	250	250	250	250

Methods

Technological characteristics of floating tablets[29, 30]

Weight variation test

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight.

$$\% \text{ deviation} = \frac{\text{Average weight of tablet} - \text{individual tablet weight}}{\text{Average weight of tablet}} * 100$$

Friability

Ten tablets were weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, de-dusted, and reweighed. The percentage friability of the tablets was calculated using the equation:

$$\% F = \{1-(W_f/W_o)\} \times 100$$

Where, % F is percentage friability, W_o is the initial weight of tablet and W_f is the final weight of tablets after revolutions.

Compressed tablets with a loss of less than 1 % are generally considered acceptable.

Hardness

The hardness of core tablets was measured using Inweka hardness tester. A total of five tablets from each formulation were taken for the study and the average of the three is reported. It is expressed in kg.

Thickness and diameter

Thickness and diameter of the tablets were determined by using Mitutoyo micrometer screw gauge. The average of five tablets from each formulation was taken. It is expressed in millimeter.

Uniformity of drug content

Drug content uniformity in the tablets was determined by randomly selecting 10 tablets and the same were powdered. The quantity equivalent to single dose of the drug was dissolved in HCl buffer solution, pH 1.2 for 5 h with occasional shaking and diluted to 100 ml with buffer. After filtration to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with the buffer. The absorbance was measured at the required λ_{max} using a UV-visible spectrophotometer. The experiments were carried out in triplicate for all formulations and average values were recorded.

The drug content was calculated using the following equation:

% Drug content = Conc. (µg/ml) × Dilution factor × 100/ 50

Drug-excipient compatibility studies[31]

Fourier transforms infrared spectroscopy (FT-IR)

In order to evaluate the integrity and compatibility of the drug in the formulation, drug-excipient interaction studies were performed. Pure drug and optimized formulations were analyzed by Fourier transform infrared (FTIR) spectroscopy. FTIR spectra of pure drug and its formulations were obtained by a FT-IR Shimadzu 8400S (Japan) spectrophotometer using the KBr pellet method. The samples were scanned from 400 to 4,000 cm^{-1}wave number.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed on pure sample of drug and its formulation. Calorimetric measurements were made with empty cell (high purity alpha alumina discs) as the reference. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10 °C min^{-1}. The energy was measured as Joules per kilocalorie.

***In vitro* floating studies[32]**

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type-II (basket) using 900 ml of 0.1 N HCl buffer solutions at 100 rpm at 37 ± 0.5°C. The time required for the formulation to rise to the surface of the dissolution medium and the duration for which the formulation constantly floated on the dissolution medium were noted as floating lag time and total time respectively.

Water uptake studies[33]

The swelling of the polymers was measured by their ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as:

$$WU\ (\%) = \frac{\text{Weight of Swollen tablet- Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

***In vitro* drug release study[34, 35,36]**

The release rate of drug from formulations was determined using USP dissolution testing apparatus II (basket type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37± 0.5 ºC and 50 to 100 rpm. Aliquots (5mL) were withdrawn at regular intervals for 12 h, sample was replaced by its equivalent volume of fresh dissolution medium to maintain the sink condition. The samples were analyzed UV-spectrophotometrically at wavelength corresponding to absorption maxima of the drugs. The release kinetics was fitted into various models using PCP dissolution v2.08 software.

Mechanism of drug release[37,38, 39]

The different mathematical models may be applied for describing the kinetics of the drug release process from dosage forms, the most suited being the one which best fits to the experimental results. The best models describe drug release from pharmaceutical dosage form resulting from a simple phenomenon, or when this phenomenon, by being the rate-limiting step, conditions all the process occurring in the system. The kinetics of release from formulations were determined by finding the best fit of the release data to zero order, first order, matrix(Higuchi), Hixson-Crowell, and Korsmeyer- Peppas plots. Higuchi developed several theoretical models to study release of high and low water-soluble drugs incorporated in the semi-solid and/or solid matrices. According to this model, drug release was described as a square root of time-dependent diffusion process based on Fick's law. This relation can be used to describe drug dissolution from several types of modified release pharmaceutical dosage forms.

$$Q_t = K_H = \sqrt{t}$$

Where, K_H is Higuchi's rate constant, and $Q_t$is the amount of drug released at time *t*. If a plot of square root of time versus cumulative amount of drug release yields a straight line, and the slope is 1 or more than 1, then the particular dosage form is considered to follow Higuchi kinetics of drug release. In some experimental situations the release mechanism deviates from the Fick's equation, following an anomalous behavior (Non-Fickian release). In these cases a more generic equation can be used.

