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Development and Evaluation of Colon Specific Sustained Release Gel Beads of Aceclofenac

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Abstract

The aim of this research was to develop controlled and sustained release formulation- gel beads of Aceclofenac, a non-steroidal anti-inflammatory drug and to study the effects of Eudragit coating on the release of Aceclofenac. The main objective was to develop a colon targeted drug delivery system to minimize or eliminate drug release in the upper gastro intestinal (GI) tract as well as to minimize GI adverse effects associated with NSAIDs. Alginate beads of Aceclofenac were formulated by ionotropic gelation and the variablesstudied.The prepared Eudragit S100 coated gel beads of aceclofenac were characterized by FTIR and DSC which confirmed the absence of any drug interaction. SEM analysis revealed increase in size of the beads and smooth surface after coatingas compared to the uncoated beads. The mean particle size was found to increase with the increase in sodium alginate concentration and decrease in concentration of calcium chloride. The %Drug Entrapment Efficiency of the prepared gel beads formulations was found in the range of 66.53±0.21 to 82.47±0.38and increased with increasein concentration of sodium alginate and calcium chloride. Reswelling time analysis revealed higher reswelling time at pH1.2 for the coated aceclofenac gel beads than at pH 7.4. With the increase in polymer and $CaCl_2$ conc. the coated beads show slow *invitro* drug release rates in dissolution media of different pH particularly in pH 1.2 (0.1N HCl). The results clearly demonstrate that eudragit coated gel beads of Aceclofenac prepared by ionotropic gelation technique could be successfully used as a prospective carrier for sustained drug deliveryand preventing GI side effects.

KEYWORDS: Aceclofenac, Eudragit S100, Alginate, Beads, Sustained release, coating.

1. INTRODUCTION

Oral drug delivery system is the most desirable, preferable and suitable route for the administration of therapeutic and pharmaceutical agents for administration.Oral sustained release drug delivery systems are formulated to release active ingredient gradually and predictably over

a long period and is successful in overcoming the limitations of conventional therapy (Ratnaparkhi & Gupta, 2013). The goal in designing sustained or controlled delivery system is toreduce the frequency of dosing or to increase the effectiveness of thedrug by localization at the site of action, reducing the dose required, orproviding uniform drug delivery (Sahoo et al., 2007).It should be able to achieve optimum therapeutic drug concentration in the blood with minimum fluctuation, improving therapy, safety, efficacy and patient compliance (Yie W. Chein, 1992).

Non-steroidal anti-inflammatory drugs (NSAIDs) generally are rapidly and completely absorbed after oral administration, reaching a peak plasma concentration in 1 to 3 hours after oral administration of the drug.The GI intolerance of NSAIDs is not only related to the inhibition of the prostaglandin synthesis but also to acute local contact of the drug with gastric mucosa when it is given orally.NSAIDs have commonly been associated with upper gastrointestinal (GI) tract side effects including a high incidence of gastric and duodenal ulceration.Attempts have been made to improve therapeutic efficacy and reduce the severity of upper GI side effects associated with various NSAIDs through modified release dosage forms of NSAIDs such as enteric-coating (EC) or sustained release (SR) formulations (Becker et al., 2004).

Aceclofenac is a non-steroidal anti-inflammatory drug, widely used inthe management of osteoarthritis, rheumatoid arthritis and ankylosingspondylitis (Raj, 2013).As with most NSAIDs, irritation of the gastrointestinal (GI) tract is one of the major side effects reported after oral administration of aceclofenac (Kilor et al., 2010).The plasma elimination half-life of Aceclofenac is around1.8-3.5h;therefore it is necessary to be administered frequently in orderto maintain the desired concentration (usually 2-3 times a day).It is generally administered in a therapeutic dose of 100 mg twice daily (Manjanna1 et al., 2013).Therefore, Aceclofenac is an ideal candidate for sustained release formulation, resulting in more reproducible drug absorption and reducing the risk of local irritations of GIT.

Literature reports various ways to overcome the GI side effects as well as dosing frequency of aceclofenac. The acute local contact of aceclofenac was overcome by formulating a combination of extended-release NSAID and immediate-release prostaglandins (Franz, 2007), dual-release compositions of Cox-2 inhibitors (Desai et al., 2007). Improvement in water solubility and hence bioavailability of aceclofenac has been achieved by formulation of soft capsules containing drug and solubilizers (Yong et al., 2007), spherical agglomerates using PVP and sodium alginate (Mutalik et al., 2007), complexation with HP-β-cyclodextrin (Dahiyaet al., 2006), solid dispersions with mixed surfactants (Joshi et., 2006),encapsulating the drug in nano-vesicle or micro-vesicle (Abdellatif &Abou-Taleb, 2016). These approaches improve the dissolution of aceclofenac, but none of these addresses the problem of GI side effects due to Aceclofenac.

