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Formulation and Evaluation of Floating Microspheres of Etodolac

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ABSTRACT

Etodolac is a non steroidal anti-inflammatory drug. it is an inhibitor of cycloxygenase which belongs to the pyranocarboxylic acid group. Which is effective in treating fever, pain, and inflammation in the body. which is degraded in stomach .Thus, the purpose of the study is to formulate a dosage form which is coated by coating polymer(s) which passed the acidic medium and exhibit significant effect in intestine. An attempt was made to formulate microspheres with two coating polymers: HPMC & Ethyl Cellulose as well as using of floating properties of polymers will release drug in controlled manner. Thus, these different type of microspheres was characterized in terms of Particles size, buoyancy study, Entrapment efficiency and In-vitro studies.

Keywords: -Etodolac, Coating polymers. etc.

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INTRODUCTION

Etodolac is a non steroidal anti-inflammatory drug which is effective in treating fever, pain, and inflammation in the body. It is an inhibitor of cycloxygenase which belongs to the pyranocarboxylic acid group. Edotolac is a racemic mixture of [+]S and [-]R enantiomere. Etodolac is well-absorbed. Bioavailability is 80% or more. C_{max} is approximately 14 to 37 mcg/ml. T_{max} is approximately 1.4 h. Food decreases C_{max} approximately 50% and increases T_{max} by 1.4 to 3.8 h. Extensively metabolized in the liver.

Etodolac should be avoided by patients with a history of asthma attacks, hives, or other allergic reactions to aspirin or other NSAIDs. Rare but severe allergic reactions have been reported in such individuals. It also should be avoided by patients with peptic ulcer disease or poor kidney function, since this medication can worsen both conditions. Etodolac is used with caution in patients taking blood thinning medications (anticoagulants), such as warfarin (Coumadin), because it increases the risk of bleeding.

Side effects

- Chest pain, weakness, shortness of breath, slurred speech, problems with vision or balance;
- Coughing up blood or vomit that looks like coffee grounds;
- Swelling or rapid weight gain;
- Nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
- Fever, sore throat, and headache with a severe blistering, peeling, and red skin rash;
- Bruising, severe tingling, numbness, pain, muscle weakness; or
- Fever, headache, neck stiffness, chills, increased sensitivity to light, purple spots on the skin, and/or seizure (convulsions).

Dose of etodolac

Capsules: 200 and 300 mg; Tablets: 400 and 500 mg; Extended Release: 400, 500 and 600 mg. The maximum recommended daily dosage of etodolac is 1000 mg. However, some patients have been found to benefit from daily dosage of 1200 mg. Daily dosages of Etodolac exceeding 1200 mg have not been evaluated.[9]

MATERIALS AND METHOD

Etodolac was obtained as a gift sample from Ranbaxy lab. Dewas. Ethyl cellulose and hydroxy propyl methyl cellulose were procured from Oxford lab. Mumbai. Acetone , liquid paraffin and hydrochloric acid were procured from G.S. Chemical testing New Delhi.

Preparation of floating microsphere[5]

The microspheres were prepared by solvent evaporation technique. The polymer ethyl cellulose and hydroxyl propyl methyl cellulose in various ratio as shown in Table 5.5 was dissolved in the mixture of ethanol and dichloromethane having ratio (1:1). The drug Etodolac was dispersed in above solution of polymers for 10 minutes under stirring at 200 rpm. The resulting dispersion was poured slowly under stirring into distilled water (dispersion medium) containing 0.01% of tween 80. The stirring speed was maintained at 500 rpm and temperature was maintained at 30^0C. Stirring was continued for 1 hours and allow evaporating dichloromethane and ethanol completely. After evaporation of dichloromethane and ethanol, the microspheres formed were collected by filtration using filter paper, then washed 3 to 4 times with distilled water and dried at room temperature for 24 hrs. after that subsequently stored in a desiccators.