Korsmeyer et al. developed a simple, semi-empirical, relating exponentially the drug release to the lapsed time.

$$Q_t / Q_\alpha = Kt^n$$

Where, $Q_t/Q_\alpha$is the fraction of drug released at time *t*; *K* is the constant comprising a structural and geometric characteristics of the tablets; and *n*, the release exponent, is a parameter that depends on the release mechanism and is thus used to characterize it.

Peppas used this *n* value in order to characterize different release mechanisms. If the *n* value is 0.5 or less, the release mechanism follows Fickian diffusion, and higher values ($0.5 < n < 1$) for mass transfer follow a non-Fickian model (anomalous transport).

Hixson-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows:

$$W_o^{1/3} - W_t^{1/3} = Ks\, t$$

Where W_o is the initial amount of drug, W_t is the remaining amount of drug in dosage form at time t, and K_S is a constant incorporating the surface volume relation.

Stability studies[40]

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The objective of stability testing is to investigate the effect of environmental factors on changes in product quality with time so as to establish its shelf life and recommend its storage conditions.

Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, leading to lower concentration of the drug in the dosage form, hence the stability of pharmaceutical preparation needs to be evaluated. The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity (RH) conditions.

A drug formulation is said to be stable if it fulfills the following requirements:

- It contains at least 90% of the stated active ingredient.
- It contains effective concentration of the added preservatives, if any.
- It does not exhibit discoloration or precipitation, nor develops foul odour.
- It does not develop irritation or toxicity.

Formulations were packed in a screw capped bottle and studies were carried out for 12 months by keeping at:

- 25± 2°C and 60 ± 5% RH

- 30 ± 2°C and 65 ± 5% RH

and for 6 months at accelerated storage condition

- 40 ± 2°C and 75 ± 5% RH

Samples were withdrawn on 0, 3, 6 and 12 months for long term storage condition and 0, 3 and 6 months for accelerated storage condition and checked for changes in physical appearance and drug content as per ICH Q1A (R_2) guidelines. Graphs were plotted using Sigmaplot 12.0 to determine the statistical significance.

Results obtained in the methods and the conclusions arrived from them are provided in the following chapters.

RESULTS AND DISCUSSION

Technological characteristics of floating tablets

The hardness of prepared floating tablets ranged between 4.2±1.53to 6.2±0.32 Kg depending upon the mixture of the polymer used. The friability of the tablet formulation varied between 0.37±0.01to 0.67±0.17%. The weight variation of prepared tablet formulation complies with Pharmacopeia limits. The thickness was around 3.9 mm. The assay for drug content varied between 98.64±0.20 to 101.07±0.54%. The results of these parameters are given in Table 3.

Table No. 3: Physical properties of effervescent floating tablets of Pioglitazone

Batch	Weight Variation	Hardness* (Kg)	Friability* (%)	Content Uniformity* (%)	Thickness* (mm)	Floating lag* time(s)	Max swelling* (%)
EF 1	Pass	4.7±0.28	0.67±0.17	99.65±0.83	3.9±0.58	63±2.3	296±8.5
EF2	Pass	6.2±0.32	0.44±0.37	99.55±0.63	3.9±0.66	65±3.2	285±7.9
EF3	Pass	5.5±0.72	0.37±0.01	99.32±0.86	3.9±0.78	65±2.7	262±6.6
EF4	Pass	5.9±0.33	0.48±0.24	97.63±0.75	3.9±0.67	75±2.5	345±8.8
EF5	Pass	4.9±0.44	0.56±0.87	101.07±0.54	3.9±0.58	79±2.6	365±7.6
EF6	Pass	4.7±0.86	0.60±0.86	101.05±0.72	3.9±0.79	75±3.7	361±8.5
EF7	Pass	4.3±0.36	0.52±0.53	98.64±0.20	3.9±0.31	86±3.9	427±9.3
EF8	Pass	4.2±1.53	0.51±0.87	99.47±0.81	3.9±0.52	86±3.3	457±6.5
EF9	Pass	4.6±0.45	0.48±0.67	98.65±0.86	3.9±0.75	86±2.2	483±4.6