The present study includes the preparation of gel beads of Aceclofenac by ionotropic gelation technique. Alginatebeads can be prepared by extruding a solution of sodium alginatecontaining the desired drug or protein, as droplets, into a divalentcross - linking solution such as Calcium

chloride (Ca^{2+})(Bokkhima et al., 2016).Gelation occurs when the extended chain sequences of these acids adopt a regular twofold conformation and dimerize by chelating calcium, forming the so called egg-box' structure(Abdellatif et al., 2016). These alginate beads then release the drug in a sustained/controlled manner. The alginate beads are then coated with Eudragit S100 which will provide the enteric coating of these beadsthus preventing the drug to come into contact with ulcer-prone area of GI lining and hence will avoid GI toxicity (Agarwal et al ., 2015).Previously, ionotropic gelation method has been utilized for the purpose of extended/ sustained release and colon targeted delivery of the drugs like Venlafaxine hydrochloride (Jain & Datta, 2016), Metronidazole (Amin et al., 2016), Diclofenac sodium (Sinhaa et al., 2015), Flurbiprofen(Abdellatif et al., 2016), Metformin hydrochloride (Nayak et al., 2016). Thus ionotropic gelation technique may be utilized to formulate sustained release gel beads of aceclofenac with eudragit S100 coating (Raval et al., 2013) to overcome the GI side effects.

2. MATERIAL AND METHOD

2.1 Material

Aceclofenac was received as a gift sample from Akums Pvt Ltd, Haridwar, India. Sodium alginate AR was procured from Alliance global, Delhi, India. Eudragit S100, Calcium chloride AR and HPMC was procured from Central Drug House, New Delhi, India. Other chemicals and reagents used were purchased from S.D. Fine Chemicals, Ltd. (Mumbai, India)and were of analytical grade. All drug solutions and buffer solutions were freshly prepared before use.

2.2 Formulation of Aceclofenac sodium alginate beads

The beads of Aceclofenac were prepared by ionotropic gelationtechniqueaccording to the formula given in Table 1. Accurately weighed drug was added to 100ml of Distilled Water and stirred on magnetic stirrer. HPMC and sodium alginate were then to the solution and stirring continued till uniform polyelectrolyte solution was formed.Calcium chloride was separately dissolved in 100 ml water and stirred on magnetic stirrer. Poly electrolyte solution of drug and polymer was added drop by drop to the $CaCl_2$ solution with the help of 21 G needle.Stirring at 500 rpm was further continued till a homogenous dispersion was formed. Theformed alginate beads were cured at different time interval. Onexpiration of this period the solution of cross linking agent wasdecanted and the alginate beads were washed repetitively for threetimes with 50ml deionized water. The alginate beads were thereafterdried at 60°C for 2h in a hot air oven (Sahoo et al., 2007; Bokkhima et al., 2016).

2.3 Coating of gel beads of Aceclofenac

Aceclofenac gel beads prepared by ionotropic gelation method were coated by Eudragit S100.2%, w/v solution of EU S100 was preparedby dissolving 2.0g Eudragit in 100ml distilled water. The drug loaded alginate wet beads were placed in this solution and was kept aside for 30

min on a magnetic stirrer.Coated gel beads were now collected and washed with water (deionized) and then air dried for whole night (Bansala et al., 2016).

Table 1: List of formulations of Aceclofenac

Formulation	Drug (mg)	Sodium Alginate	HPMC	Calcium Chloride	Eudragit S100
F_1	200	2%	.20%	3%	2%
F_2	200	3%	.20%	3%	2%
F_3	200	4%	.20%	3%	2%
F_4	200	5%	.20%	3%	2%
F_5	200	2%	.20%	4%	2%
F_6	200	3%	.20%	4%	2%
F_7	200	4%	.20%	4%	2%
F_8	200	5%	.20%	4%	2%
F_9	200	2%	.20%	5%	2%
F_{10}	200	3%	.20%	5%	2%
F_{11}	200	4%	.20%	5%	2%
F_{12}	200	5%	.20%	5%	2%

2.4 Evaluation Parameters

2.4.1 Percentage Yield

The % yield of the gel beads was determined from total weight of beads obtained and total weight of drug and polymers used.

2.4.2 Physicochemical Characterization

The particle size distribution analysis was performed by using an optical microscope. A minimum of 50 dried beads per batch were counted for the determination of particle size and mean diameter is calculated (Yellanki and Nerella, 2010).

The shape and surface characteristics of beads were observed bySEM (Scanning Electron Microscopy). The samples of beads were mounted on the stubs and sputter which were coated with the gold in Bio-rad E-5200 auto sputter coated. It was operated at an acceleration voltage of 15Kv.