Table 1 Formula for different batches

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Etodolac	100mg	100mg	100mg	100mg	100mg	100mg
2	Ethyl cellulose	400mg	500mg	450mg	550mg	300mg	350mg
3	HPMC	200mg	100mg	150mg	50mg	300mg	250mg
4	Ethyl alcohol	5ml	5ml	5ml	5ml	5ml	5ml
5	Dichloromethane	5ml	5ml	5ml	5ml	5ml	5ml
6	Tween 80 (%)	0.01	0.01	0.01	0.01	0.01	0.01

Evaluation[1,2,3,6]

Determination of particle size:

Particle size of microspheres was determined by using optical microscopy method. Eye piece of the microscope was fitted with a micrometer. This eye piece micrometer was calibrated using a standard stage micrometer. microspheres was taken and suspended in liquid paraffin oil. This sample of suspension was mounted on a slide and placed on the mechanical stage. The size of the particle was determined with the help of the eye-piece micrometer. Particles size of 200 microspheres was determined and average was calculated.

Floating behavior of floating microsphere:

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 mL of 0.1 N HCl containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 8 hrs. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres .'

% Buoyancy = Weight of floating microsphere/ Initial weight of floating microsphere x 100

Percentage yield:

The prepared microspheres were collected and weighed from different formulations. The measured weight was divided by the total amount of drug and polymers which were used for the preparation of the microspheres to obtained percentage yield.

Drug entrapment efficiency:

To determine entrapment efficiency, 10.0 mg accurately weighted microspheres were crushed and dissolved in 100.0 mL 0.1 N HCl. The microspheres were kept to soak for overnight. After that the solution was filtered through 0.45 µ membrane filter. After appropriate dilution with 0.1 N HCl the drug content was determined spectrophotometrically at 279.6.0 nm

% Drug entrapment efficiency = Calculated drug concentration/ Theoretical drug concentration x 100

FT- IR spectrophtometric analysis:

To identify the interaction of drug etodolac with polymers, FT-IR spectrophtometric analysis was carried out by KBr disc method and spectrum was recorded in the range of 4000 cm^{-1} and 450 cm^{-1}.

Scanning electron microscopy

The shape and surface morphology of the microspheres were examined using scanning electron microscopy (JSM-6390, Japan). Microspheres were dusted onto double-sided carbon dust, which was placed onto a sample carrier in the shape of cylinder. After fixing the samples on the stubs, capture a photomicrograph.

***In-vitro* drug release profile**

A USP basket apparatus was used to study *in-vitro* drug release from floating microspheres. *In-vitro* drug release studies were carried out for all batches in USP type I dissolution test apparatus at 100 rpm and the dissolution medium was 900 mL of 0.1 N HCl solution. Microspheres containing 100.0 mg of drug was used for dissolution study. One mL of the aliquot was withdrawn at predetermined intervals. Required dilutions were made with 0.1 N HCl solution and filter the solution and analyzed for the drug content spetrophotometrically (UV 1800, Shimadzu, Japan) at 279.6.0 nm against suitable blank. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.

Kinetic modeling of dissolution profiles [4]

The drug release kinetics was studied by various kinetic models such as Korsmeyer-peppas, Higuchi plot, First order plot and Zero order plot. To study the release kinetics, data obtained

from *In-vitro* drug release studies were plotted in various kinetic models. Zero order as cumulative amount of drug released Vs time, First order as log cumulative percentage of drug remaining Vs time, and Higuchi's model as cumulative percentage of drug released Vs square root of time. The best fit model was confirmed by the value of correlation coefficient near to 1. The data was presented for the most appropriate model.

