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Preparation and evaluation of indomethacin microcapsules using ion gelation technique

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Abstract

Microcapsules are one of the multi particulate delivery system to achieve sustained or controlled release drug delivery to improve bioavailability and stability of drug. The main objective of the study is to extend drug release and to reduce dosing frequency. The purpose of the present investigation was to formulate and evaluate microcapsules of indomethacin by ion gelation technique. Microcapsules were prepared using hydroxyl propyl methyl cellulose and ethyl cellulose as coating material by evaporation of solvent in ion gelation technique. Microcapsules were characterized for their surface morphology, particle size, drug entrapment efficiency and *In vitro* drug release study. Microcapsules are spherical in nature. The controlled effect of microcapsules depends on the polymer concentration and type of polymers used in the formulation. In this study the microcapsules containing hydroxy propyl methyl cellulose in the concentration of 0.5% as the coating material shows better release of drug. About 95.4% of the drug was released in 18 hours from microcapsules containing HPMC in the concentration of 0.5%.

1. INTRODUCTION

Microcapsules are one of the particulate delivery system to achieve extended release and to improve bioavailability [1]. Microencapsulation is a rapidly expanding technique as it involves applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation provides the mean of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and controlling the release of drug [2].

Microcapsules are having several advantages. They are mainly used for prolonged or sustained release of the drug. Most of the drugs are microencapsulated to reduce the GIT irritation and the inflammation due to the formation of the peptic ulcers and duodenal ulcers [3]. A liquid can be converted in to the pseudo-solid for easy handling and storage like the drug Epraginone. Hygroscopic properties of the core material can be reduced the microencapsulation process. It also decreases the odour and volatility. The drugs can be protected from the atmospheric conditions like moisture, light and oxygen. The popular method for the encapsulation of the drugs within water in soluble polymer is the Ion gelation technique [5].

The main purpose of the present research was to develop a controlled release drug delivery system of Indomethacin microcapsules[6] (Non steroidal anti-inflammatory drug) for oral administration using hydroxyl propyl methyl cellulose and ethyl cellulose polymers in order to increase the drug release rate and also reduce the gastric intestinal irritation and duodenal ulcers.

2. MATERIALS AND METHODS

2.1 Materials

Indomethacin was received from Yarrow Chem. Products (Mumbai),Hydroxy propyl methyl cellulose received from Yarrow Chem. Products (Mumbai),Ethyl cellulose received from Lobea chemie pvt.ltd (Mumbai),Calcium chloride Merck specialties private limited (Mumbai),Sodium alginate received from Finar chemicals limited (Ahemdabad).

Table 1: Formula for Indomethacin Microcapsules

S. No.	Formulation Code	Drug (g)	Polymer (g)	Sodium Alginate (g)	Anhydrous Calcium chloride (%)	Core coat ratio
1	HPMC1	0.1	0.1	0.1	10	1:1
2	HPMC2	0.1	0.2	0.1	10	1:2
3	EC1	0.1	0.1	0.1	10	1:1
4	EC2	0.1	0.2	0.1	10	1:2

2.2 Methodology

Indomethacin microcapsules are prepared by using Ion gelation technique. Microcapsules were prepared by dropping the drug loaded polymeric solution using the syringe in to the aqueous solution. [7]

2.2.1 Ion Gelation Method

a) Calculated amount of polymer was taken in a beaker and water was added until it forms a smooth paste.

b)Add the required amount of drug to the above paste and add a little bit of water until it dissolves completely.

c)Add the sodium alginate in the required amount and start mixing it with the addition of water, mix it until it forms a smooth paste.

d)Take about 10mg of calcium chloride in 100ml of water, stirrer it until it gets dissolved.

e)Then keep the calcium chloride solution on the magnetic stirrer rotating at a speed of 1000rpm.

f)Add the above polymer drug mixture into the calcium chloride solution, with the help of a syringe of 5ml needle sized injection.

g)Filter the above solution with the help of the filter paper and throw the filtrate and separate the microspheres

h)Dry them under hot air oven until they form into solid particles.

