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FORMULATION AND *IN-VITRO* EVALUATION OF MUCOADHESION AND FLOATING MICROSPHERES OF ETODOLAC USING IONIC GELATION METHOD

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Etodolac,
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ABSTRACT: The purpose of this study is to formulation and evaluation of floating and mucoadhesion microspheres of etodolac using ionic gelation method. The floating and mucoadhesion microspheres were studied for micromeritic properties were found to be within limits. The percentage yield of floating microsphere formulation F1 to F6 and mucoadhesive microspheres M1 to M3 were in the range of 77.14 ± 0.64 to 92.74 ± 0.74%. The *in-vitro* buoyancy of formulation F1 to F6, it was range from 71.96 ± 1.04 to 82.96 ± 1.07. Among all formulation, F6 was found to be highest *in-vitro* buoyancy 82.96 ± 1.07. The results also showed that the larger the particle size, the longer the floating time. The entrapment efficiency of floating microspheres F1 to F6 and mucoadhesive microspheres were in the range of 77.43 ± 2.72 to 98.11 ± 2.59. Formulations prepared with sodium alginate alone have shown maximum drug release at 12 h in the ratio of 1:3. Formulations prepared with sodium alginate along with HPMC K 4M retard the drug release. Among all formulations of floating microspheres, F3 was considered as optimized for floating microspheres. From the release kinetics data, it was evident that floating optimized formulation follows zero order release kinetics. From the dissolution data of mucoadhesive microspheres by ionic gelation method M1, formulation has shown maximum drug release at 12 h. When an increase in the polymer concentration retards the drug release more than 12 h. Hence, M1 was considered as optimized formulation for mucoadhesive microspheres, and it was followed zero order release kinetics.

INTRODUCTION: Drug Delivery System: The oral route of drug administration is the most important method of administering drugs for systemic effects. The parenteral route is not routinely used or not possible to self-administration of medication. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects.

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It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. If it cannot, the drug is primarily relegated to administration in a hospital setting or physician's office. Of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. The reasons for this preference are well known [1].

Novel Drug Delivery System: Today, a pharmaceutical scientist is well versed with the fact that the overall action of a drug molecule is not

merely dependent on its inherent therapeutic activity, rather on the efficiency of its delivery at the site of action. An increasing appreciation of the latter has led to the evolution and development of several drug delivery systems (DDS) aimed at performance enhancement of the potential drug molecules.

A review of the literature has revealed the recent several technical advancements have led to the development of various Novel Drug Delivery Systems (NDDS) that could revolutionize the method of drug delivery and hence could provide definite therapeutic benefits [2]. It is a fact that the conventional immediate release drug delivery systems, when taken frequently in a day, can maintain drug concentration levels in therapeutically effective range. However, this results in significant fluctuations in plasma drug levels. Till date, remedies have been found for most of the diseases; but still, research is going on to improve the existing therapy.

To bring a new drug molecule in the market, it involves a lot more than an investment of time and money. In the pre-GATT era, the patents of drug molecules/ formulations are expiring. The new way of patenting the drug is to use "Novel Drug Delivery Systems," *i.e.*, NDDS with improved bioavailability (BA). To formulate a drug or to re-formulate it in the form of NDDS is not a Herculean task if one goes methodically and skillfully. This is where the formulation development studies play an important role.

Oral Controlled Drug Delivery: Drug absorption at the desired rate means, first to reach the effective plasma level within an acceptable short period; second, to avoid an overshoot in the case of rapidly absorbed drugs and third to maintain effective plasma levels over the desired period. Although the intensity of the pharmacological effect is related to the drug concentration at the site of action, which is in turn, related to the plasma drug concentration, an ideal situation is obtained when the concentration is continuously maintained between minimum effective and maximum safe levels (Therapeutic Index). Invariably, conventional drug dosage forms do not maintain the drug. Blood levels within the therapeutic range for an extended period. To achieve the same, a drug may be administered repetitively using a fixed dosing interval. This causes several potential problems as like sawtooth kinetics characterized by large peaks and troughs in the drug concentration-time curve **Fig. 1**, frequent dosing for drugs with short elimination half-life, and above all the patient noncompliance. Controlled release (CR) DDS attempt to sustain drug blood concentration at relatively constant and effective levels in the body by spatial placement or temporal delivery. Thus, CRDDS offer various advantages *viz.* reduce blood level fluctuations, minimize drug accumulation, employ less total drug, improve patient compliance, and minimize local and systemic side effects [3, 4, 5, 6, 7].

