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## PREPARATION AND EVALUATION OF MICROSPHERES OF FLURBIPROFEN

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Microspheres,  
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**ABSTRACT:** Microsphere drug delivery systems have used to improve patient compliance, decreases toxicity, and increase efficacy. Also, the use of microspheres to deliver drugs has many other merits, like control-release of the drug, increase bioavailability and target delivery of the drug to the desired site. In this research shows the utility of encapsulating hydroxypropyl methyl cellulose (Methocel K4M) in biodegradable microsphere delivery system, to be delivered orally *via* a capsule, to gives desired therapeutic action. Microsphere formulations have advantage over conventional tablet or capsule formulations, since it increases the surface area exposed to the absorption site and thus increasing the absorption of the drug and decreasing the dosing frequency of the drug. Flurbiprofen is a non-steroidal anti-inflammatory agent which is used widely in various colon diseases ulcerative colitis, Crohn's disease, carcinomas and infections. Flurbiprofen shows maximum absorption in the lower gastrointestinal tract regions, and shows half life 4 - 5 h, it shows low bioavailability orally. The microsphere formulations were evaluated for its production yields, actual drug content, encapsulation efficiency, % Swelling Index release study is done by in vitro release analysis.

## INTRODUCTION:

**Controlled Release Dosage Forms:** Controlled release drug delivery (CRDD) has become the norm in dosage form design and intensive research has been undertaken in achieving better drug product effectiveness, reliability and safety. Controlled drug delivery system is the one, which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time. It releases the bioactive agent (drug) over an extended period of time, the dosage form can control the rate of release of the incorporated bioactive agent & maintained constant drug concentration at biophase: target tissue or cell<sup>1, 2, 3</sup>.

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing. Other advantages of using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored the possible toxicity or non biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort due to the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations<sup>4, 5</sup>.

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**MATERIALS AND METHODS:** Flurbiprofen gift sample available from Teva Pharma (Pvt.) Ltd., while hydroxypropyl methyl cellulose (Methocel K4M) (Colorcon Ltd., UK). Central composite design was successfully applied from Design Expert software, version 7.0.0, State-Ease, Inc., Minneapolis. Microsoft Excel, DD solver and SPSS 17.0 (SPSS Inc) were used for the assessment of drug release data. Microspheres formulations were evaluated for release study, percentage yield, actual drug content and encapsulation efficiency.

### Preparation Method of Microspheres:

#### Preparation of Chitosan Alginate Microspheres:

The sodium alginate microspheres were prepared by ionotropic gelation method. Sodium alginate microspheres formed as alginate undergoes ionotropic gelation by sodium ions developed from the reaction of alginate and acetic acid.

**a) Preparation of Dope Solution:** Sodium Alginate was dissolved in distilled water at specific concentration; the solution was stirred thoroughly after drug added.

#### b) Preparation of Coagulation Solution:

Homogeneous aqueous solution of chitosan and calcium chloride in various ratios were prepared. The gelation medium was prepared by dissolving chitosan in 1% glacial acetic acid. Solutions mixed for 2 hr's before use and pH of Coagulation fluid adjusted  $4.5 \pm 0.1$ . The homogenous alginate solution was extruded using a 22G syringe needle into the coagulation / gelation medium. The distance between the edge of the needle and the surface of the gelation medium was about 10 cm. The gel microspheres formed were left in the solution with gentle stirring for specific time at room temperature to be cured. After microspheres were collected, washed with distilled water twice and oven-dried subsequently ( $40^\circ\text{C}$ )<sup>6</sup>.

#### Procedure for Preparation of Drug loaded Sodium Alginate Microspheres:

The weighed amount of sodium alginate was dissolved in water. The amount of sodium alginate was added in various percentages (2.0% - 4.0%), stirred for 1 h using mechanical stirrer (Remi equipments, Mumbai). The weighed amount of flurbiprofen was dispersed in to polymeric solution and stirred for 30 min. and then allowed to stand in sonicator till the

removal of entrapped air bubbles. After sonication, this solution was added dropwise from the distance 5 cm using syringe fitted with needle (22G) in to coagulation fluid 200 ml consisting of calcium chloride solution (3%) and chitosan (0.5 - 1.5) dissolved in 1% acetic acid in 250 ml beaker kept on magnetic stirrer at room temperature. Microspheres were left for curing for specified time and after curing, microspheres were collected by filtration and washed twice with distilled water and allowed to dry at  $40^\circ\text{C}$  for 24 h. The dried microspheres were weighed and stored for further evaluation<sup>7, 8, 9, 10, 11, 12, 13</sup>.

**Selection of Optimize Batch:** The criterion for selection of optimum was primarily based on the values of % drug entrapment efficiency, % drug release study and microspheres size. Linear regression plots were obtained using MS-Excel. Prepared flurbiprofen loaded chitosan microspheres were evaluated for microspheres size, sphericity, % entrapment efficiency, % drug content, % swelling index and % drug release.

#### Selected parameters were as follow,

- Conc. of Sodium Alginate (% w/w) : 1-4
- Conc. of Drug (% w/w) : 1.5
- Conc. of  $\text{CaCl}_2$  (% w/w) : 3
- Chitosan (% w/w) : 0.5-1.5
- Curing Time (min) : 10
- Needle (G) : 22

#### Evaluation of Microspheres:

**Particle Size and Shape:**<sup>14</sup> About 100 microspheres were randomly picked up thrice and their sizes of dried microspheres were measured by using Stage micrometer. Shape of microspheres was observed by visual observation.