Fourier Transform Infrared (FTIR) analysis was carried out with the help of Shimadzu 8400 FTIR Spectrometer, Japan by KBr pellets method at the range of 4000 to 400cm^{-1}.FTIR of drug alone and with polymers were recorded and spectra were plotted to study the drug interactions.

Differential Scanning Colorimetry (DSC) was performed using DSC-60 Shimadzu, Japanand is used for recording the thermal behaviour of drug alone and of the mixture of drug &

polymers.For DSC study the sample was warmed in sealedaluminium pans at a rate of 50°C/min over a temperature range of 25 to 2500˚Cunder nitrogen gas at a flow rate of 30 ml/min.

2.4.3 Drug Entrapment Efficiency

Entrapment efficiency was calculated to determine the ability of microbeads to entrap the drug. About 50 mg of accurately weighed drug loaded gel beads were crushed in a glass mortar and pestle and mixed with 100 ml phosphate buffer (pH 6.8) and kept for 24 hours. The solution was stirred on a magnetic stirrer for 30 min, filtered and 1ml of the filtrate after dilution wasanalyzed spectrophotometrically at 274nm (Rajest et al., 2004). The drug entrapment efficiency was calculated as per the following formula. Concentration of drug was calculated with the help of standard calibration curve of aceclofenac.

2.4.4 Reswelling Time Study

The swelling properties of the drug loaded microbeads (both coated and uncoated) were determined in buffer solution of two different pH range (i.e. 1.2 and 6.8 buffer solutions).10mg of dried coated and uncoated beads were placed in a beaker to which 100ml of buffer solutions was added and then allowed to swell at 37°C. Coated gel beads were observed visually and the time was recorded with the help of stopwatch at which beads reswell (Hu et al., 2015).

2.4.5 *In Vitro* Drug Release Study

The release profiles of Aceclofenac from coated gel beads were examined in three different buffer solutions (pH 1.2, 6.8 &7.4) to mimic the various physiological GI-tracts. The media of pH 1.2 represented the gastric condition; pH 6.8 was a compromise condition between pH of the gastric and small intestine and pH 7.4, which is simulated intestinal fluid. The study was carried out in the Rotating Paddle type Dissolution Apparatus at constant speed (100 rpm) and the temperature of themedium was maintained at 37°±0.5°C for 8 hours.100 mg of drug loaded coated alginate beads were evaluated fordrug release.The dissolution studies were carried out in 900 mlof pH 1.2 buffersfor two hours.Aliquots of 10 ml every 60 min were withdrawn and immediately replaced thedissolution medium with fresh buffer solution to maintain sink conditions.After 2 hours the dissolution medium was replaced with fresh phosphate buffer solution of pH 6.8 and dissolution process was continued for 4 hours.After 6 hours from zero the phosphate buffer solution was replaced with fresh phosphate buffer solution of pH 7.4 for 2 hours. Process of sampling was repeated same as above. The samples were taken at the following intervals of 1, 2, 3, 4, 5, 6, 7 and 8 hours respectively.The sampleswithdrawn were filtered through a 0.45 µm membrane filter and after appropriate dilution,and then estimated for aceclofenac concentration using UV spectrophotometer (Mutalik et al.,2008

2.4.6 Dissolution Kinetics of Drug Release

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic mode (cumulative amount of drug released vs. time), First order (log cumulative percentage of drug remaining vs. time), Higuchi's model (cumulative percentage of drug released vs. square root of time), and Korsmeyer's (log cumulative percentage of drug released vs. log time).

3. RESULT AND DISCUSSION

3.1 Percentage Yield

The percentage yield of the coated gel beads was found in the range of 73.25±0.22 to 89.51±0.24%(Table 2).The results revealed that the percentage yield of the formulation was found to with the increase in sodium alginate concentration and $CaCl_2$ concentration. It was observed from the results that formulation F11 showed highest 89.51 % yield.

3.2 Physicochemical Characterization

The particle size of prepared Aceclofenac coated gel beads as determined by optical microscope was found to be in the range of 1.57±0.33 to 2.52±0.12 nm (Table 2).The results indicated a proportional increase in the mean particle size of gel beads with the increase in the amount of sodium alginate in the formulations. This could be attributed to an increase in relative viscosity at higher concentration of sodium alginate and formation of large droplets during addition of polymer solution to the gelling agent.Further, the increase in the concentration of calcium chloride would significantly decrease the mean particle size of beads. It has been stated that when a drop of alginate solution comes in contact with calcium ions, gelation occurs instantaneously. As Ca^{+2} ions, penetrates into interior of droplets, water is squeezed out of the interior of droplets resulting in contraction of beads (Pralhad and Rajendra, 2004). The size of the spherical matrix could easily be controlled by varying the stirring speed and cross-linking time of the system.