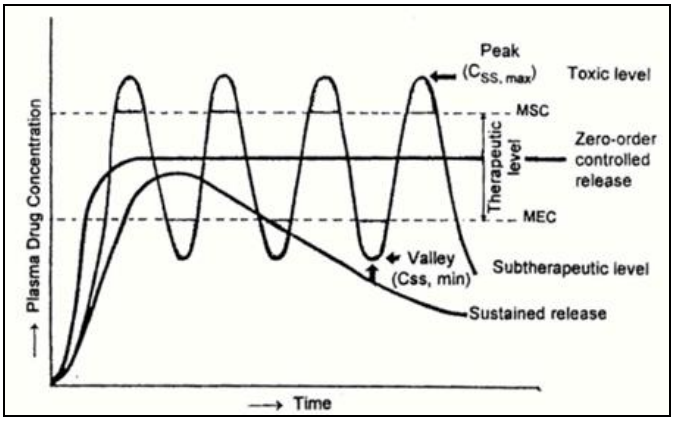

FIG. 1: PLASMA LEVEL PROFILES FOLLOWING CONVENTIONAL AND CONTROLLED RELEASE DOSING [10]

MATERIALS AND METHODS: Etodolac Gift Sample Provided by Sura Labs, Dilsukhnagar, Hyderabad. Sodium alginate, carbopol 934, calcium chloride, HPMC K 4M, sodium bicarbonate were Gifted from Merck Specialities Pvt. Ltd., Mumbai, India.

Methods:

Formulation of Floating Microspheres: The floating microspheres were prepared by Ionic gelation method. The polymeric solution was prepared by dissolving sodium alginate, sodium bicarbonate, and in the combination of carbopol was dissolved in distilled water, as shown in **Table 1**. The drug was dissolved in the polymeric solution. The prepared drug-polymer solution was added dropwise by a syringe into 100 ml of 5% Calcium chloride, being stirred at 200 rpm for 10 min. The formed microspheres further allowed to stir in the solution of crosslinking agents for an additional 1h.

TABLE 1: FORMULATION OF FLOATING MICROSPHERES

Formulation code	Drug (mg)	Sodium alginate (mg)	HPMC K 4M	Sodium bicarbonate (mg)
F1	1000	1000	-	200
F2	1000	2000	-	200
F3	1000	3000	-	200
F4	1000	750	250	200
F5	1000	1500	500	200
F6	1000	2250	750	200

Formulation of Mucoadhesive Microspheres: The mucoadhesive microspheres were prepared by Ionic gelation method. The polymeric solution was prepared by dissolving sodium alginate and in a combination of carbopol was dissolved in Distilled water, as shown in **Table 2**. The drug was dissolved in the polymeric solution. The prepared drug-polymer solution was added dropwise by a syringe into 100 ml of 5% calcium chloride, being stirred at 200 rpm for 10 min. The formed microspheres further allowed to stir in the solution of crosslinking agents for an additional 1h.

TABLE 2: FORMULATION OF MUCOADHESIVE MICROSPHERES

S. no.	Formulation code	Drug (mg)	Sodium alginate (mg)	Carbopol 934 (mg)
1	M1	1000	500	500
2	M2	1000	1000	1000
3	M3	1000	1500	1500

Evaluation Parameters and Procedures: [8-15]

Percentage Yield: The prepared floating microspheres were weighed after drying for all formulations. Then the percentage yield was calculated using the following formula:

% Yield = Actual weight of dried microspheres / Total weight of drug and excipients × 100

Drug Entrapment Efficiency: [13] Microspheres equivalent to 100 mg of the drug Etodolac was taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10 ml of methanol and the volume was made up to 100 ml with 0.1N HCl. Kept it for sonication about 1 h.

Then the solution was filtered through Whatmann filter paper, and the absorbance was measured after suitable dilution spectrophotometrically at the respective wavelength.

The amount of drug entrapped in the microspheres was calculated by the following formula:

% Drug entrapment efficiency = Experiment drug content / Theoretical drug content × 100

Micromeritic Properties: The microspheres were characterized by their micromeritic properties such as bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose.

The Angle of Repose: Angle of repose was determined using the funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. The radius of the heap (r) was measured the angle of repose (θ) was calculated using the following formula.

$$\theta = \tan^{-1} h/r$$

Bulk Density: Apparent bulk density (ρ_b) was determined by pouring the powder blend into a graduated cylinder. The bulk volume ($V_{b)}$ and the weight of the powder (M) were determined.

$$\rho_b = M / V_b$$

Tapped Density: The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tappings). The minimum volume (V_t) occupied in the cylinder, and weight of the blend was measured.

The tapped density (ρ_t) was calculated using the following formula.

$$\rho_t = M / V_t$$

Compressibility Index or Carr's Index: The simplest way for measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index.

$$\text{Carr's Index} = \rho_b - \rho_t / \rho_b \times 100$$

Where, ρ_t = tapped density, ρ_b = bulk density

Hausner's Ratio (H): It is an indirect index of ease of powder flow. It is calculated by the following formula:

$$\text{Hausner's ratio (H)} = \rho t/\rho b$$

Where ρ_t = tapped density, ρ_b = bulk density.

In-vitro **Buoyancy:** Floating microspheres (equivalent to 25 mg) were dispersed in 100 ml of 0.1N hydrochloric acid solution (pH 1.2) to simulate gastric fluid at 37 °C. The mixture was stirred with a paddle at 50 rpm, and after 12 h, the layer of buoyant microspheres (W_f) was pipetted and separated by filtration simultaneously sinking microsphere (W_s) was also separated. Both microspheres type were dried at 40 °C overnight. Each weight was measured, and buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microsphere.

$$\text{Buoyancy} = W_f / W_f + W_s \times 100$$

Where W_f and W_s = the weights of the floating and settled microspheres, respectively. All the determinations were made in triplicate.