*Standard deviation, n=3

Fourier transform infrared spectroscopy (FT-IR)

The spectrum was measured in the solid state as Potassium bromide dispersion. The bands were recorded using the FT-IR technique. FT-IR spectral study revealed that similar characteristic peaks appear with minor differences, for the pure drug and drug formulation, as shown in figure 3. For drug and formulation, N-H stretching showed at 3363.97 and 3350.46 cm^{-1} respectively. For drug vibration (C=O) was 1745.64 and 1689.53 and for formulation 1743.71 & 1687.77 cm^{-1}. For C-O Ar group for drug and formulation 1242.20 and 1242.80 respectively. Similarly, 1612.54 and 1622.19 for drug and formulation respectively. Hence it was confirmed that no chemical interaction had taken place between the drug and the polymer used.

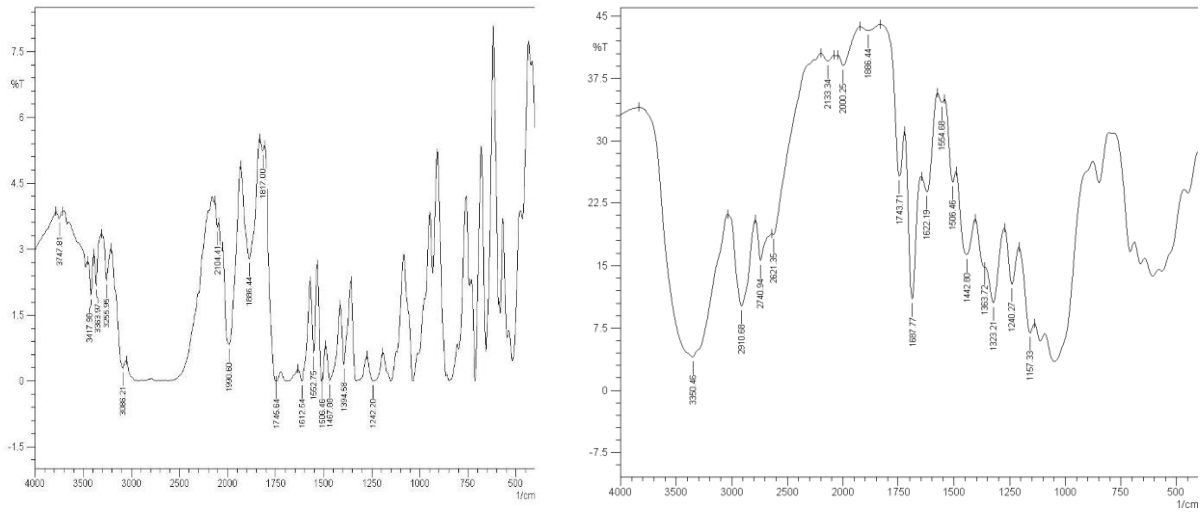

Figure No. 3: FT-IR Spectra of effervescent floating tablet of Pioglitazone (EF1) and Pioglitazone pure drug

Differential scanning calorimetry (DSC)

DSC is a quick and trustworthy method to screen drug and excipient compatibility, and to provide maximum information about the possible interactions. DSC study was carried out for Pioglitazone and its formulation EF1. Thermogram of pure drug shows a sharp endothermic peak at 203.21^{o}C, which corresponds to its melting point. Matrix tablet formulation EF1 also showed endothermic peak at 200^{o}C, which corresponds to the melting point of the drug. The evaluation of thermograms obtained from DSC revealed no interaction between the drug and the excipients. From the thermograms, it was evident that melting point of Pioglitazone had

not changed when it was formulated as a floating matrix tablet. The thermograms obtained are presented in figure 4.