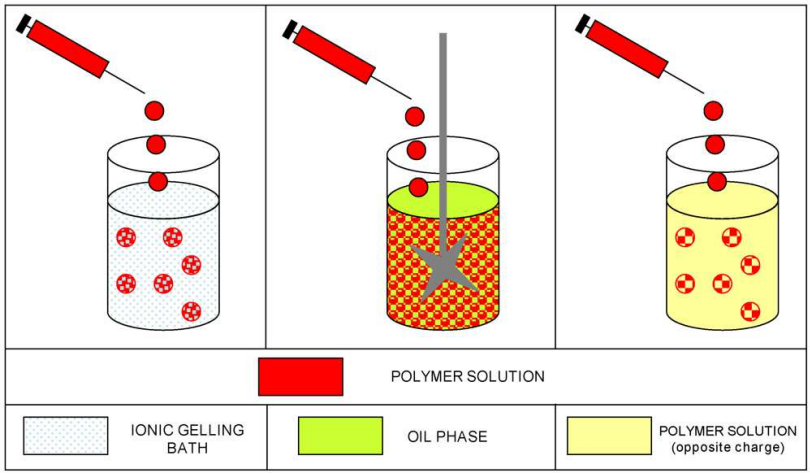


Fig.1: Process of ion gelation method

2.3 Evaluation

The prepared Indomethacin microcapsules were evaluated for the following parameters:

2.3.1 Micromeritic properties [8]

a) Angle of repose (θ)

The flow characterization of microspheres were assessed by determining the angle of repose which is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plain the sufficient quantities of the microspheres were passed through a funnel

from a particular height (1cm) on to a flat surface until it forms a heap, which should touch the tip of the funnel. The height (1cm) and the radius (r) of the heap were measured. The angle of repose was calculated using the formula

Angle of repose (θ) =tan -1 (h/r)

b) Hausner's ratio

Hausner's ratio is an indirect index of ease of meaning the powder flow. It is calculated by the following formula:

Hauser's ratio = Tapped density / Bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

c) Particle size analysis [9]

Microspheres were separated in to different size fraction for sieving for10 min using a mechanical shaker (Geologist Syndicate Pvt ltd, India) contain9ing the standard sieves having the mesh size of #14, #18, #20, #25, and #30. The particle size distribution of the microspheres for all the formulation was determined and the mean particle size of the microspheres was calculated using the following formula:

$$\text{Mean particle size} = \frac{\sum \text{Mean particle size of the fraction} \times \text{Weight fraction}}{\sum \text{Weight fraction}}$$

2.3.2 Percentage yield [10]

The percentage yield was calculated by using the formula

$$\text{Percentage yield} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

2.3.3 Determination of the drug content [11]

100 Mg of Indomethacin microspheres were taken and powdered and transferred in to a100 ml volumetric. The volume was made up to the mark with 6.8 pH Phosphate buffer and then kept aside for 12 hrs with occasional shaking. Then the solution filtered through the membrane filter (0.45µg pore size) and 1 ml of this solution was diluted using phosphate buffer of pH 6.8 and analyzed using a spectrophotometer for the Indomethacin content at 320 nm using a regression equation derived from the standard graph (R^2=0.999) to get the particle drug content. All the experimental units are analyzed in triplicate (n=3).

2.3.4 Drug encapsulation efficiency [12]

Drug encapsulation efficiency was calculated using the formula:

$$\text{Drug encapsulation efficiency} = \frac{\text{ACTUAL DRUG CONTENT}}{\text{THEORETICAL DRUG CONTENT}} \times 100$$

2.3.5 Swelling Index [13]

Microspheres (100 mg) were placed in little excess of the phosphate buffer (ph6.8) and allowed to swell to constant weight. The microspheres were removed, blotted with filter paper and their changes in weight were measured at pre-determined time intervals of 0, 1, 2, 3, 4, 5, 6 hours. The degree of swelling was then calculated from the formula.

$$SR = (W_g - Wo) / W_o$$

Where Wg = final weight

W_o = initial weight of the formulation

2.3.6 *In vitro* drug release studies

In vitro dissolution studies were performed by using USP Type 1 dissolution apparatus [14] at 50 rpm. The microspheres were weighed and filled in the empty capsule shells and placed in the basket. The dissolution medium (900ml) consisted of Phosphate buffer pH 7.4. The temperature was maintained at 37± 2°C. An aliquot (5ml) was withdrawn at specific time intervals and replenished with an equivalent volume of dissolution fluid. Drug content was determined by U.V-VISIBLE spectrophotometer [15] at 320 nm.

3. RESULTS

The results of in vitro release profile [16] obtained for all the formulations were plotted in modes of data treatment as follows:

1.Zero – order kinetics model - cumulative % drug release versus time.

2.First – order kinetics model – log cumulative percentage remaining versus time.