Ex-vivo **Mucoadhesion Study:** The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen, and immediately after that, the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 37 °C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation.

$$\% \text{ Mucoadhesion} = W_a - W_1 / W_a \times 100$$

Where W_a is the weight of microspheres applied, W_1 is the weight of microspheres leached out.

In-vitro **Drug Release Study:** The dissolution study of floating microspheres were performed over a 12 h period using USP type I (Basket) Dissolution Testing Apparatus (Lab India) 900 ml of 0.1N HCl was used as dissolution medium agitated at 100 RPM, at the temperature of 37 ± 0.5 °C. 5 ml samples were withdrawn at the required time intervals for estimating drug release. The samples were analyzed by UV spectrophotometry at 225 nm wavelength.

In-vitro **Drug Release Kinetics:** The release data obtained were fitted into various mathematical models. The parameters 'n' and time component 'k,' the release rate constant and 'R,' the regression coefficient were determined by the Korsmeyer-Peppas equation to understand the release mechanism. To examine the release mechanism of Etodolac from the microspheres, the release data were fitted into Peppa's equation,

$$Mt / M\infty = Ktn$$

Where Mt / M∞ is the fractional release of the drug, 't' denotes the release time, 'K' represents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusional exponent and characterize the type of release mechanism during the release process.

If n<0.5, the polymer relaxation does not affect the molecular transport, hence diffusion is Fickian.

If n>0.5, solid transport will be non-fickian and will be relaxation controlled. Other equations to study the drug release kinetics from dosage forms

Zero Order: This model represents an ideal release to achieve prolonged pharmacological action. This applies to dosage forms like transdermal systems, coated forms, osmotic systems, as well as Matrix tablets containing low soluble drugs.

$$\% R = kt$$

First Order: The model is applicable to hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

$$\text{Log (fraction unreleased)} = kt/2.303$$

Matrix (Higuchi Matrix): [8] This model applies to systems with the drug dispersed in the uniform swellable polymer matrix as in case of matrix tablets with the water-soluble drug.

$$\% R = kt\ 0.5$$

Peppas Korsmeyer Equation: [9] This model is widely used when the release mechanism is well known or when more than one type of release phenomenon could be involved. The 'n' values could be used to characterize different release mechanisms as:

$$\% R = kt\, n$$

$$\log \% R = \log k + n \log t$$

Drug and Excipient Compatability Studies:

Fourier Transform Infrared spectroscopy (FTIR): Fourier Transform Infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on an FTIR spectro-photometer by the ATR (attenuated total reflectance) technique. For this technique, ZnSe crystal was used to know the wavelength of those drug and carriers. The spectra were scanned over a frequency range 4000 cm^{-1}-550 cm^{-1}.

Differential Scanning Calorimetry (DSC): The possibility of any interaction between the drug and the carriers during the preparation of etodolac microsphere was assessed by carrying out thermal analysis of drug and polymer alone as well as a physical mixture and Etodolac microsphere using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in a sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350 °C under a nitrogen flow of 50 mL/min.

SEM (Scanning Electron Microscope) Studies: The surface morphology of the layered sample was examined by using SEM (JEOL Ltd., Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to aluminum stubs were coated with a thin layer (30^0A) of gold by employing POLARON - E 3000 sputter coater. The samples were examined by SEM with direct data capture of the images onto a computer.

RESULTS AND DISCUSSION:

Pre-compression Evaluation: Floating and mucoadhesive microspheres were subjected to micromeritic properties. The angle of repose values indicates that the floating and mucoadhesive microspheres have good flow properties. The bulk density of all the formulations was found to be in the range of 0.32 ± 0.010 to 0.44 ± 0.017 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.39 ± 0.018 to 0.50 ± 0.015 micrometers showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18, which show that the floating and mucoadhesive microspheres have good flow properties. All the formulations have shown the Hausner ratio ranging between 0 to 1.2, indicating the floating microspheres have good flow properties. The mean particle size was found to be in the range of 381.55 ± 2.54 to 493.24 ± 2.43 micrometer.