Surface structure and morphology of the beads were observed by Scanning Electron Microscopy (Figure 1). The SEM images indicated that the surface of uncoated formulation was found to be roughand after coating with Eudragit S100 the surface became smooth and size of beads were increased. The percent increase in the size of beads after coating was in the range of 16±0.22 %

to 17.5 ± 0.13 %. The shape of beads may not be completely spherical and smooth because during the oven drying shrinking of the beads occurred (Madhavi et al., 2016).

The molecular interactions of aceclofenac, sodium alginate and HPMC in the microbeads were investigated using FTIR spectroscopy (Figure 2).FTIR spectroscopy was performed for drug alone and drug with polymers (sodium alginate, HPMC and Eudragit S100) and for formulation F_{11}.Principle peaks of aceclofenac at 665.4, 1255.6, 1280.6, 1506, 1589.2 1716.64, 2935.50, 2970.2 and 3319.3 cm^{-1} were seen in all the plots. This similarity of peaks confirmed the identity of drug for formulation development in present study and revealed the absence of any drug-polymer interaction which proves the suitability of the polymers for the development of Aceclofenac coated gel beads.

The thermal behaviour of pure drug Aceclofenac, physical mixture of drug with polymers and formulation F_{11} was characterized by DSC (Figure 3). A sharp endothermic peak at 154 °C was shown by the pure drug sample.Endothermic peaks obtained from other graphs showed the presence of characteristic endothermic peak of Aceclofenac and no significant difference was observed. Formulation F_{11} showed sharp peak at temp 155.20 °C, slightly higher than as observed for the pure drug which indicated the improved the thermal stability of the alginate beads (Rajesh & Popat, 2016).

3.3 Drug Entrapment Efficiency

Drug entrapment efficiency of all the formulation was determined and it was found to be in the range of 66.53±0.54 to 83.94±0.71% (Table 2). The %DEE of the beads was found to increase with the increase in conc. of sodium alginate and calcium chloride. It was due to formation of more gel beads on increasing sodium alginate conc.thus entrapping the greater amount of the drug. This may be attributed to the greater availability of active calcium binding sites in the polymeric chains and, consequently, the greater degree of cross-linking as the amount of sodium alginate increased. However, on increasing the conc. of $CaCl_2$ hard and complex gel was formed which resulted in more drug entrapment (Abdalla et al., 2015). Formulation F_1 (SA=2%, $CaCl_2$=2%) was found to possess least %DEE i.e. 66.53±0.54% and maximum %DEE of 83.94±0.71%was found in formulation F_{11}(SA=5%, $CaCl_2$=5%).

Table 2:Various Parameters of formulations of Aceclofenac coated gel beads

Formulation	%age yield	Particle size (nm)	% DEE
F_1	74.55±0.26	1.68±0.03	66.53±0.21
F_2	78.17±0.12	1.87±0.12	72.84±0.32
F_3	82.13±0.03	2.19±0.01	74.91±0.07
F_4	85.47±0..4	2.52±0.12	76.49±0.19
F_5	73.25±0.22	1.61±0.04	68.92±0.28
F_6	79.94±0.28	1.82±0.06	74.35±0.34

F_7	81.34±0.08	2.11±0.22	77.18±0.18
F_8	88.15±0.13	2.45±0.09	80.67±0.09
F_9	86.39±0.13	1.57±0.33	72.53±0.04
F_{10}	75.56±0.36	1.74±0.05	76.76±0.12
F_{11}	89.51±0.24	1.97±0.01	83.94±0.47
F_{12}	80.87±0.03	2.33±0.06	82.47±0.38

