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Research Article

In vitro Characterization of Ethodolac Gastro Retentive Hollow Microballons

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ABSTRACT

Etodolac has been used for treatment of Rheumatoid Arthritis(RA) and Osteoarthritis. It is a BCS class II drug i.e. low solubility &high permeability and major absorption site is stomach region. It shows dissolution rate-dependent bioavailability. This work was carried out to improve the dissolution rate and controlled release of drug so it could retain in the stomach for longer period of time delivering to the site of action i.e. stomach. Aim of the present work is to prepare and characterization of Gastro Retentive Hallow Micro Balloons of etodolac by using two acid resistant polymers such as Eudragit RS 100 & ethyl cellulose with different ratio, Eudragit RS 100 is water insoluble over the entire range of pH it swells in stomach in swollen state it is permeable to water and dissolved actives. In this study solvent diffusion /evaporation technique was used to prepare a gastro retentive hallow micro balloons for etodolac and influence of several factors on various physical characteristics, including particle size, buoyancy, drug entrapment /loading, *in vitro* dissolution drug release characters are investigated.

INTRODUCTION

Oral Gastro Retentive Drug Delivery System

Gastro retentive drug delivery system belongs to oral controlled drug delivery system group that are capable to retain in the stomach by passing the gastric transit. These dosage forms are also defined as floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. [1, 2]

Approaches to Gastric Retention

5 Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: [3-5]

1. Floating systems.
2. Swelling and expanding system
3. Bio-adhesive systems
4. High- density systems
5. Modified-shape systems

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Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non effervescent and gas generating (effervescent) system. [6]

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. [7-10]

MATERIALS AND METHODS

Preformulation Studies

Raw material analysis of Etodolac:

Description: White or almost white crystalline powder (Fig 1).

Melting point: Melting point of etodolac was determined by capillary method. Melting point of a drug sample is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by lowering as well as widening in the melting point range. Results were shown in Table 2.

Solubility test: Shake Flask Method

Solubility studies done by using shake flask method; an excess amount of ethodolac was transferred to a 250 ml of conical flask containing 100ml of dissolution media. The solubility study was performed at a temperature of 25°C.

The flask was shaken for 24 hrs by keeping conical flask on rotary shaker at 200 RPM. A portion of drug solution dissolved in buffer solution was filtered and absorbance was measured at 265 nm using UV-visible double beam spectrophotometer.

The amount of drug dissolved in dissolution medium were calculated and reported. The test was prepared in triplicate in the selected buffer (pH 1.2, 4.4, 6.8 and 7.4 buffer solutions). Results were shown in Table 3.

Percentage Purity: Assay

Weigh 0.25g and dissolve in 60 ml of methanol, titrate with 0.1M tetra butyl ammonium hydroxide, determining the end-point potentiometrically (2, 4 and 25), Carry out a blank titration. 1ml of 0.1 M tetra butyl ammonium hydroxide is equivalent to 0.02874g of$C_{17}H_2NO3$.

Preparation of Standard Calibration Curve for Etodolac

I Stock solution: A weighed amount of Etodolac (100 mg) was taken in a 100 ml volumetric flask and dissolved in 50 ml of phosphate buffer 7.4. Final volume was made up to the mark with phosphate buffer 7.4.

II Stock solution: From the I stock solution 1 ml was withdrawn and dilute to 100ml phosphate buffer 7.4 to get a concentration of 10 mcg/ml. From the standard stock solution samples of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ml were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with phosphate buffer 7.4 to get final concentration 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 mcg/ml. the absorbance was measured at 277 nm. Results were shown in Table 4 and Fig. 2. [11]

Incompatibility Study (Drug Excipients) FT-IR

The physicochemical compatibility between etodolac and the excipients used in the research was tested by Infrared (IR) Spectroscopy using ABB Bomem IR spectroscopy. The Fourier-Transformed Infrared (FTIR) spectra of the sample were obtained, using an FTIR spectrophotometer. About 2mg of the samples were mixed with potassium bromide of equal weight and compressed to form a KBr disc. The samples were scanned from 500 to 4000 cm^{-1}. Results were shown in Fig. 3, 4 and 5.

Differential scanning calorimetry (DSC) Study

Thermal analysis is an important evaluation technique to find any possible interaction between the drug and used polymers. Any of such interaction may reduce the drug entrapment efficiency of the polymer and may also alter the efficacy of the drug. Such Interaction can be identified by any change in thermo gram. Results were shown in Fig. 6, 7.

Formulation of Micro-Balloons

Floating Microballoons containing Etodolac were prepared using Emulsion solvent evaporation technique (Table 1).