TABLE 3: MICROMERITIC PROPERTY OF FLOATING AND MUCOADHESION MICROSPHERES OF ETODOLAC

S. no.	Formulation code	Mean partical size (µm)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausners ratio	Carrr's Index	Angle of Repose(θ)
1	F1	381.55±2.54	0.32±0.010	0.39±0.018	1.21±0.04	11.13±0.11	28.49±1.71
2	F2	455.22±2.52	0.35±0.012	0.40±0.015	1.14±0.05	12.5±0.64	27.72±1.89
3	F3	471.52±2.05	0.40±0.007	0.47±0.014	1.17±0.03	14.8±0.24	30.88±2.78
4	F4	385.15±1.08	0.36±0.014	0.44±0.014	1.22±0.01	18.18±0.33	27.00±1.93
5	F5	451.84±2.07	0.41±0.015	0.47±0.015	1.14±0.02	12.76±0.26	26.02±1.80
6	F6	493.24±2.43	0.40±0.012	0.48±0.021	1.2±0.01	16.66±0.33	26.56±1.43
7	M1	473.9±2.16	0.39±0.018	0.45±0.022	1.15±0.03	13.33±1.5	26.80±1.68
8	M2	482.12±2.21	0.41±0.015	0.48±0.027	1.17±0.01	14.5±0.86	27.11±1.59
9	M3	477.5±2.15	0.44±0.017	0.50±0.015	1.13±0.02	12±0.35	26.56±1.68

All values represented as mean ± standard deviation (n=3)

The Yield of Floating and Mucoadhesive Microspheres: The percentage yield of floating microsphere formulation F1 to F6 and mucoadhesive microspheres M1 to M3 were in the range of 77.14 ± 0.64 to 93.64 ± 0.55 (as shown in **Table 4**). To observe the effect of polymer concentration on the percentage yield of the floating microspheres, formulations were prepared at a varying concentration of Sodium alginate and along with carbopol 934.

***In-vitro* Buoyancy for Floating Microspheres:** The purpose of preparing floating microspheres was to extend the gastric residence time of a drug. The buoyancy test was carried out to investigate the floatability of the prepared microspheres.

The microspheres were spread over the surface of 0.1 N HCl and the fraction of microspheres buoyant and settled down as a function of time was quantitated. The *in-vitro* buoyancy of formulation F1 to F6, it was range from 71.96 ± 1.04 to 82.96 ± 1.07, respectively (as shown in **Table 4**). Among all formulation, F6 was found to be highest in-vitro buoyancy 82.96 ± 1.07. The results also showed a tendency that the larger the particle size, the longer the floating time.

Entrapment Efficiency for Floating and Mucoadhesive Microspheres: The entrapment efficiency of floating microspheres F1 to F6 and mucoadhesive microspheres were in the range of 77.43 ± 2.72 to 98.11 ± 2.59 respectively (as shown in **Table 4**) among all the formulations F5 98.11 ± 2.59.

TABLE 4: PERCENTAGE YIELD, *IN-VITRO* BUOYANCY AND INCORPORATION EFFICIENCY OF FLOATING MICROSPHERES OF ETODOLAC

S. no.	Formulation code	Percentage yield	*In-vitro* buoyancy (in sec)	Entrapment efficiency (%)
1	F1	77.14±0.64	71.96±1.04	77.43±2.72
2	F2	82.29±0.69	75.43±2.02	87.34±2.84
3	F3	85.35±0.66	79.32±0.97	87.11±3.01
4	F4	93.08±0.72	73.41±1.03	92.30±2.88
5	F5	80.48±0.65	75.33±1.32	79.76±1.58
6	F6	86.05±0.51	82.96±1.07	91.94±2.17
7	M1	90.17±0.43	-	98.11±2.59
8	M2	92.74±0.74	-	83.91±2.02
9	M3	90.64±0.55	-	90.38±2.34

All values represented as mean ± standard deviation (n=3)