Zero order:

Graph was plotted between cumulative amount of drug released Vs time

$$\mathbf{C = K_0\, t}$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration Vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

First order:

Graph was plotted between log cumulative percentage of drug remaining Vs time

$$\mathbf{Log\ C = Log\ C_0 - kt/2.303}$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi's model:

Graph was plotted between cumulative percentage of drug released Vs square root of time.

$$\mathbf{Q = Kt^{1/2}}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer-Peppas:

The dissolution data was also fitted to the well known Korsmeyer Peppas equation (as log cumulative percentage of drug released Vs log time), which is often used to describe the drug release behavior from polymeric systems and the exponent n was calculated through the slope of the straight line.

$$\mathbf{M_t / M_\infty = Kt^n}$$

where M_t / M_∞ is the fractional solute release, M_t is the amount of drug released at time *t*, M_∞ is the amount of drug release after infinite time, t is the release time.

K is a kinetic release rate constant characteristic of the drug/polymer system and n is the diffusional exponent that characterizes the mechanism of drug release. If the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

Stability study

Stability of a pharmaceutical product can be defined as "the capability of a particular formulation (dosage form or drug product) in a specific container closure system to maintain within its physical, chemical, microbiological, therapeutic and toxicological, therapeutic and toxicological specifications throughout its shelf life". From the prepared microspheres which showed appropriate balance between the percentage yields and the percentage release was selected for stability studies. The prepared formulation were placed in borosilicate screw capped glass containers and stored at different temperatures i.e. room temperature (27° ± 2°C), oven temperature (40° ± 2°C) and in refrigerator (2°C - 8°C) for a period of 90 days. The samples were assayed for drug content at regular intervals of two week.

RESULT AND DISCUSSION

Particle size:

The particle size distribution of each formulation was measured using an optical microscope and the particle size was calculated by measuring nearly 200 particles with the help of a calibrated ocular micrometer. The average particle size of the optimized batch was found to be 475.0 µm (Table 2).

Table 2 Particle size

Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Particle size	489	490	468	488	480	475

Percentage yield:

Percentage yield of different formulations was determined. Percentage yield of the optimized batch was found to be 78.04 % w/w (Table 3)

Table 3 Percentage yield

Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
% yield	78.27	82.02	69.54	78.52	76.56	85.02

Entrapment efficiency:

The entrapment efficiency of Etodolac floating microspheres was in the range 75.40 to 83.64 % w/w. It was found that when the concentration of HPMC increased, the entrapment efficiency was decreased but on increasing EC concentration, entrapment efficiency increased which may be due to compact internal matrix of the resultant microsphere which may prevents the drug entrapment.

Table 4 Entrapment efficiency

Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Entrapment efficiency [a]	75.40	81.14	70.92	78.79	76.50	83.64

Floating behavior of microspheres:

Floating ability of different formulation was found to be differed according to Ethyl cellulose and HPMC ratio. F_1-F_3 formulations showed less floating ability (55.58-75.54%) in 8 hours. F_4-F_6 formulation showed best floating ability (64.76-74.12%) as showed in Table 6. The floating ability of microsphere is increased by increasing the HPMC ratio.

Table 6 Percentage buoyancy for different formulation

Formulations	F1	F2	F3	F4	F5	F6
% buoyancy [a]	55.58	57.51	75.54	64.76	67.12	74.12

a Mean, $n = 3$.

FT-IR spectrum of final formulation:

FT-IR of pure drug and formulation F6 was noted to determine drug stability and interaction. Pure Etodolac showed characteristic peaks at wave number 1580cm^{-1}, 1620 cm^{-1}, 1063cm^{-1}, 1075 cm^{-1}, 935 cm^{-1}, 740 cm^{-1}, which were present in formulation F6. It showed that the drug was stable during the formulation process.