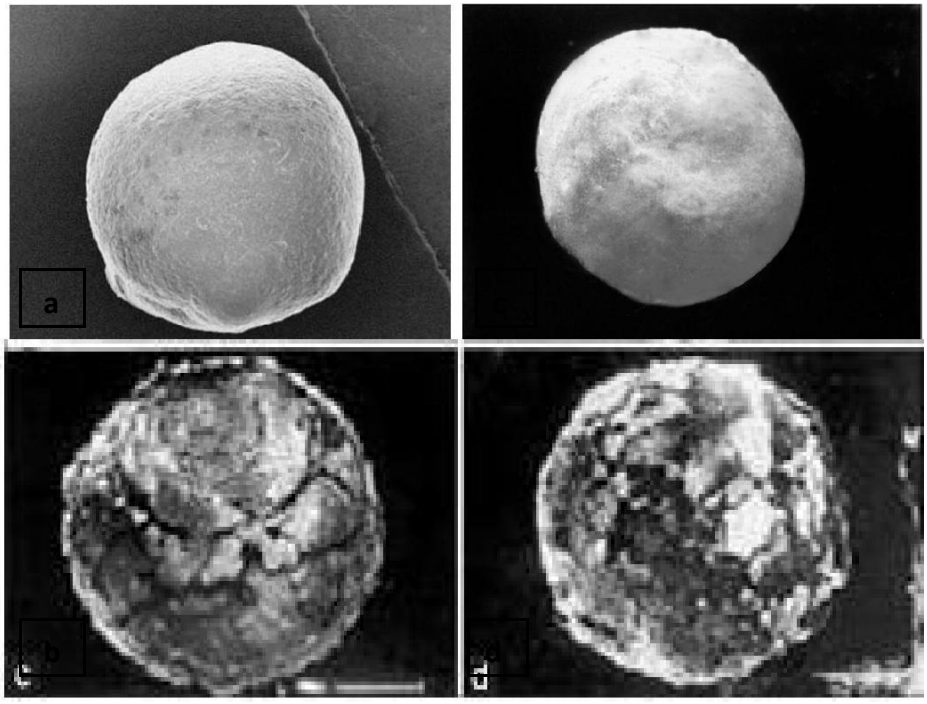

Figure 1: SEMof coated Formulation F_{11}(a) under 40X magnification(b) under 100X magnification. SEM of uncoated Formulation F_{11}(c) under 40X magnification (d) under 100X magnification.

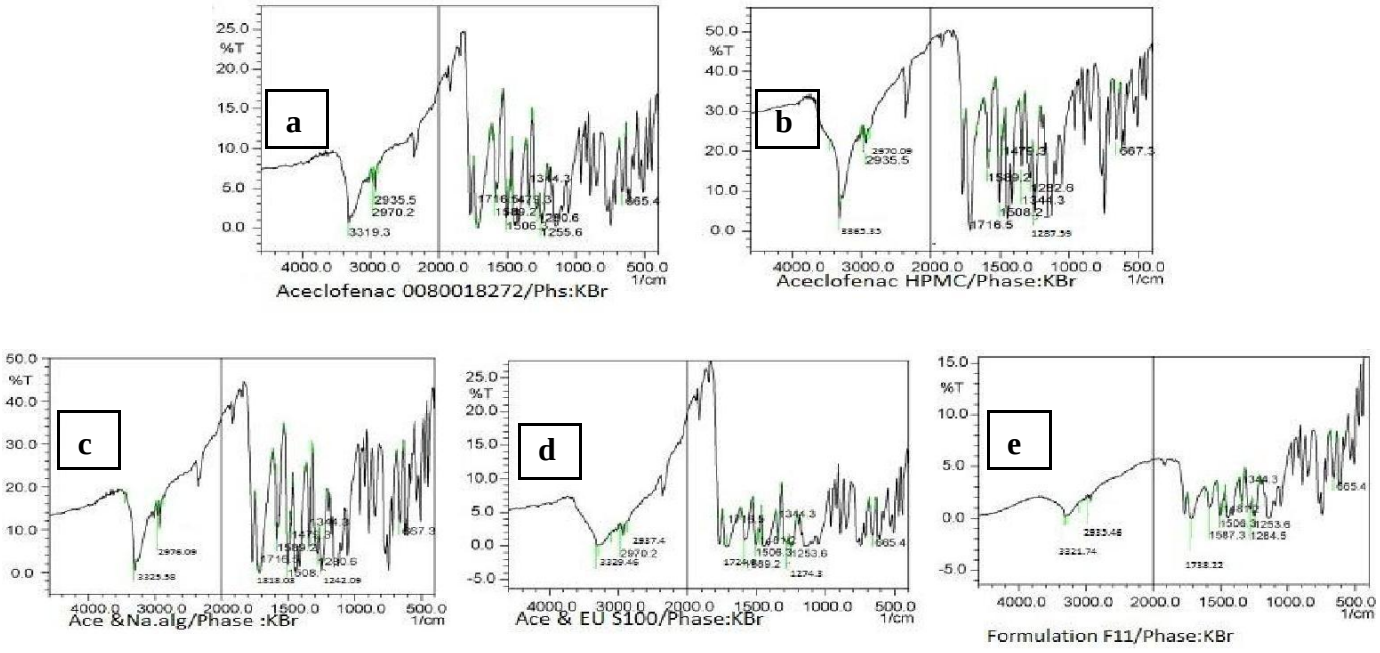

Figure2: (a) FTIR of pure Aceclofenac (b) FTIR of Aceclofenac & HPMC (c) FTIR of Aceclofenac & sodium alginate (d) FTIR of Aceclofenac &EU S100 (d) FTIR of Formulation F_{11}