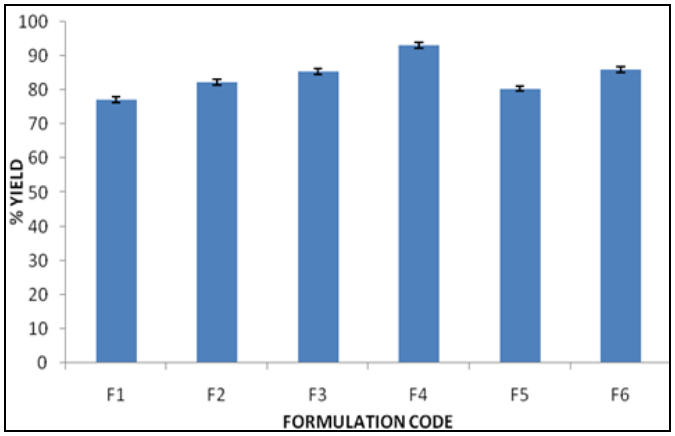

FIG. 2: COMPARISON OF YIELD OF FLOATING MICROSPHERES OF ETODOLAC

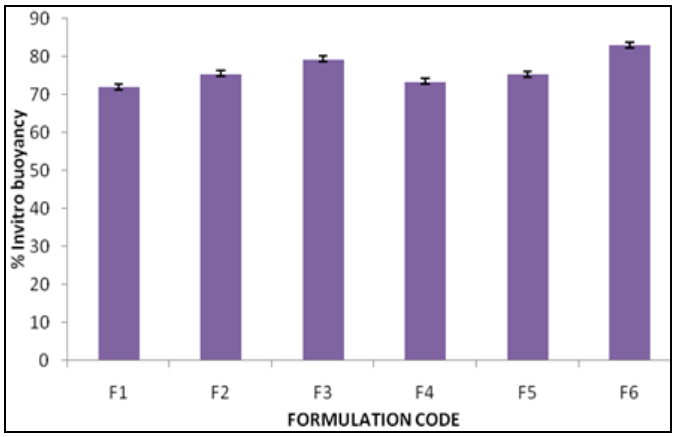

FIG. 3: COMPARISON OF PERCENT *IN-VITRO* BUOYANCY OF FLOATING MICROSPHERES OF ETODOLAC

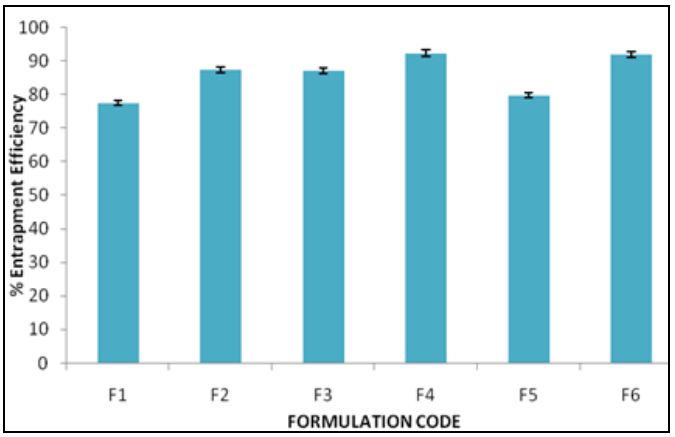

FIG. 4: COMPARISON OF DRUG ENTRAPMENT EFFICIENCY OF FLOATING MICROSPHERES OF ETODOLAC

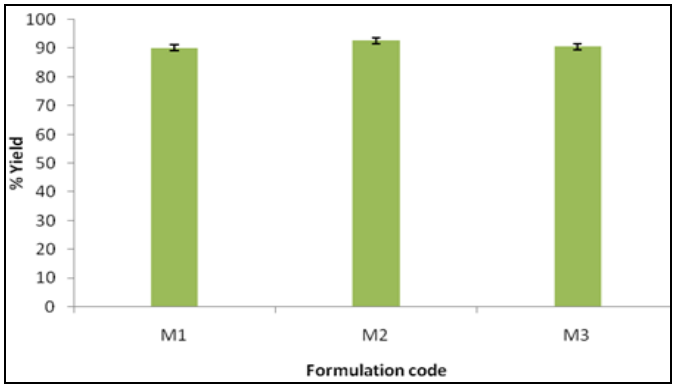

FIG. 5: COMPARISON OF YIELD OF MUCOADHESIVE MICROSPHERES OF ETODOLAC

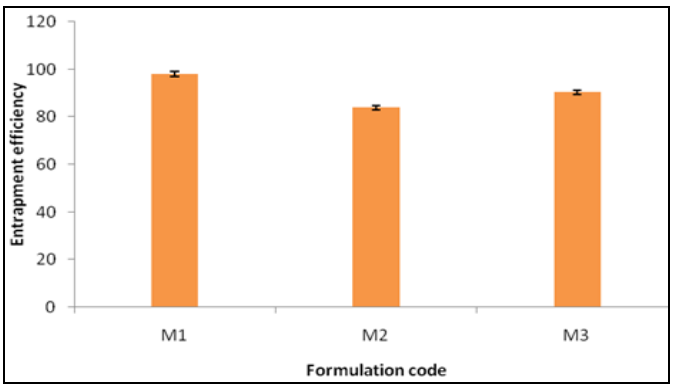

FIG. 6: COMPARISON OF DRUG ENTRAPMENT EFFICIENCY OF MUCOADHESIVE MICROSPHERES OF ETODOLAC

***In-vitro* Drug Release:** From the dissolution data of floating microspheres by ionic gelation method, Formulations prepared with Sodium alginate alone has shown maximum drug release at 12 h in the ratio of 1:3. Formulations prepared with sodium alginate along with carbopol retard the drug release. Among formulations of floating microspheres, F3 was considered as optimized for floating microspheres.

***Ex-vivo* Mucoadhesion Study:** From the dissolution data of mucoadhesive microspheres by ionic gelation method M1 formulation has shown maximum drug release at 12 h. When increase the polymer concentration retards the drug release more than 12 h. The mucoadhesive property of the microspheres was evaluated by *in-vitro* adhesion testing methods called *in-vitro* wash off test / *ex-vivo* mucoadhesion study.