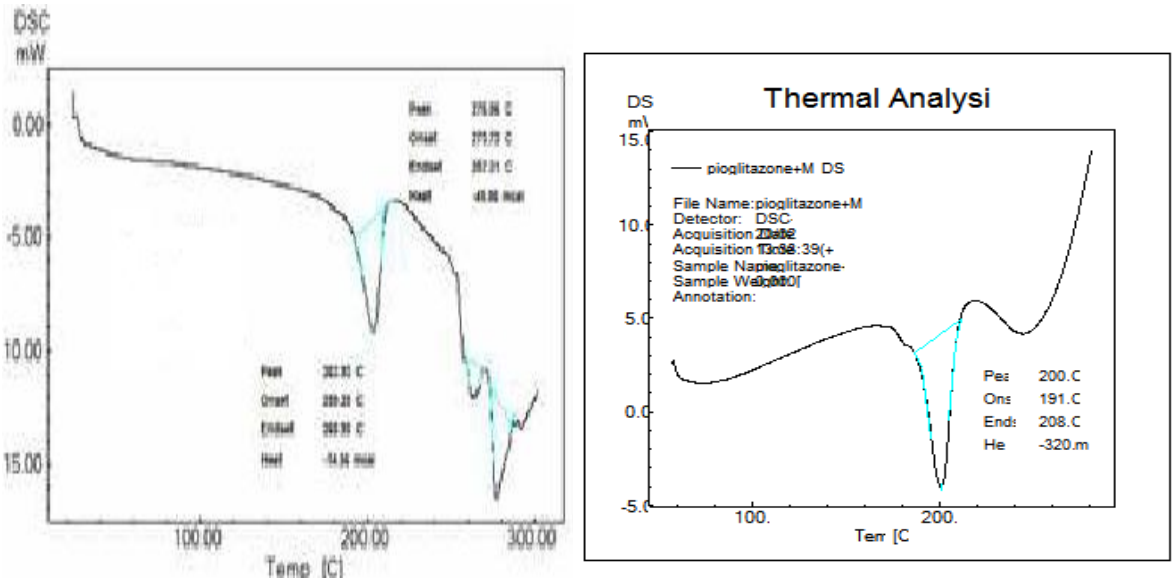

Figure No. 4: DSC thermograms of effervescent floating tablet of Pioglitazone (EF1) and Pioglitazone pure drug

***In vitro* buoyancy studies**

To provide *in vitro* buoyancy, an effervescent approach was adopted. Sodium bicarbonate was added as a gas-generating agent. 0.1 N HCl was used as dissolution medium to the tablet matrix, the acidic fluid interacted with Sodium bicarbonate resulting in the generation of CO_2. The generated gas was entrapped and protected within the gel, formed by the hydration of polymers. The density of the tablet fell below 1g/ml, the tablet became buoyant. Polymers produced tablets with good gel strength, entrapping CO_2 within and impart stability and persistent buoyancy. The system need to float in a few minutes after contact with gastric fluid, to prevent the dosage form from being pushed into the small intestine together with food. Thus, Sodium bicarbonate was essential to achieve optimum buoyancy. Normally, gastric emptying time was 4 h. The extended gastric residence time of the drug in the stomach caused increased absorption due to the fact that the proximal part of the intestine was the main absorption site for pioglitazone. Moreover, during formation of the floating tablets, evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix. The duration of floating and floating behavior is presented in figure 5.