Table 1: Formulation of Ethodolac-loaded Gastro Retentive Hollow Microballons

Formulation Code	Drug (mg)	Ethyl Cellulose (mg)	Eudragit RS 100 (mg)	DSC & Ethanol	PVA (%)
F1	200	500	-	1:1	0.5
F2	200	500	250	1:1	0.5
F3	200	500	500	1:1	0.5
F4	200	250	500	1:1	0.5
F5	200	750	250	1:1	0.5
F6	200	750	500	1:1	0.5

Figure 1: Preparation of Etodolac Microballoons

Two different polymers in ratio were used to prepare the different ratio were used to prepare the different formulations of micro-balloons.The drug polymer mixture was dissolved in a mixture of dichloromethane (DCM) and ethanol. The mixture was dropped in to 0.5% polyvinyl alcohol solution (100 ml) and the resulting solution was stirred with a propeller-type agitator at 1300 rpm and various temperature ranges for 6 h. The floating Micro-balloons formed were screened, washed with water and Dried at room temperature in desiccators. [11-14]

Micromeritic Properties [6, 7]

Bulk Density

Apparent bulk density (g/ ml) was determined by pouring bulk blend into a graduated cylinder via a large funnel and measuring the volume and weight, as its bulk density was calculated using the formula. Results were shown in Table 5.

Bulk density= W/ V b

Tapped Density

Tapped density was determined by placing a graduated cylinder containing a known mass of blend on a mechanical tapper apparatus until the powder bed has reached a minimum. Tapped density was calculated using the formula. Results were shown in Table 5.

Tapped density (t) = W/ V t

Carr's Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of granules were determined, which is given as Carr's compressibility index. Results were shown in Table 5.

Cl = Vi – Vo / Vi x100

Hausner's Ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.0–1.5. It was determined by the ratio of tapped density and bulk density using the formula for determination of Hausner's ratio. Results were shown in Table 5.

Hausner's ratio = Vo / Vi

Angle of repose

Angle of repose was determined by using funnel method. Poured Accurately Weighed blend was poured from funnel which was raised vertically until a maximum cone height (h) was obtained and diameter (d) was measured. The angle of repose was calculated by formula. Results were shown in Table 5.

θ = tan-1 (h/r)

Characterization of Microballoon [11-14]

Particle Size

The size of microspheres of each formulation was determined using a microscope fitted with an ocular micrometer, and stage micrometer and average particle size was determined. Results were shown in Table 6 and Fig. 8.

Surface Morphology Study:

Scanning Electron Microscopy (SEM)

The surface morphology of microballoons was examined using scanning electron microscope (JEOL, JSM-670F Japan). Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 3.0 KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology. Results were shown in Fig. 9 and 10.

Determination of Production Yield

The prepared microballoons were collected and weighed. The weight of microballoons was divided by the total weight of all the non- volatile components that were used for the preparation of the microballoons and multiplied by 100 gives the % yield of microballoons as follows: Results were shown in Table 7 and Fig. 11.

$$\% \text{ Yield} = \frac{\text{Actual weight of the product}}{\text{Total weight of excipients and drug}} \text{ X } 100$$

Entrapment Efficiency (EE)

The various batches of the floating microspheres equivalent to 50 mg of Etodolac from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved in (5 ml) ethanol in volumetric flask (100 ml) and made the volume with 0.1 N HCL. This solution is then filtered through Whitman filter paper no. 45. After filtration, the sample was observed in UV spectrophotometer and the absorbance was measured at 249 nm against 0.1 N HCL as a blank. The percentage drug entrapment was calculated as follows. Results were shown in Table 8 and Fig. 12.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \text{ X } 100$$

***In Vitro* Buoyancy**

Micro-balloons (200mg) were spread over the surface of a USP dissolution apparatus (type II) was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microballoons were recovered separately. Results were shown in Table 9 and Fig. 13.

The microballoons were dried and weighed. Buoyancy percentage was calculated using following formula:

$$\text{Buoyancy percentage (\%)} = \frac{\text{Micro-balloons remained floating}}{\text{Total mass of micro-balloons}} \text{ X } 100$$

***In Vitro* Drug Release Studies**

In vitro drug release from microballoons was determined using USP dissolution apparatus type 11 (paddle type). The dissolution test was performed using 0.1N HCl (pH 1.2) as dissolution fluid (900 ml) maintained at37 ± 0.5˚C at 100 rpm. The samples (5ml) of the solution were withdrawn from the dissolution apparatus for 12h, and the samples were replaced with fresh dissolution medium each time to maintain the sink condition. With drawn samples were analysed using UV-VIS double beam spectrophotometers at 272 nm against suitably constructed calibration curve. All measurements were carried out in triplicate, and average values were plotted. Results were shown in Table 10 and Fig. 14.

Drug Release Kinetics

The release data obtained were treated according to zero order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug release versus root time) and Korsemeyer-Peppas (log cumulative percentage of drug released versus log time) equation models. Results were shown in and Fig. 15 - 18.