TABLE 5: *IN-VITRO* DRUG RELEASE DATA OF ETODOLAC FLOATING MICROSPHERES F1 TO F6

S. no.	Cumulative % drug release						
	Time (h)	F1	F2	F3	F4	F5	F6
	0	0	0	0	0	0	0
1	1	8.24±0.98	6.22 ±1.05	4.83±1.15	4.07 ±1.28	4.23±1.11	2.16±1.24
2	2	12.14±1.25	10.11±1.12	9.23±2.24	12.32±0.98	9.56±1.64	5.91±1.52
3	3	23.08±2.05	18.42±1.85	15.65±1.08	21.44±2.01	16.43±1.54	10.96±1.47
4	4	30.64±1.56	26.32±2.04	22.42±0.98	30.23±1.41	22.71±2.12	18.65±0.97
5	5	41.55±1.81	33.08±2.17	31.32±1.64	38.86±1.06	31.78±0.95	25.41±2.17
6	6	53.34±2.14	41.15±1.53	39.44±1.55	43.29±1.75	38.92±1.04	31.32±1.61
7	7	63.41±1.74	50.28±1.67	47.54±1.34	51.65±2.11	48.64±2.06	39.68±2.05
8	8	79.27±2.05	61.33±1.74	56.63±1.27	60.46±1.62	56.38±1.26	48.36±1.04
9	9	88.75±1.34	73.28±1.97	63.43±1.31	69.45±1.47	62.81±1.40	57.65±1.67
10	10	99.12±2.08	84.36±2.17	71.32±1.55	78.34±1.09	70.30±1.55	64.84±2.21
11	11		95.34±2.08	82.14±2.43	85.34±1.14	78.64±1.07	72.11±1.33
12	12			94.14±2.11	90.91±2.07	85.48±2.17	80.55±1.41

TABLE 6: *IN-VITRO* DRUG RELEASE DATA OF ETODOLAC MUCOADHESIVE MICROSPHERES

S. no.	Time (h)	Cumulative % drug release		
		M1	M2	M3
1	0	0	0	0
2	1	8.56 ± 1.67	5.07± 1.26	2.16±1.24
3	2	15.48 ± 2.15	11.12± 0.98	5.91±1.52
4	3	23.18 ± 1.06	18.41± 1.41	10.96±1.47
5	4	34.29 ± 0.96	25.87± 0.86	18.65±0.97
6	5	41.28 ± 2.04	35.14± 0.78	25.41±2.17
7	6	48.65 ± 1.62	41.88± 1.07	31.32±1.61
8	7	56.43 ± 1.34	49.32± 1.12	39.68±2.05
9	8	65.87 ± 2.11	56.87± 1.16	48.36±1.04
10	9	73.34 ± 1.47	62.87± 1.96	57.65±1.67
11	10	82.65 ± 1.32	71.59± 0.84	64.84±2.21
12	11	88.65 ± 2.06	78.23± 0.39	72.11±1.33
13	12	94.55±0.92	88.49± 1.64	80.55±1.41

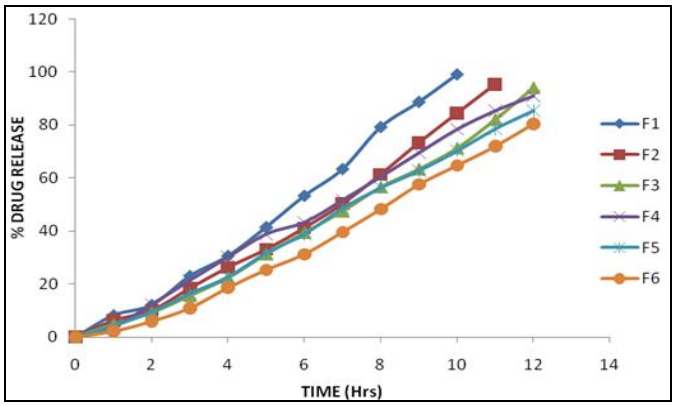

FIG. 7: *IN-VITRO* DRUG RELEASE PROFILE OF ETODOLAC FLOATING MICROSPHERES

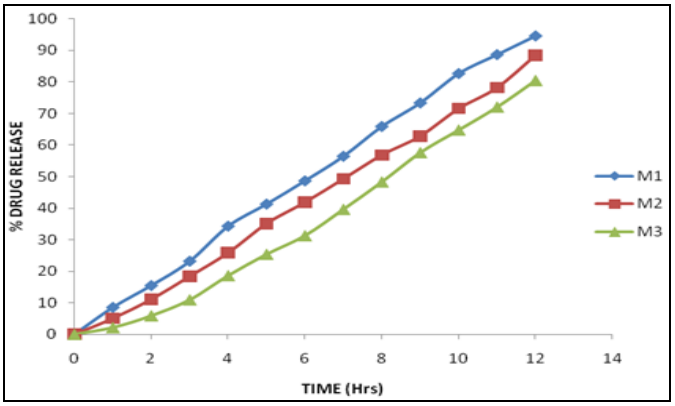

FIG. 8: COMPARISON OF *IN-VITRO* DRUG RELEASE PROFILE OF ETODOLAC MUCOADHESIVE MICROSPHERES

TABLE 7: *EX-VIVO* MUCOADHESION TEST TO AFFECTS MUCOADHESIVE PROPERTIES OF THE MICROSPHERES

S. No	Formulation Code	After 1 h	After 2 h	After 3h	After 4 h
1	M1	92	84	81	76
2	M2	94	90	84	79
3	M3	93	88	80	74

The numbers of microspheres adhering to the tissue were calculated after 30 min, 1 h, and hourly at 4 h. After determination, it was found that all formulations showed more than 75% mucoadhesion. Based on *in-vitro* drug release of mucoadhesive microspheres, M1 was considered as optimized formulation.