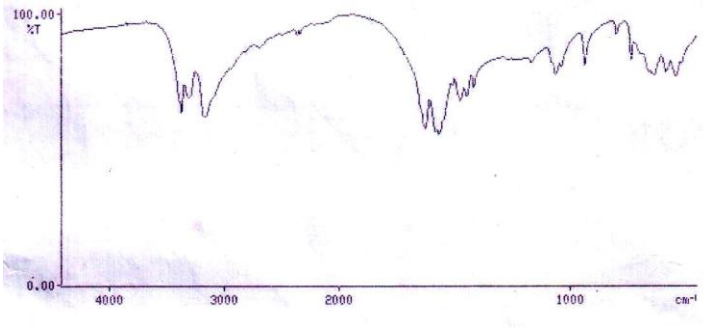

Figure 1 FT-IR-spectroscope of etodolac

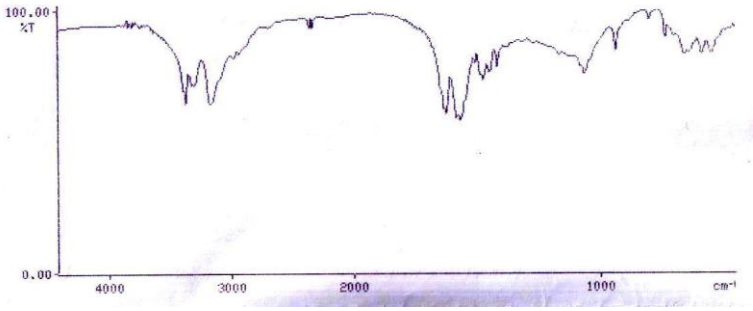

Figure 2 FT-IR-spectroscope of formulation F6

Scanning electron microscopy:

The shape and surface morphology of the microspheres were studied by SEM. The microspheres were spherical in shape with no visible irregularities as shown in Figure. 3. To observed surface morphology, photographs were taken at higher magnification (10,000 X) and it was found that small pores were observed at the surface which may be due to evaporation of solvent during

drying process (Figure 3).

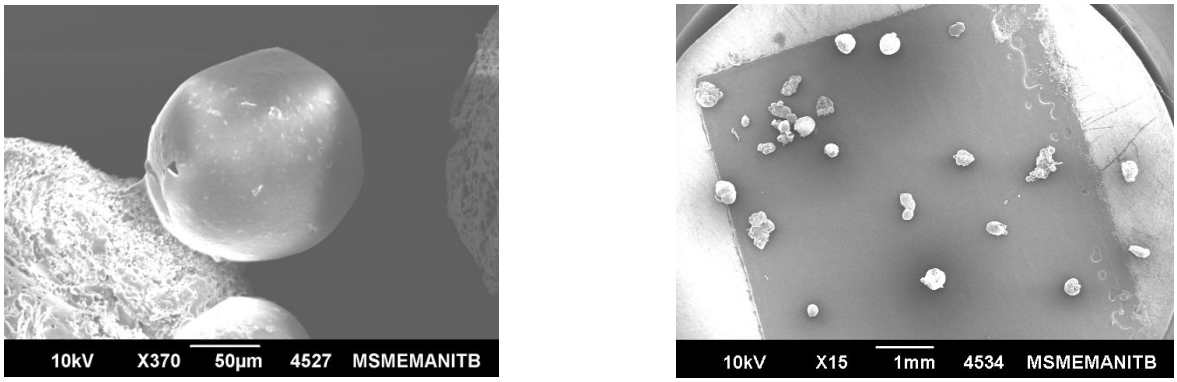

Figure 3 SEM photograph of etodolac microspheres (F6)

***In-vitro* dissolution release profile**

In-vitro study was performed by using USP dissolution apparatus type I. The release was found in the range of 78.87 to 99.94% at the end of 12 hrs. The formulation F6 showed 97.68 % release at the end of 12 hrs. It was found that microsphere prepared only with ethyl cellulose showed less release compare to formulation prepared with combination of ethyl cellulose and HPMC. As the proportion of HPMC was increased release rate also increased it may be due to the water solubility character of HPMC.