3.1 Characteristics of Indomethacin

Table 2: List of Values Micromeritic Properties of Indomethacin Pure Drug

Property	Value
Angle of repose	30.15
Bulk density	0.5g/ml
Tapped density	0.72g/ml
Carr's index	31
Hauser's ratio	1.44
Melting point	155-160^{O}C

Table 3: Micromeritic Results of Indomethacin Microcapsules

Formulation code	Bulk density	Tapped density	Hauser's ratio	Carr's index	Angle of repose
HPMC1	0.58±0.02	0.617±0.07	1.13	13.3	22.58±0.32
HPMC2	0.56±0.03	0.625±0.03	1.12	11.6	26.3±0.23
EC1	0.52±0.02	0.595±0.04	1.14	14.39	24.22±0.3
EC2	0.61±0.04	0.685±0.04	1.13	13.8	26.56±0.2

Table 4: Swelling Index of Indomethacin Microcapsules

Formulation code	1 (hr)	2 (hr)	3 (hr)	4 (hr)	5 (hr)	6 (hr)
HPMC1	19.2±0.20	29.1±0.26	33.55±0.20	47.5±0.2	54.6± 0.1	65.4±0.25
HPMC2	20.1±0.26	30±0.25	36.1±0.20	49.4±0.15	56.7±0. 1	68.6±0.26
EC1	14.9±0.20	25.7±0.2	31.51±0.35	43.3±0.2	50.2±0.2	61.59±0.2
EC2	17.63±0.2	28.5±0.1	32.84±0.2	46.2±0.2	51.9±0.35	63.3±0.1

Table 5: Drug Encapsulation Efficiency, Drug Content of Indomethacin Microspheres

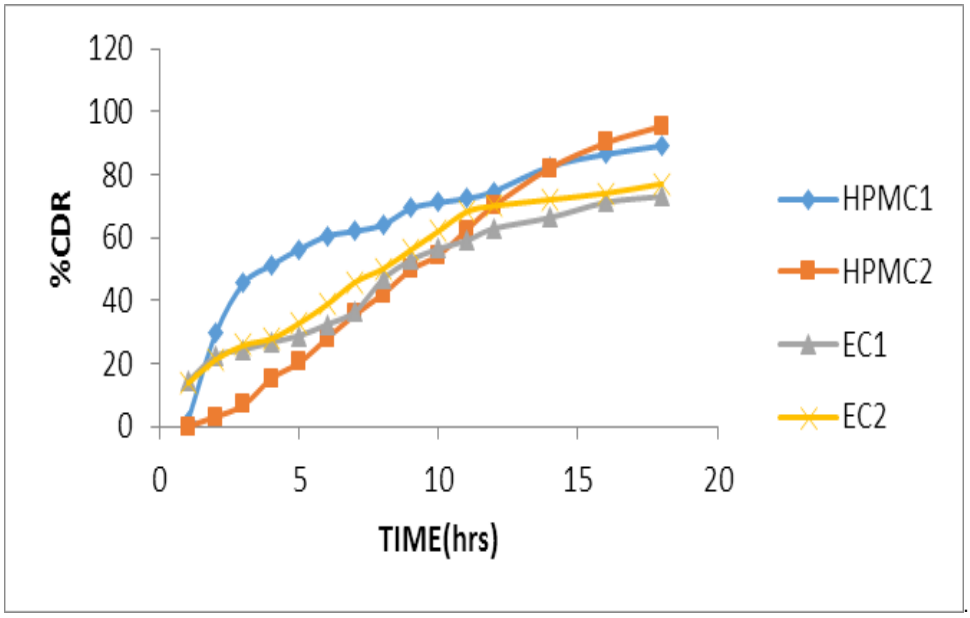
Formulation code	Theoretical drug content (%)	Encapsulation efficiency (%)	Practical drug content (%)
HPMC1	100	74	74
HPMC2	100	78.2	78.2
EC1	100	72	72
EC2	100	71.6	71.6

Table 6: *In vitro* Dissolution Studies of Indomethacin Microcapsules cumulative Percentage Drug Release

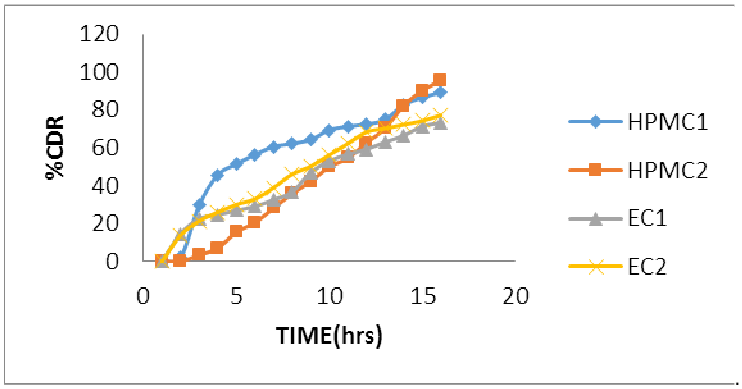
Time (hr)	HPMC1 (%)	HPMC2 (%)	EC1 (%)	EC2 (%)
1	1.935	0.006	14.47	13.78
2	29.63	3.19	22.41	21.27
3	45.6	6.90	24.51	25.87
4	51.3	15.36	26.81	29.92
5	56.34	20.35	28.91	32.88
6	60.52	28.12	32.50	38.84
7	62.1	35.66	36.62	45.94
8	64.2	42.12	46.81	50.12
9	69.3	49.8	52.92	56.14
10	71.2	54.5	56.50	62.12
11	72.4	62.5	59.12	68.21
12	74.8	70.24	62.92	70.12
14	82.6	82.12	66.41	72.14
16	86.5	90.12	71.21	74.14
18	89.2	95.4	73.12	77.13