Drug- Excipient Compatability Studies:

FTIR:

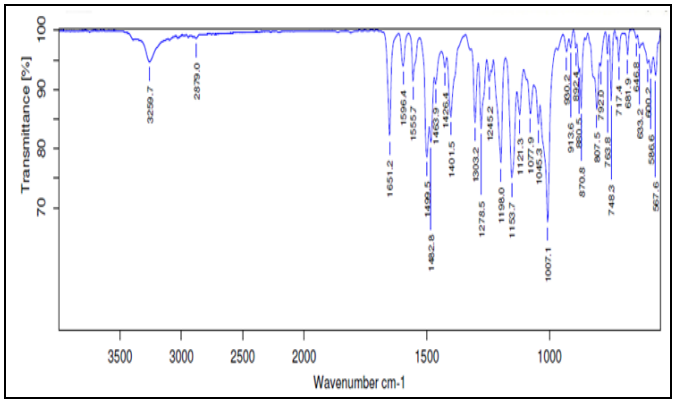

FIG. 9: FTIR OF ETODOLAC PURE DRUG

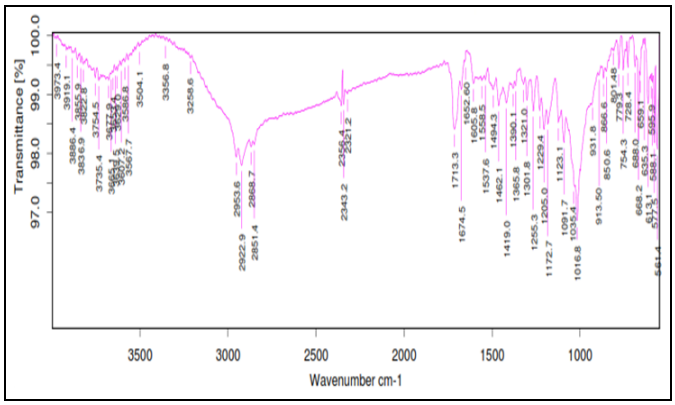

FIG. 10: FTIR OF OPTIMIZED FLOATING MICROSPHERES F3 FORMULA

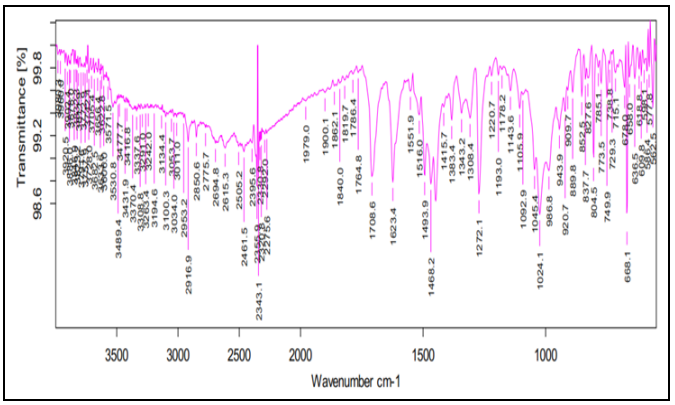

FIG. 11: FTIR OF OPTIMIZED MUCOADHESIVE MICROSPHERES M1 FORMULA

DSC:

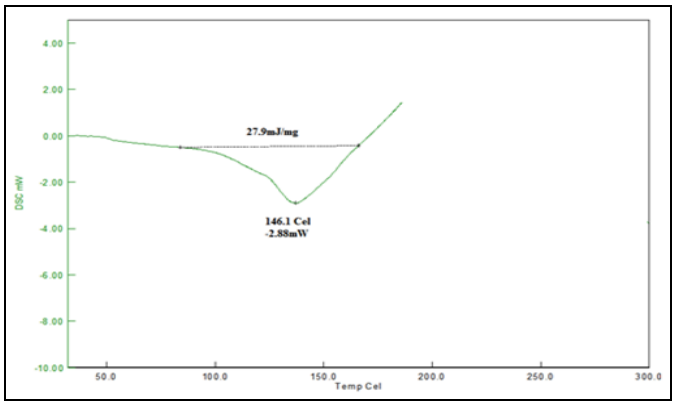

FIG. 12: DSC OF ETODOLAC PURE DRUG

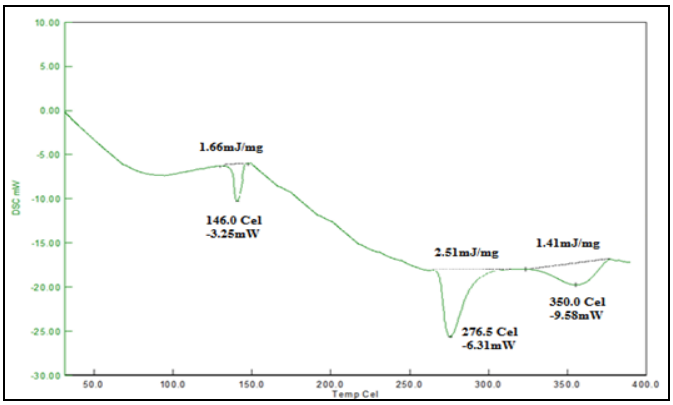

FIG. 13: DSC OF ETODOLAC + SODIUM ALGINATE + HPMC K4M

SEM (Scanning Electron Microscope) Studies:

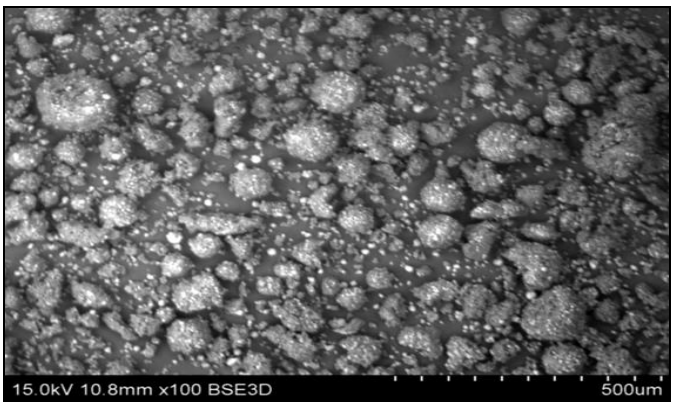

FIG. 14: SEM OF ETODOLAC PURE DRUG

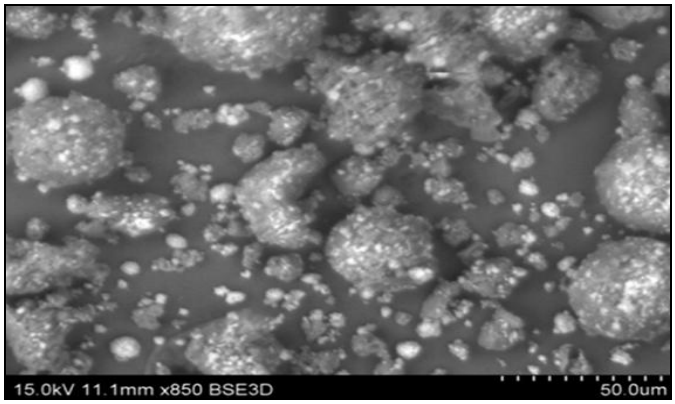

FIG. 15: SEM OF ETODOLAC FLOATING MICROSPHERES OPTIMISED F3 FORMULATION

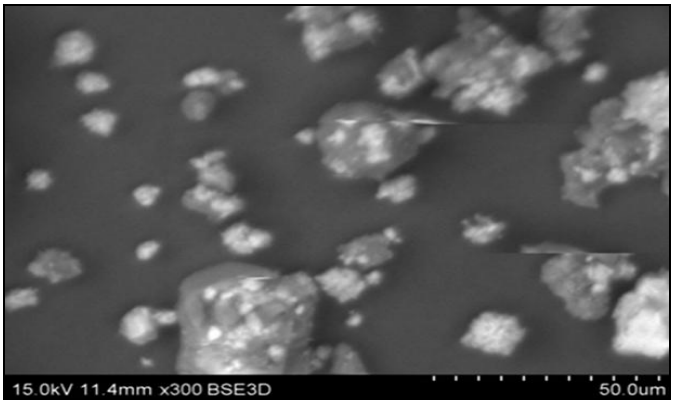

FIG. 16: SEM OF ETODOLAC MUCOADHESIVE MICROSPHERES M1 OPTIMISED FORMULATION

CONCLUSION: The floating and mucoadhesion microspheres were studied for micromeritic properties such as bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, which were found to be within limits. The percentage yield of floating microsphere formulation F1 to F6 and mucoadhesive microspheres m1 to m^3 were in the range of 77.14 ± 0.64 to 92.74 ± 0.74%. The *in-vitro* buoyancy of formulation F1 to F6, it was range from 71.96 ± 1.04 to 82.96 ± 1.07. Among all formulation, f6 was found to be highest *in-vitro* buoyancy 82.96 ± 1.07. The results also showed that the larger the particle size, the longer the floating time. The entrapment efficiency of floating microspheres F1 to F6 and mucoadhesive microspheres were in the range of 77.43 ± 2.72 to 98.11 ± 2.59. Formulations prepared with sodium alginate alone has shown

maximum drug release at 12 h in the ratio of 1:3. Formulations prepared with sodium alginate along with HPMC K 4M retard the drug release. Among all formulations of floating microspheres, F3 was considered as optimized for floating microspheres. From the release kinetics data, it was evident that floating optimized formulation follows zero order release kinetics.

From the dissolution data of mucoadhesive microspheres by ionic gelation method M1, the formulation has shown maximum drug release at 12 h. When an increase in the polymer concentration retards the drug release more than 12 h. Hence, M1 was considered as an optimized formulation for mucoadhesive micro-spheres. From the release kinetics data, it was evident that mucoadhesive optimized formula was followed zero order release kinetics.

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