Table 7 Parameters for dissolution studies

Batch No	F_1 –F_6
Dissolution medium	0.1 N HCL
Volume of D.M.	900 ml
Dilution factor	3
Amount of drug	100 mg
RPM	50
Temperature	37.5^0 C

Table 8: CDR of various formulations of Floating microspheres of etodolac

Time(hrs)	F-1	F-2	F-3	F-4	F-5	F-6
0.5	5.21	6.76	12.65	5.87	6.65	6.43
1	13.86	15.92	21.52	12.88	16.24	10.85
2	17.48	22.54	33.56	17.82	21.04	25.6
3	23.90	28.13	43.51	37.40	34.55	32.84
4	29.80	33.50	48.54	45.21	49.76	40.67
5	35.21	40.71	54.92	55.25	57.14	51.7
6	40.18	45.82	63.84	63.53	68.82	60.63
7	46.50	48.93	72.09	68.19	74.26	67.72
8	51.61	52.27	84.49	73.63	78.47	74.45
9	59.52	55.64	92.15	78.00	80.91	79.45
10	61.52	60.57	99.13	81.99	84.08	85.46
11	69.62	68.72		85.15	87.07	90.65
12	78.87	73.18		86.52	92.28	97.68

Stability Study

The drug content of the formulation was determined in the period of 1 month, 2 month and 3 month. There was no significant change in drug content of floating microspheres which was stored at different temperature so floating microspheres was stable.

Table 9: Stability study of formulation

Time period	Initial (0 day)	After 1 months	After 2 months	After 3 months
Temperature (27^{o}C)	99.95	99.94	99.93	99.93
Temperature (40^{o}C)	99.96	99.94	99.93	99.91
Temperature (2^{o}C-8^{o}C)	99.96	99.95	99.94	99.92

Compatibility study by FT-IR study:

FT-IR spectrum was recorded to determine the compatibility between drug and polymers. FT-IR spectrum of pure drug, polymer and physical mixture of drug-polymer was recorded.

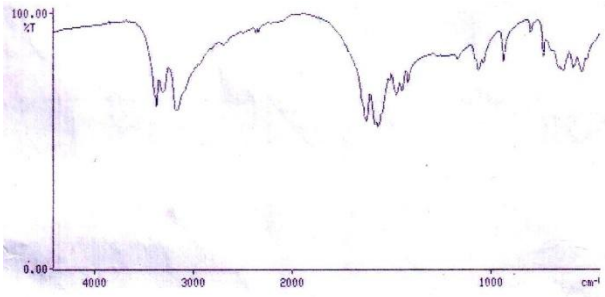

Figure 4 FT-IR spectroscope of pure drug etodolac

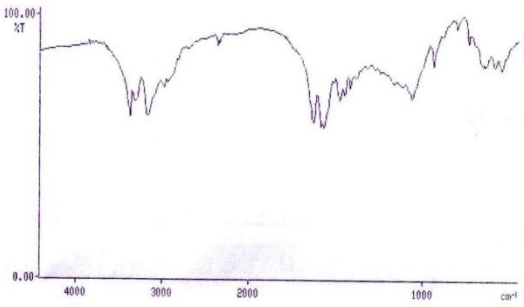

Figure 5 FT-IR of physical mixture (Drug + Hydroxy propyl methyl cellulose + Ethyl cellulose)

CONCLUSION

Floating microspheres of etodolac were prepared by a solvent evaporation method. *In-vitro* data obtained from floating microspheres of etodolac exhibited good buoyancy and release the drug in controlled manner via a diffusion mechanism. It was noticed that increase in the HPMC concentration, increased the drug release and good buoyancy. Microspheres of different size and drug content could be obtained by varying the formulation variables. The drug release was

sufficiently sustained and non-Fickian transport of the drug from floating microspheres was confirmed. Hence the floating microspheres of etodolac prepared with ethyl cellulose and HPMC may provide a convenient dosage form for achieving best performance regarding flow, release and floating properties.

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