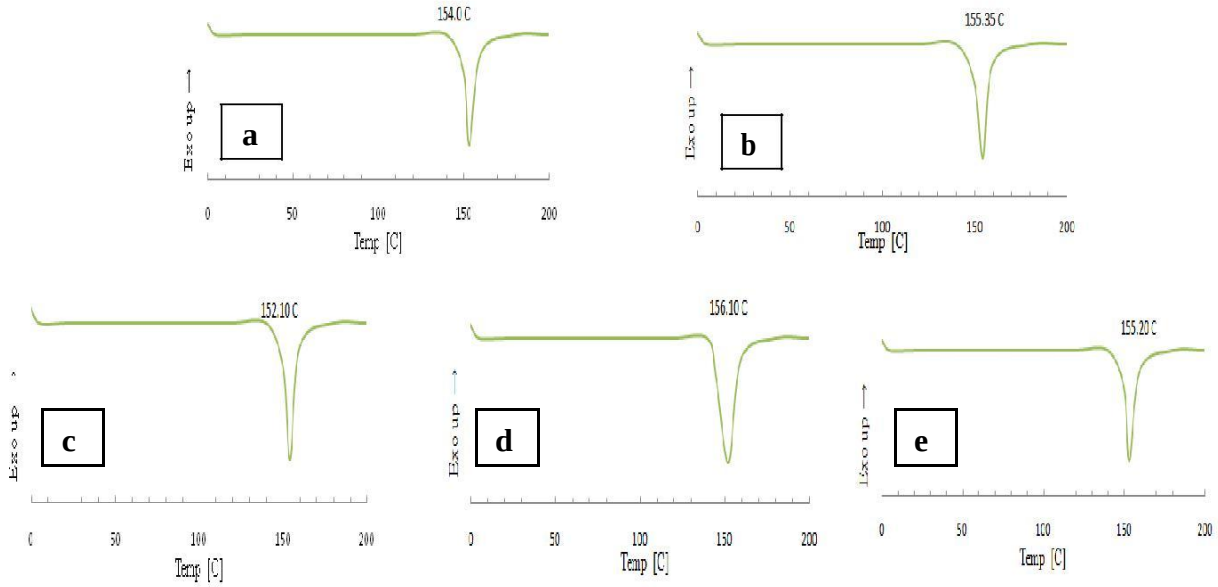

Figure3: (a) DSC of pure Aceclofenac (b) DSC of Aceclofenac & HPMC (c) DSC of Aceclofenac & sodium alginate (d) DSC of Aceclofenac &EU S100 (d) DSC of Formulation F_{11}

3.4 Reswelling Time Study

Reswelling time of the prepared gel beads, both coated and uncoated was found to be in the range b/w 11 to 30 minutes at pH7.4 and 8-34min at pH1.2 respectively (Table 3). It was observed that at both pH the reswelling time of the coated beads were higher than the uncoated beads.Also, the reswelling time of coated beads at pH 1.2 was found to be higher than at pH 7.4 because Eudragit S100 do not form pores at lower pH (Figure 4). It was also observed that the reswelling time of the coated gel beads increased with the increase in conc. of sodium alginate and calcium chloride due to the formation of more hard and rigid gel which had more complexity and less porosity.

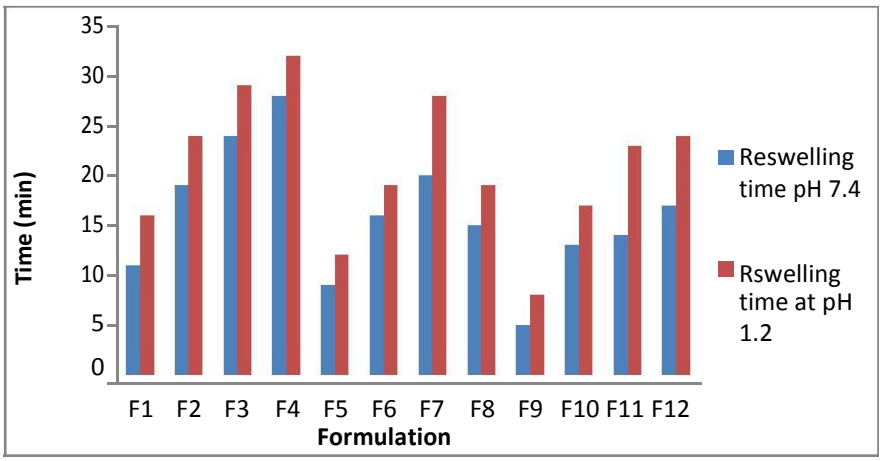

Fig.6 Comparison of reswelling time of coated gel beads at pH 1.2 & pH 7.4 Table 3: Reswelling time of coated gel beads of Aceclofenac