RESULTS AND DISCUSSION

Pre-Formulation Studies:

Raw Material Analysis of Etodolac

The given drug etodolac is tested for the given test as per the IP standard and limits. The assay value obtained by procedure as per I.P showed a purity of 96 % which was found to be in the range of I.P standard. Thus the evaluation of the drug ensures its quality as per standard of the Indian pharmacopeia and thus it can be included for further study for the formulation. Table is enlisted in Table 2.

Table 2: Identification test for Etodolac

S.NO	TEST	METHOD
1	Loss on drying	
2	Melting point	145 to 148 ˚c (293 to 298˚F)
3	Sulphated ash	NMT 0.1 per cent
4	Assay	NLT 98%, & NMT102%

Solubility

Etodolac is soluble in methanol and sparingly soluble in water.

Table 3: Solubility of Etodolac in Different Solvents

S. No	Pure Drug	Solubility
1	Ethanol	Very slightly soluble
2	DCM	218 mg / ml

Standard Calibration Curve of Etodolac

The calibration curve was constructed with phosphate 7.4buffer solution and results were shown in Table 4 and Fig. 2. The regression coefficient obtained was 0.99 which shows better correlation between both the axis.

Table 4: Standard Calibration Curve of Etodolac

S. No	Concentration (µg)	Absorbance
1	0	0
2	1	0.033
3	2	0.059
4	3	0.081
5	4	0.109
6	5	0.132
7	6	0.172
8	7	0.185
9	8	0.218
10	9	0.256
11	10	0.275

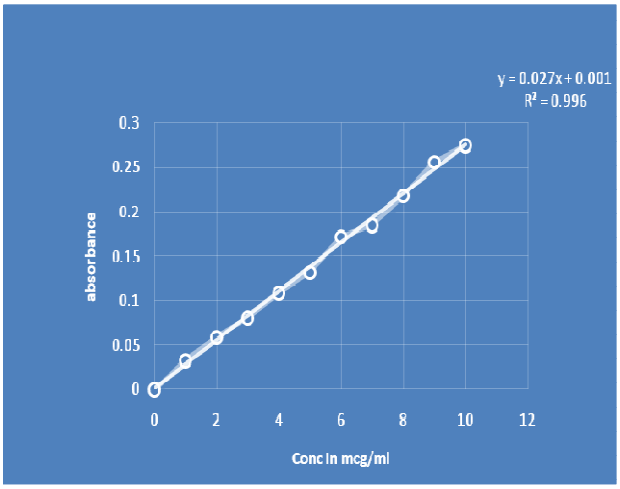

Figure 2: Calibration Curve of Etodolac

Drug - Excipient Incompatibility Study

FT-IR (Fourier transforms Infrared Spectroscopy): FTIR spectrum of Etodolac exhibited peak at 3343 CM -1 due to N-H stretching, 1743 CM -1 due to c=o, 1412 CM -1 due to C-H group which confirm the structure of etodolac. Drug-polymer compatibility studies were carried out using FTIR spectroscopy to establish any possible interaction of etodolac with the polymer used in the formulation. Thus results indicate that the characteristic absorption peak due to pure etodolac have appeared in the formulated micro balloons without any significant change in their position indicating no chemical interaction between etodolac and polymers . Results were shown in Fig. 3, 4 and 5.