At initial time

At 18th Sec

At 8th h

Figure No. 5: Photographs of in vitro floating behavior of effervescent floating tablet at different time intervals

Water uptake studies

The polymers swelling could be determined by water uptake. The % swelling of the tablet was determined at different predetermined time intervals. The complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations. The maximum percentage of swelling of EF8, when compared to all other formulations and least % swelling was found in EF5. Water uptake profile is shown in figure 6. Rapid increase in % swelling was observed in EF1, EF4, and EF8 at 1 h. EF8 showed a gradual increase in swelling till 8 h. As described by Seipmann and Peppas diffusion of drug significantly depends on the water content in the tablet. This may be because the mobility of the polymer chains strongly depends on the water content of the

system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling to the system. Also, this higher water content could predict the higher penetration of the gastric fluid into the tablet, leading to faster carbon dioxide gas generation, and thus reduction in the floating lag time. Consequently, faster and higher swelling of the tablet led to an increase in the dimensions of the tablet, leading to increasing the gel barrier and thus decreasing diffusion rates. The swelling behaviour of tablet from 0 min to 8 h is shown in figure 7. All the tablets showed better radial and axial swelling, but maximum was shown by EF8.

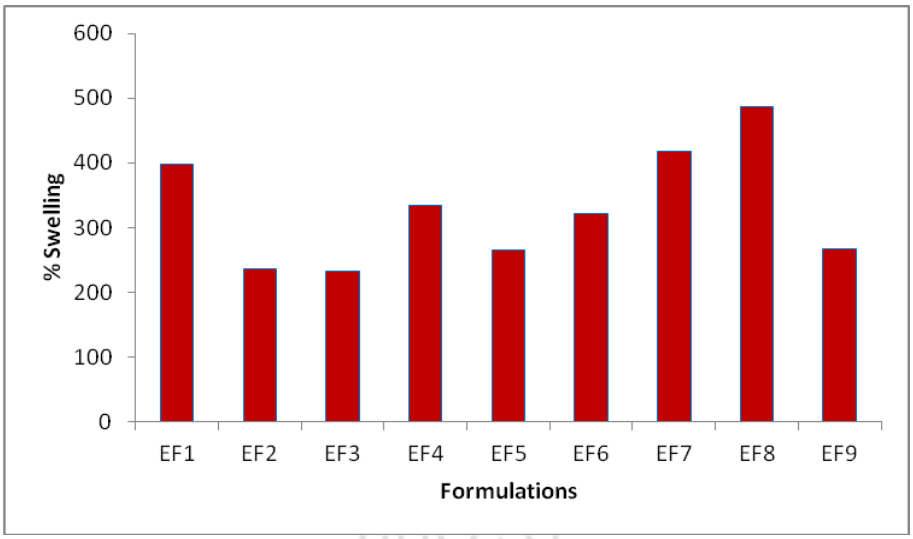

Figure No. 6: % swelling index of floating tablets of Pioglitazone at the end of 8 h

Figure No. 7: Axial and radial Swelling of Pioglitazone effervescent floating tablet

***In vitro* drug release studies**

It has been reported that floating drug delivery systems can prolong the gastric retention time and thus increase the overall bioavailability of drug like Pioglitazone that shows better absorption at the proximal part of the intestine. The concentration of gum, polymer, and diluent had a remarkable influence on the drug release. Increase in the concentration of gum with decrease in lactose concentration, decreased the drug release. This may be due to the formation of thick gel barrier. The *in vitro* drug release profile is presented in figures 8. The EF1, EF5, EF6, and EF9, exhibited more than 75% drug release at 12 h. The EF1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost up to 12 h. B8 showed the least drug release among all other formulations; this may be due to the formation of a thick gel barrier on the tablet. As the thickness of the gel barrier increased, the drug took more time to diffuse through it; this was observed in other formulations which showed higher swelling index. However, this was not true in case of EF1 because of the presence of higher concentration of lactose. The controlled release of drug from the formulations might be because of the diffusion of release medium into the matrix, which in turn would have caused drug diffusion out of the tablets. The ideal controlled drug delivery systems should release the drug in a pre-determined manner. The objectives of the systems were to ensure safety and efficacy of the drugs, as well as improve patient compliance. The results showed that the Carrageen gum could be used for the preparation of gastric floating controlled delivery systems.