Formulation	Reswelling time(min) At pH 7.4	Reswelling time(min) At pH 1.2
F_1	11-13	16-18
F_2	19-21	24-26
F_3	24-26	29-31
F_4	28-30	32-34
F_5	9-11	12-14
F_6	16-18	19-22
F_7	20-22	28-30
F_8	15-17	19-21
F_9	5-7	8-9
F_{10}	13-14	17-20
F_{11}	14-16	23-25
F_{12}	17-19	24-26

3.5 *In Vitro* Drug Release Study

Aceclofenac sodium release from formulated gel beads was performed in different media, in simulated gastric fluid (SGF) pH 1.2 for initial 2h, mixed phosphate buffer pH6.8 for the period up to 6h and simulated intestinal (SIF) pH 7.2 at end of 9h studies. Formulation F_1 (containing 2% sodium alginate 0.2% HPMC, 3% $CaCl_2$)showed the maximum drug release of 94.16±0.21% in 8 has compared to other formulationswhereas minimum drug release was shown by formulation F_{11} (containing 4% sodium alginate, 0.2% HPMC, 5% of calcium chloride)i.e. 62.22±0.05% drug in 9 h.

The results (Table 4-7) indicated that when concentration of sodium alginate and calcium chloride was increased the drug release rates from the formulation were decreased.This was due to the more sustained effect with increase in the concentration of sodium alginate which was due

to the increased number of the apparent cross-linking points formed within the calcium alginate beads with increasing alginate concentration in the formulation. It was also found that with increased concentration of $CaCl_2$, the drug release rate becomes more sustained. When concentration of calcium chloride was increased more Ca^{+2} ions were present for complex formation and cross linking with alginate, due to which strong, rigid and hard gel beads were formed with less pores, which may reduce the penetration of dissolution medium into core of the matrix, therefore decreasing the release rate.

All the formulations were coated with Eudragit S100, the concentration of Eudragit S100 was constant (2%) in all the formulations. In-vitro drug release studies showed that there was not more than 9.36±0.14% drug release in simulated gastric fluid pH 1.2 in any formulation. This indicated the pH dependent dissolution of Eudragit S100, which does not dissolve in acidic pH1.2. All the formulations releasedmore drug in phosphate buffer pH 6.8.It wasreported that, the drug release from the coatedbeads of nifedipine and verapamil was minimal at pH 1.5 (18%), whereas at pH 6.8, approximately 99%nifedipine and verapamil was released (Dai et al., 2008, Pasparakis &Bouropoulos, 2006).Thus we can conclude that the amount of drug released from the Aceclofenac gel beads at pH 1.5 was relatively lowwhich protects the stomach from gastric irritation, whereasthe release reaches to maximum at pH 6.8.

Table 4: Percentage of aceclofenac release from coated gel beads (F_1, F_5 & F_9)

Time (hrs)	Cumulative % drug release ± S.D.		
	F_1	F_5	F_9
1	4.28±0.23	3.77±0.09	2.93±0.14
2	9.36±0.14	7.34±0.18	6.82±0.27
3	20.21±0.06	18.33±0.24	16.81±0.19
4	43.99±0.24	39.19±0.12	32.44±0.26
5	56.96±0.16	50.03±0.14	49.09±0.31
6	76.38±0.34	69.19±0.16	61.21±0.48
7	83.31±0.32	81.83±0.32	75.31±0.05
8	94.16±0.21	91.19±0.43	83.17±0.17

Average of three determinations

Table 5: Percentage of aceclofenac release from coated gel beads (F_2, F_6 & F_{10})

Time (hrs)	Cumulative % drug release ± S.D.		
	F_2	F_6	F_{10}
1	3.94±0.12	3.11±0.46	3.10±0.01
2	7.34±0.06	7.01±0.05	5.99±0.08
3	17.16±0.25	17.17±0.13	16.97±0.14
4	39.01±0.42	28.93±0.15	26.06±0.57
5	49.18±0.07	40.16±0.43	40.95±0.16
6	60.79±0.16	59.74±0.19	57.02±0.17
7	74.22±0.21	70.80±0.34	63.01±0.24
8	85.10±0.36	81.64±0.18	72.43±0.32

Average of three determinations

Table 6: Percentage of aceclofenac release from coated gel beads (F_3, F_7& F_{11})

Time (hrs)	Cumulative % drug release ± S.D.		
	F_3	F_7	F_{11}
1	1.93±0.23	2.93±0.12	2.27±0.09
2	6.14±0.14	6.83±0.34	5.65±0.41
3	14.20±0.35	16.81±0.36	14.27±0.23
4	26.52±0.13	24.22±0.29	21.32±0.14
5	37.22±0.62	33.89±0.14	30.11±0.19
6	44.85±0.05	45.51±0.06	40.01±0.21
7	58.14±0.23	54.39±0.28	46.15±0.27
8	63.26±0.46	65.06±0.15	57.23±0.16
9	74.68±0.41	71.13±0.37	62.22±0.05