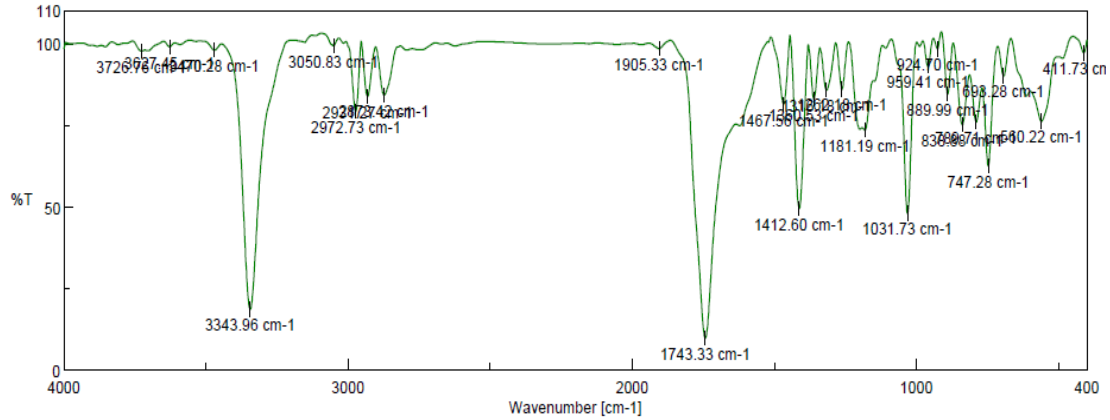

Figure 3: FTIR Spectram of Etodolac

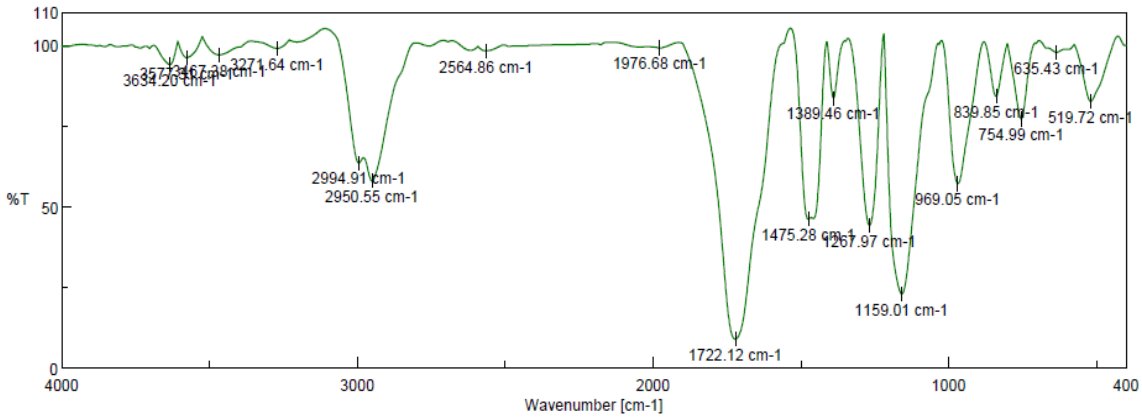

Figure 4: FTIR Spectrum of Ethyl cellulose

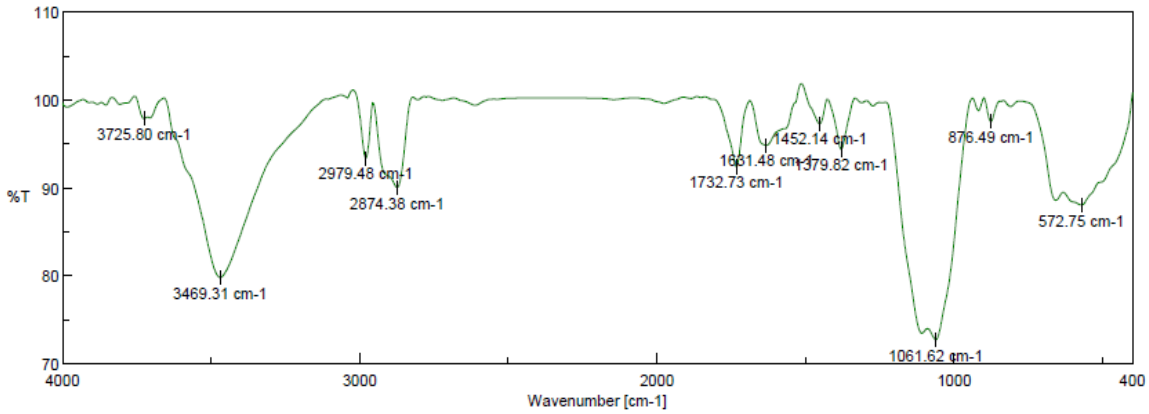

Figure 5: FTIR spectrum of Etodolac Microballoons

Differential Scanning Calorimetry (DSC)

The results of DSC were observed for the integrity of the drug in micro balloons formulation prepared by the entrapment process, in the DSC curve of selected F4 formulation, the endothermic melting peak concerning etodolac. According to this data, there was no interaction between drug, Eudragit RS 100 and ethyl cellulose in microballoons results showed that there was no interaction between the drugs and the polymer. Results were shown in Fig. 6 and 7.

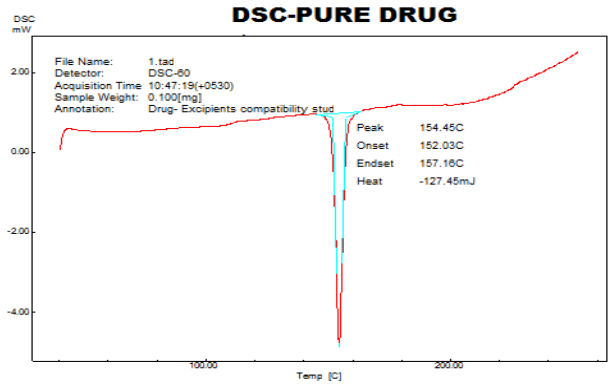

Figure 6: Differential Scanning Calorimetry of Etodolac Drug

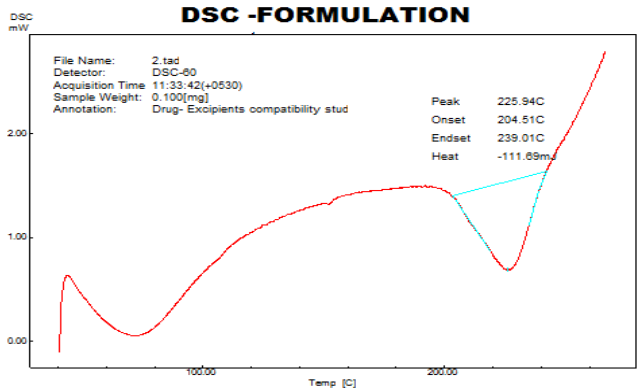

Figure 7: DSC Thermo Grams of Drug Loaded Micro Balloons Formulation.