Table 7: Zero Order Data of Indomethacin Microcapsules

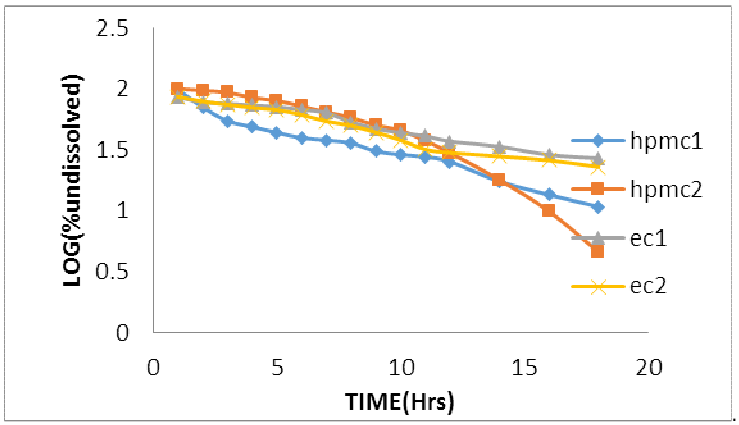
Time	% CDR HPMC1	Log % Undissolved	% CDR HPMC2	Log % Undissolved	% CDR EC1	Log % Undissolved	% CDR EC2	Log % Undissolved
1	1.935	1.9915	0.006	1.999	14.47	1.9321	13.78	1.9356
2	29.63	1.8474	3.19	1.985	22.41	1.8898	21.27	1.8961
3	45.6	1.7356	6.90	1.968	24.51	1.8779	25.87	1.8700
4	51.3	1.6875	15.36	1.927	26.81	1.8645	29.92	1.8456
5	56.34	1.6401	20.35	1.901	28.91	1.8518	32.88	1.8269
6	60.52	1.5964	28.12	1.856	32.50	1.8293	38.84	1.7865
7	62.1	1.5786	35.66	1.808	36.62	1.8020	45.94	1.7329
8	64.2	1.5539	42.12	1.762	46.81	1.7258	50.12	1.6979
9	69.3	1.4871	49.8	1.700	52.92	1.6728	56.14	1.6421
10	71.2	1.4594	54.5	1.658	56.50	1.6385	62.12	1.5784
11	72.4	1.4409	62.5	1.574	59.12	1.6115	68.21	1.5023
12	74.8	1.4014	70.24	1.473	62.92	1.5691	70.12	1.4754
14	82.6	1.240	82.12	1.252	66.41	1.5250	72.14	1.4450
16	86.5	1.1303	90.12	0.994	71.21	1.4579	74.14	1.4126
18	89.2	1.033	95.4	0.662	73.12	1.4294	77.13	1.3593



Graph 1: In Vitro Dissolution Profile



Graph 2: Zero Order Plots



Graph 3: First Order Plots

4. DISCUSSION

The present study reports a novel approach to prepare microspheres of the anti- inflammatory and analgesic drug Indomethacin by using the polymers like the ethyl cellulose and hydroxyl propyl methyl cellulose for the better treatment of the pain with the decrease dosage in the treatment so that the side effects like the peptic ulcers and the duodenal ulcers can be reduced.

The microspheres of Indomethacin were prepared by ion gelation technique by using synthetic polymers like ethyl cellulose and HPMC with a view to obtain the controlled release of the Indomethacin. Various evaluation parameters like particle size, percentage yield, drug content, entrapment efficiency, in vitro drug release kinetics were also assessed.

5. CONCLUSION

The Indomethacin microspheres were prepared successfully using the synthetic polymers (EC, HPMC) as rate controlling polymers for the ion gelation technique. Entrapment efficiency was in the range of 72-78 %. The encapsulation efficiency depends on the type of the polymer, and the concentration of the polymer. The order of entrapment efficiency was found to be HPMC2>HPMC1>EC2>EC1. The swelling index of the Indomethacin microspheres was increased with increase in the polymer concentration. In-vitro release of the Indomethacin microspheres was slow and prolonged for more than 14 hrs and the maximum of the 95.4% of the drug was released within the 18 hrs for microcapsules containing HPMC as the polymer which contain drug and polymer in the ratio of 1:2.

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