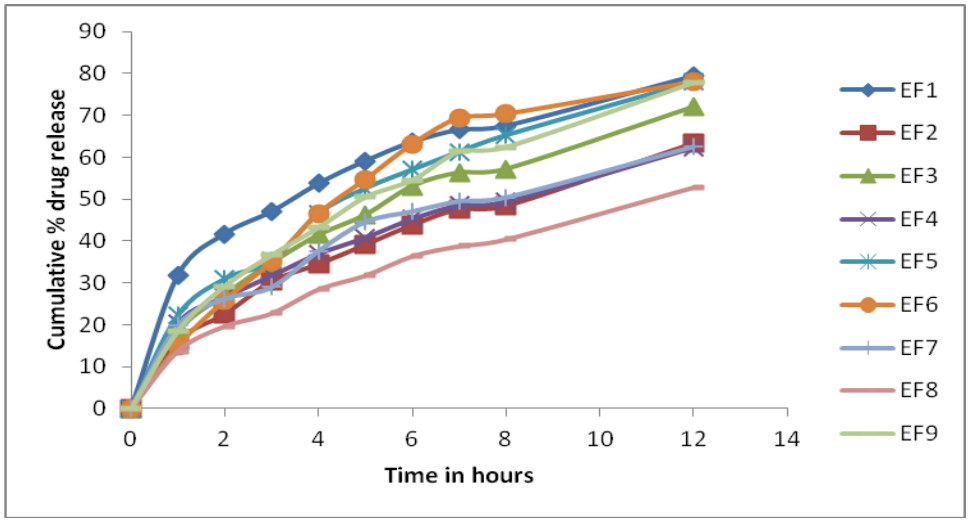

Figure No. 8: *In vitro* drug release profiles of Pioglitazone effervescent floating tablets (EF1-EF9)

Mathematical model fitting of obtained drug release data

The *in vitro* drug dissolution profiles were fitted to various models and release data was analyzed on the basis of Korsmeyer-Peppas equation and Higuchi kinetics. The diffusion exponent ranges from 0.3772–0.6998. The release rates *k* and *n* values of each model were calculated by PCP disso v2.08 software. Co-efficients of correlation (R^2) were used to evaluate the accuracy of the model fitting. The R^2, *k*, and *n* values are given in table 6.08. On calculating and comparing R^2 values for, Korsmeyer-Peppas, Matrix, and other models, EF4, EF5, and EF7, gave a good fit to the Matrix model, and the remaining formulations best fitted the Korsmeyer-Peppas model. EF1, EF4 and EF7 exhibited Fickian release and other formulations showed non-Fickian or anomalous release. EF4 and EF7 best fitted to the matrix model with Fickian release; B5 best fitted to the matrix model with non-Fickian release. If the value of '*n*' in Korsmeyer-Peppas is 0.5 or less, the release mechanism follows a Fickian diffusion, and for anomalous or non-Fickian, release the release is mainly by diffusion with *n* values between 0.5-1. This model was used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well-known or, when more than one type of release phenomenon could be involved. The fundamental of diffusion is based on Fick's laws, which describes the macroscopic transport of molecules by a concentration gradient.

Table No. 4: Kinetic treatment of dissolution profile of tablets (Values of r^2, k, and n for tablets) and mechanism of drug release

Batch	Korsmeyer – Peppas			Matrix		Mechanism of drug release	Release kinetics
	n	R^2	k	R^2	k		
EF1	0.3772	0.9982	32.1077	0.9812	25.7943	Fickian	Peppas
EF2	0.5738	0.9983	16.1110	0.9953	18.3367	Non-Fickian	Peppas
EF3	0.5715	0.9976	18.8613	0.9967	21.3088	Non-Fickian	Peppas
EF4	0.4661	0.9983	19.9024	0.9987	18.7889	Fickian	Matrix
EF5	0.5381	0.9949	21.8757	0.9968	23.3909	Non-Fickian	Matrix
EF6	0.6998	0.9867	17.2306	0.9776	24.3020	Non-Fickian	Peppas
EF7	0.4964	0.9898	18.1986	0.9950	19.0932	Fickian	Matrix
EF8	0.5676	0.9982	13.6702	0.9957	15.3660	Non-Fickian	Peppas
EF9	0.6209	0.9976	18.2819	0.9938	22.5235	Non-Fickian	Peppas

6.9 Stability studies

Stability studies were performed for the optimized formulation FE1to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25ºC/60% RH, 30ºC/65% RH for 12 months and 40ºC/75% RH for 6 months. There was no significant change in the physical appearance and drug content during the study period. The results of drug content determination during stability testing period are reported in table 5.