Preparation of Micro Balloons

Preparation of etodolac loaded hollow microballons was done by the solvent evaporation technique using different concentrations of acid resistant polymers such as Ethyl cellulose, Eudragit RS 100 dispersed in DSC and Ethanol as a solvent system The mixture was poured in to 100ml of 0.5% polyvinyl alcohol solution with syringe and the resulting solution was stirred with a propeller-type agitator at 1300 rpm and various temperature ranges for 6 h. The hollow Micro-balloons formed were screened, washed with water and Dried at room temperature in desiccators.

Characterization of Microballoons

Micro meritic Properties Prepared micro balloons were tested for different micro metric properties, like Bulk density, tapped density angle of repose ,C.I, Hausner's ratio all the values were within the limit (Table 5).

Particle Size of Micro Balloons

Result of the study the average particle size of Micro balloons were found to be 79.46±0.07, 88.17±0.09, 79.74±0.08 for F1,F2,F3 formulation and 127.91±0.05, 94.18±0.10 and 110.4±0.07 for F4, F5 and F6 formulations, respectively. The particle size increased with increasing polymers concentration. This is due to the increase viscosity of the solution and the decrease in stirring efficiency. Also with increasing polymer concentration, the hardening time of the micro balloons was shortened. Therefore, a shorter time was provided for the breakup of droplets, and large micro balloons were formed. Results were shown in Table 6 and Fig. 8.

Table 5: Micro Meritics Properties of Different Floating Microballoons

Formulation code	Bulk density	Tapped density (gm/cm3)	Corr's compresibility	Hausner's ratio	Angle of repose
F1	0.41 ± 0.03	0.44 ±0.02	7.31 ± 0.03	1.08	24°58'
F2	0.48 ± 0.14	0.58±0.10	17.24 ± 0.12	1.23	35°48'
F3	0.54 ± 0.18	0.59±0.11	8.48 ± 0.21	1.08	41°54'
F4	0.47 ± 0.03	0.52±0.02	10.63±0.03	1.10	25°41
F5	0.49 ± 0.01	0.54±0.01	10.20± 0.02	1.11	33°50'
F6	0.52 ± 0.12	0.61±0.08	14.76±1.09	1.17	38°67'

Each value is average of three separate determinations ±SD

Table 6: Particle Size Analysis

Formulation Code	Particle Size (µm)
F1	79.46±0.07
F2	88.17±0.09
F3	79.74±0.08
F4	127.91±0.05
F5	94.18±0.10
F6	110.4±0.07

Each value is average of three separate determinations ±SD

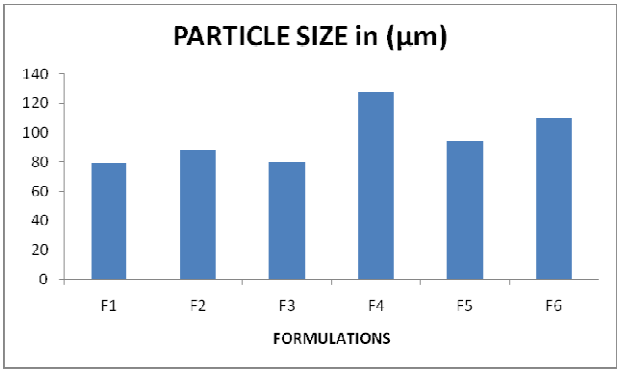

Figure 8: Particle size analysis

Surface Morphology:
Scanning Electron Microscopy (SEM)

The scanning electron microscope showed that the developed hollow micro balloons were spherical with porous surface by over view & hollow space with Transactional view images were shown in Fig. 9 and 10.