Average of three determinations

Table 7: Percentage of aceclofenac release from coated gel beads (F_4, F_8 & F_{12})

Time (hrs)	Cumulative % drug release ± S.D.		
	F_4	F_8	F_{12}
1	3.27±0.05	3.94±0.17	3.11±0.09
2	6.3±0.23	5.66±0.26	5.62±0.15
3	19.33±0.14	17.32±0.42	13.27±0.14
4	33.48±0.16	31.44±0.13	29.37±0.39
5	45.27±0.18	46.73±0.25	41.78±0.32
6	53.16±0.32	53.29±0.36	52.32±0.15
7	66.76±0.15	62.26±0.12	65.32±0.52
8	77.31±0.17	74.52±0.08	71.39±0.12

3.6 Dissolution Kinetics of Drug Release

The drug release data obtained was subjected to zero order, first order,Higuchi's, Kosermayer's in order to establish the drug releasemechanisms and kinetics of drug release from the formulation. In-vitro drug release data of all formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order of kinetic equation and Higuchi's model to determine the mechanism of the drug release.Linear regression analysis of all formulations indicated that r^2 values of zero order plots were in the range of 0.96 to 0.98 and for first order plot the r^2 values in the range of 0.87 to 0.94. These values showed that all the formulations followed the zero order kinetics of drug release.From Higuchi's plots it was observed that the r^2 values were found in the range of 0.79 to 0.85. From the results of linear regression analysis of all formulations it was indicated that all the formulation were governed by diffusion control process.

Table-20: Regression analysis data of aceclofenac loaded coated gel beads

Formulation	a=slope	Zero order	First order	Higuchi

	b=intercept r²=regression coefficient			
F_1	a	13.193	-0.149	37.01
	b	-9.6473	2.206	-23.922
	r^2	0.9723	0.8706	0.8234
F_2	a	11.474	-0.0997	32.154
	b	-8.3427	2.1238	-20.696
	r^2	0.9775	0.9004	0.8241
F_3	a	8.7393	-0.0646	26.517
	b	-6.046	2.0765	-17.908
	r^2	0.9862	0.9366	0.8502
F_4	a	10.359	-0.0794	29.062
	b	-7.4704	2.0909	-18.682
	r^2	0.9798	0.9251	0.8296
F_5	a	12.915	-0.0888	35.199
	b	-10.096	2.1151	-23.4
	r^2	0.9738	0.8743	0.8135
F_6	a	10.93	-0.0615	30.27
	b	-9.4211	2.1151	-20.536
	r^2	0.9664	0.8917	0.7973
F_7	a	8.5435	-0.0615	25.83
	b	-6.3125	2.0734	-17.73
	r^2	0.985	0.9413	0.8432
F_8	a	9.9748	-0.0735	28.01
	b	-7.0482	2.0806	-17.891
	r^2	0.9747	0.9331	0.8268
F_9	a	11.402	-0.0961	31.798
	b	-9.2209	2.1218	-21.216
	r^2	0.9738	0.9074	0.8147
F_{10}	a	9.999	-0.073	27.92
	b	-7.8238	2.0833	-18.406
	r^2	0.9713	0.9342	0.8147
F_{11}	a	7.5662	-0.0498	22.811
	b	-6.0591	2.0579	-16.046
	r^2	0.9832	0.9483	0.8369
F_{12}	a	9.888	-0.0712	27.519
	b	-8.1976	2.0833	-18.497
	r^2	0.9686	0.9307	0.807

4. CONCLUSION

The study has revealed that ionotropic gelation technique can be successfully employed for the preparation of aceclofenac gel beads by utilizing sodium alginate and calcium chloride as drug release modifiers. Eudragit S 100 coating further helps in overcoming the problem of gastric

damage during the use of NSAID Aceclofenac.Selection of polymer is important to achieve more entrapmentefficiency and to sustain the release of drug from beads. Effect of various formulation variables such as sodium alginate concentration, calcium chloride concentration and curing time of alginate beads were studied.The particle size of the gel beads were found to increase with the increase in sodium alginate and calcium chloride concentration. SEM of beads showed uncoated beads to be spherical and rough in surface whereas coated beads had a smooth surface. FT-IR and DSC studies did not reveal any significant drug interactions.The reswelling time of coated beads at pH 1.2 was found to be higher than at pH 7.4. The drug release from the beads was affected by the pH of the dissolution medium and results showed more sustained effect in acidic medium(pH 1.2). The results indicated that the more sustained effect withincrease in the concentration of sodium alginate and Cacl2. The entire process is feasible in an industrial scale and demands pilot study.

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