Results showed that changes in the parameters evaluated, were very small and were not significant.

Table No. 5: Stability study data of effervescent floating tablet formulation (EF1) of Pioglitazone

Stability condition	Sampling interval (months)	Physical appearance	% Drug content B1 (mean ± S.D*)
25º±2ºC/60±5% RH	**0**	No change	99.36 ± 0.14
	3	No change	99.21 ± 0.10
	6	No change	98.44 ± 0.14
	12	No change	98.36 ± 0.17
30º±2ºC/65±5% RH	**0**	No change	99.36 ± 0.18
	3	No change	99.13 ± 0.13
	6	No change	98.68 ± 0.14
	12	No change	98.14 ± 0.12
40º±2ºC/75±5% RH	**0**	No change	99.36 ± 0.95
	3	No change	98.61 ± 0.77
	6	No change	96.35 ± 0.22

*Standard deviation, n=3

SUMMARY AND CONCLUSION

The Effervescent floating tablets of Pioglitazonewere prepared by direct compression technique. For each tablet formulation, drug, Carrageenan gum, Aloe vera gel powder, sodium bicarbonate, and other diluents were blended homogeneously for 15 min followed by addition of magnesium stearate. The total weight of each tablet was 250 mg. The amount of Carrageenan gum used was in the range of 30–40 mg, whereas Aloe vera gel powder was

used in the range of 40-80 mg. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a Rimek rotary tablet machine. Totally, nine formulations were prepared by changing the amount of the ingredients.

The hardness of prepared floating tablets ranged between 4.2±1.53to 6.2±0.32 Kg depending upon the mixture of the polymer used. The friability of the tablet formulation varied between 0.37±0.01to 0.67±0.17%. The weight variation of prepared tablet formulation complies with Pharmacopeia limits. The thickness was around 3.9 mm. The assay for drug content varied between 98.64±0.20 to 101.07±0.54%. The spectrum was measured in the solid state as Potassium bromide dispersion. The bands were recorded using the FT-IR technique. FT-IR spectral study revealed that similar characteristic peaks appear with minor differences, for the pure drug and drug formulation, as shown in figure 3. For drug and formulation, N-H stretching showed at 3363.97 and 3350.46 cm^{-1} respectively. For drug vibration (C=O) was 1745.64 and 1689.53 and for formulation 1743.71 & 1687.77 cm^{-1}. For C-O Ar group for drug and formulation 1242.20 and 1242.80 respectively. Similarly, 1612.54 and 1622.19 for drug and formulation respectively. Hence it was confirmed that no chemical interaction had taken place between the drug and the polymer used.

The evaluation of thermograms obtained from DSC revealed no interaction between the drug and the excipients.

From the thermograms, it was evident that melting point of Pioglitazone had not changed when it was formulated as a floating matrix tablet.

As described by Seipmann and Peppas diffusion of drug significantly depends on the water content in the tablet. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling to the system. Also, this higher water content could predict the higher penetration of the gastric fluid into the tablet, leading to faster carbon dioxide gas generation, and thus reduction in the floating lag time. Consequently, faster and higher swelling of the tablet led to an increase in the dimensions of the tablet, leading to increasing the gel barrier and thus decreasing diffusion rates. The swelling behaviour of tablet from 0 min to 8 h is shown in figure 7. All the tablets showed better radial and axial swelling, but maximum was shown by EF8.

The objectives of the systems were to ensure safety and efficacy of the drugs, as well as improve patient compliance. The results showed that the Carrageen gum could be used for the preparation of gastric floating controlled delivery systems.

The stability studies for the optimized formulation FE1 were carried out at 25ºC/60% RH, 30ºC/65% RH for 12 months and 40ºC/75% RH for 6 months. There was no significant change in the physical appearance and drug content during the study period.

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