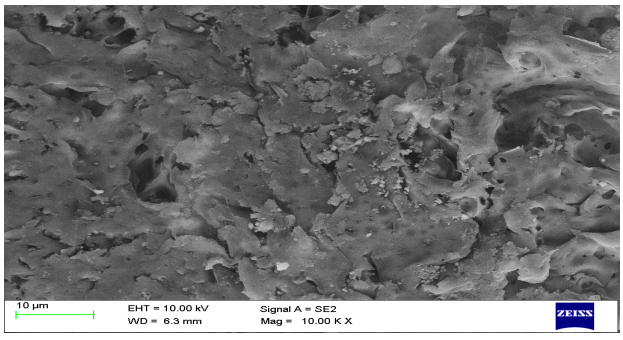

Figure 9: Surface morphology

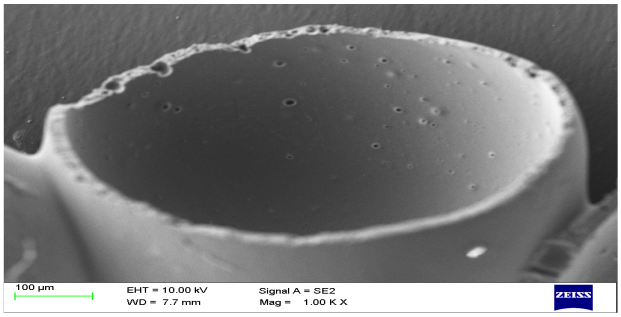

Figure 10: SEM-Showing Hollow Micro Balloon

Determination of Production Yield

Production yield were found to be 84.45±0.15, 88.76±0.17, 86.45±0.13, 88.84±0.18, 87.64±0.11 and 85.16±0.14 for F1, F2, F3, F4, F5 and F6 formulations, respectively. As shown in Table 7 and Fig. 11.

Table 7: Percentage Yield of Formulated Microballoons

Formulation Code	Percentage Yield (%)
F1	44.45±0.15
F2	58.76±0.17
F3	80.45±0.13
F4	88.84±0.18
F5	77.64±0.11
F6	79.16±0.14

Each value is average of three separate determinations ±SD

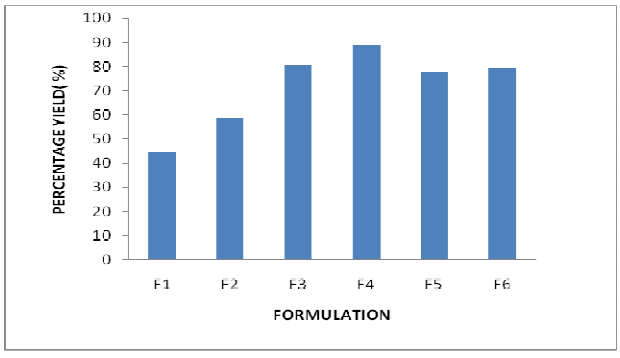

Figure 11: Percentage Yield of Etodolac Microballoons Formulations

Entrapment Efficiency (EE)

The percentage loading efficiencies were found to be 72.14±0.09, 75.63±0.09, 70.94±0.08, 85.63±0.07, 72.45±0.08 and 80.27±0.09 for F1, F2, F3, F4, F5 and F6 formulations, respectively and results were shown in Table 8 and Fig. 12.

Table 8: Drug loading Entrapment Efficiency of etodolac microballoons formulation

Formulation Code	Entrapment Efficiency (%)
F1	65.14±0.09
F2	70.63±0.09
F3	72.94±0.08
F4	85.63±0.07
F5	72.45±0.08
F6	80.27±0.09

Each value is average of three separate determinations ±SD

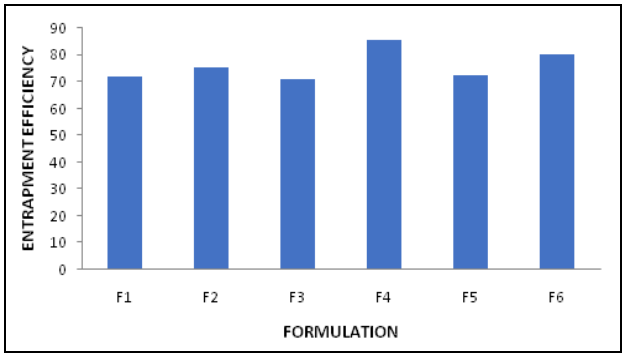

Figure 12: Entrapment Efficiency of Etodolac Microballoons

Buoyancy Percentage

The Buoyancy percentage for all batches was almost above 70% which were studied for 12h. The highest percentage was obtained with formulation F4. Average buoyancies in percentage were found to be in the range of 72.43 ± 0.21 to 73.64 ± 1.73 for F1 to F6 formulations. Out of all 6 formulations F4 formulation is 80.19 ± 0.63 which is highest. Results were shown in Table 9 and Fig. 13.

Table 9: Buoyancy percentage (%)

Formulation Code	Buoyancy Percentage (%)
F1	42.43 ± 0.21
F2	63.28 ± 1.82
F3	68.84 ± 0.82
F4	80.19 ± 0.63
F5	77.52 ± 2.04
F6	73.64 ± 1.73

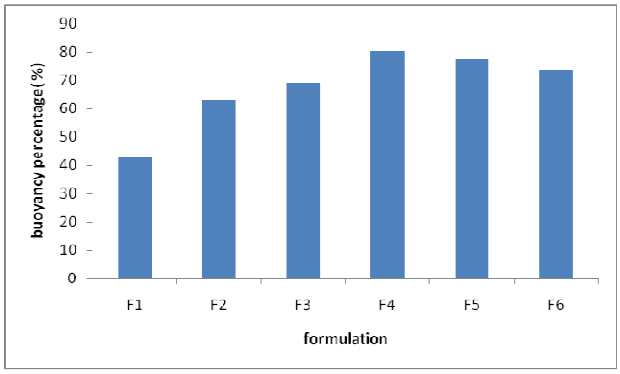

Figure 13: Buoyancy percentage (%)

***In vitro* Drug Release Studies**

The *in vitro* drug release of formulations F1, F2, F3, F4, F5 and F6 was found to be good within 12 hrs. Among all 6 formulations F4 is having 98.58±0.45 % drug release at 12hr. As the concentration of polymer increased, there was an increase in diffusional path length. Results were shown in Table 10 and Fig. 14.

Table 10: *In Vitro* Drug Release Formulation (F1 to F6)

Time in Hr	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	27.88 ± 0.5	17.78±0.30	15.53±0.12	12.50±0.50	8.59±0.23	6.00±0.12
2	43.54 ± 0.2	28.45±0.41	22.53±0.51	18.79±0.44	14.78±0.45	10.53±0.23
3	62.65±0.5	36.93±0.52	28.78±0.80	24.67±0.23	21.54±0.12	16.46±0.15
4	73.54±0.09	48.89±0.66	37.72±0.03	32.67±0.52	28.60±0.23	22.56±0.23
5	87.19±0.3	63.76±0.5	45.67±0.64	39.49±0.33	35.85±0.12	29.53±0.45
6	97.45±0.06	74.78±0.02	59.34±0.02	48.76±0.55	44.69±0.22	35.56±0.12
7	-	87.45±0.05	66.73±0.04	58.96±0.41	53.76±0.24	42.67±0.15
8	-	96.84±0.04	79.78±0.02	66.95±0.04	63.26±0.22	48.75±0.23
9	-	-	87.46±0.04	75.98±0.20	69.54±0.15	57.74±0.45
10	-	-	95.32±0.60	81.79±0.0.41	76.58±0.45	65.42±0.21
11	-	-	-	89.95±0.23	85.34±0.12	72.62±0.24
12	-	-	-	98.58±0.45	90.52±0.65	80.64±0.67

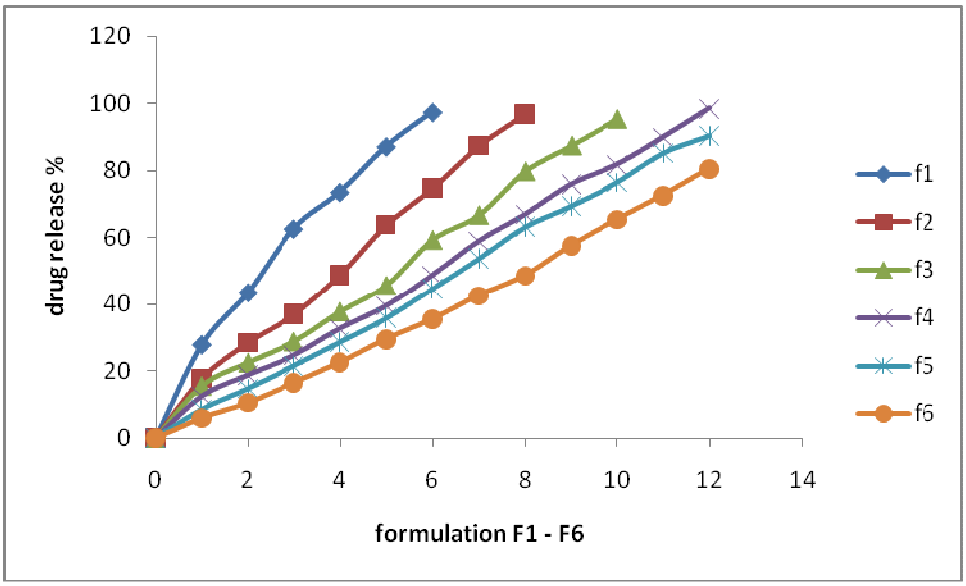

Figure 14: *In Vitro* Drug Release Profiles of Etodolac Formulations (F1 to F6)

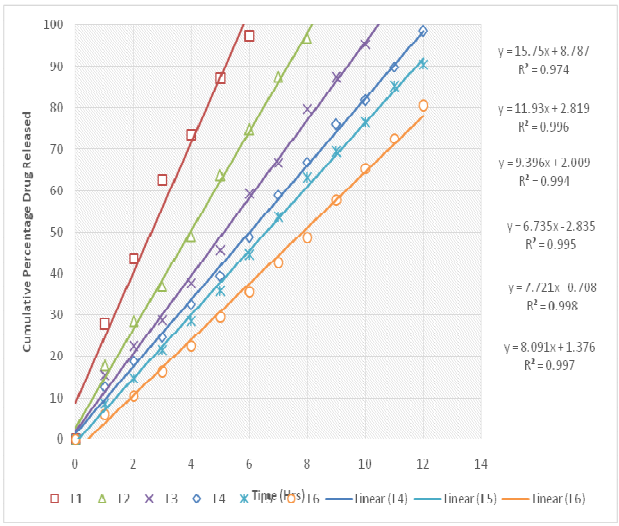

Figure 15: Zero Order Kinetics

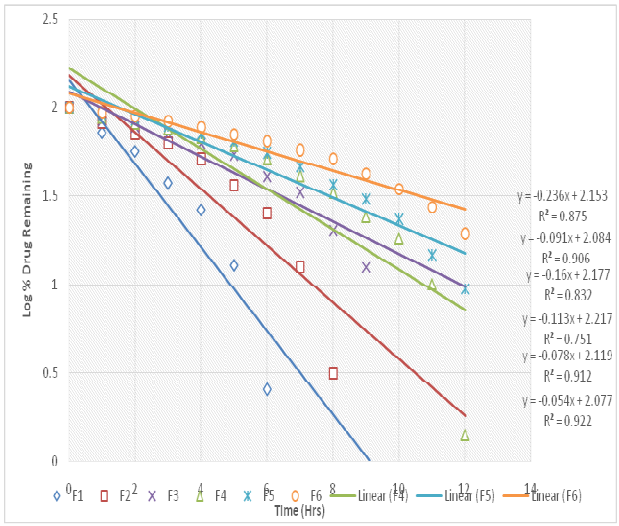

Figure 16: First Order Kinetics

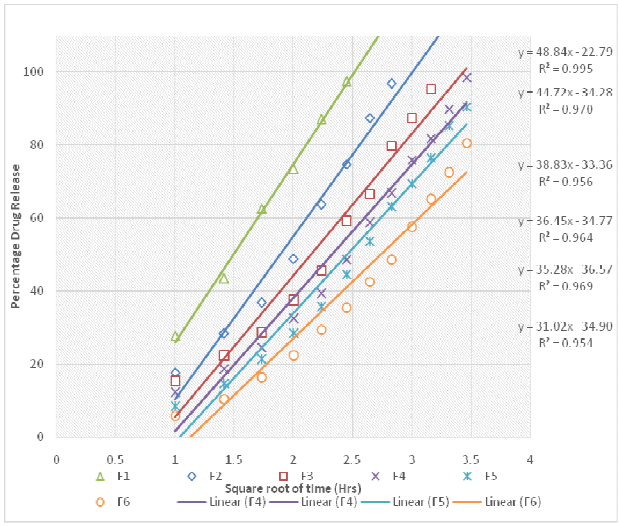

Figure 17: Higuchi Release Kinetics

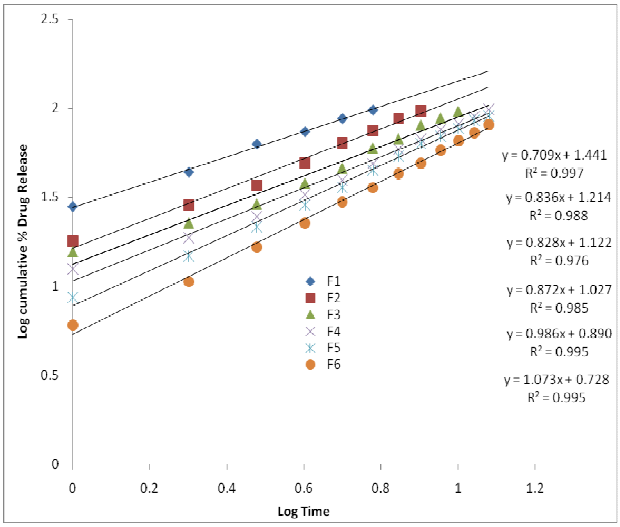

Figure 18: Korsmeyer-Peppas Equation Release Kinetics

Drug Release Kinetics

The kinetics and mechanism of drug release were determined using zero order, and first order, Higuchi model and Korsmeyer-Peppas equation. All formulations were found to be linear (Fig. 15 to Fig. 18).

CONCLUSION

As per the work we are concluding Gastro Retentive Hollow micro balloons loaded with Etodolac were prepared by the solvent evaporation technique using different concentrations of acid resistant polymers such as Ethyl cellulose, Eudragit RS 100 dispersed in DSC and Ethanol as a solvent system. Prepared Hollow micro balloons showed significant floating ability, good surface morphology, entrapment efficiency, Buoyancy percentage and sustain drug release for 12 hrs. In- vitro &in -vivo drug release of micro balloons was influenced by polymer concentration. As per the results among all the formulations F4 formulation with 1:2 Ethyl cellulose & Eudragit RS 100 shown 80.19 ± 0.63% buoyancy, 88.84±0.18 % yield ,85.63±0.07% entrapment efficiency and 98.58±0.45% of *in vitro* drug release at 12 hrs it shows the potent sustain release.

Future Aspects of Work

Prepared Hollow micro balloons may prove to be potential candidate for multiple unit delivery devices adaptable to any intra gastric candidate.

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