#### Percentage Drug Content and % Entrapment Efficiency:

<sup>14-20</sup> An accurately weighed quantity of 10 mg microspheres were taken and crushed in mortar with pestle and dissolved in 10 ml of phosphate buffer. The resultant suspension was centrifuged 3600 rpm for 30 min. The solution was sonicated for 2 - 3 h using sonicator (Citizen). The resultant dispersion was filtered through Whattman's filter paper (no. 041) and analysed at 270 nm using UV spectrophotometry (Shimadzu, 1800). The experiments were done in triplicate and results were calculated.

**A) Percentage Drug Content:** The % drug content was calculated by formula:

$$\% \text{ Drug content} = \text{DW/TW} \times 100$$

Where, DW – amount of drug found in total dried microspheres, TW - Total weight of dried microspheres.

**B) % Entrapment Efficiency:** The encapsulation efficiency was calculated according to the following relationship.

$$\% \text{ Entrapment efficiency} = \text{AQ/TQ} \times 100$$

Where, AQ- actual amount of drug found in the microspheres, TQ- Theoretical amount of drug found in the microspheres.

**Equilibrium Swelling studies:** <sup>20, 21, 22, 23</sup> The accurately weighed dried microspheres were placed in USP dissolution apparatus II containing 900ml, phosphate buffer (pH 6.8) maintained at  $37 \pm 2$  °C and allowed to swell upto constant weight. The microspheres were removed, blotted with filter paper, and changes in weight were measured. The experiments were carried out in triplicate. The degree of swelling (Swelling index) was then calculated from the formula,

$$\text{Swelling index} = (\text{W}_g - \text{W}_o) \times 100 / \text{W}_o$$

Where,  $\text{W}_o$  is the initial weight of microspheres and  $\text{W}_g$  is the weight of microspheres at equilibrium swelling in the medium.

**In-vitro Dissolution Studies:** <sup>7, 8, 9</sup> *In-vitro* dissolution studies were performed for all the formulation using USP XXIII Dissolution test apparatus II (paddle type). An accurately weighed sample of microspheres containing 150 mg of flurbiprofen drug was dropped into 900 mL of 0.1 N HCl pH 1.2 maintained at a temperature of  $37 \pm 0.5$  °C and stirred at a speed of 50 rpm.

At different time intervals, a 5 mL aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37 °C. After 2 h same procedure was done into phosphate buffer 6.8 pH. The collected samples were filtered using Whatman's filter paper (No.041) and analyzed at  $\lambda_{\text{max}}$  247 nm using a UV-visible spectrophotometer

against 0.1N HCl and phosphate buffer 6.8 pH as blank. The results expressed were the mean of three experiments.

**TABLE 1: DISSOLUTION TEST DETAILS FOR DISSOLUTION OF MICROSPHERES**

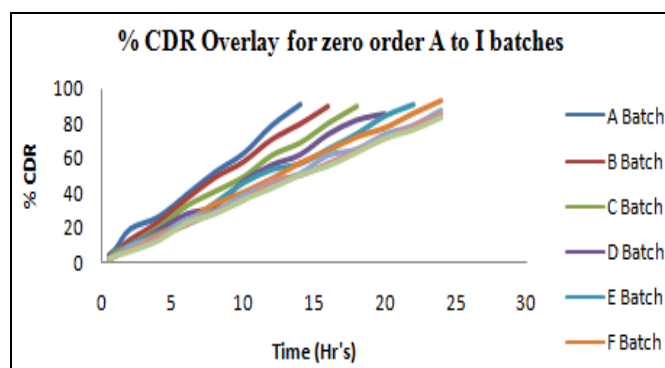
S. no.	Specification	Standard values
1	Apparatus	USPXIII dissolution apparatus II
2	Speed	50 rpm
3	Volume of media	900 ml
4	Dissolution Media used.	0.1 N HCL solution, phosphate buffer 6.8 pH
5	Stirrer	Paddle type.
6	Aliquot taken at each time interval of 1 h	5 ml
7	Temperature	$37 \pm 0.5$ °C.
8	$\lambda$ max	270 nm

**Surface Morphology of the Microspheres:** <sup>20, 23</sup>

The external surface morphology and their internal cross section image of optimized batch of microspheres were obtained by scanning electron microscope (SEM, Philips XL20, Holland) under vacuum. The samples for SEM were prepared by mounting dried microspheres on a double adhesive tape stuck to an aluminium stub.

The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope (JSM-6360A, JEOL and Tokyo, Japan) chamber. The samples were then randomly scanned and photomicrographs were taken at the acceleration voltage of 10 kV.

## RESULTS:



**FIG. 1: DISSOLUTION PROFILE OF A TO I FORMULATIONS**

**TABLE 2: PERCENTAGE DRUG RELEASE FROM CHITOSAN ALGINATE MICROSPHERES – A TO I ZERO ORDER BATCHES**

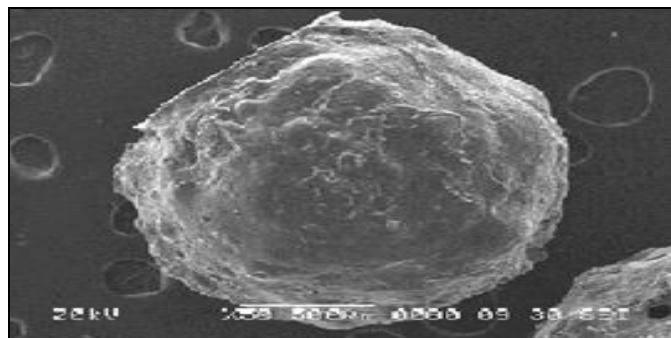
Batches/Time (h)	A	B	C	D	E	F	G	H	I
0.5	3.96	2.9	2.58	2.35	2.11	1.98	1.83	1.79	1.72
1	7.93	5.8	6.8	4.7	4.22	3.92	3.66	3.88	3.45
2	19.0	12.9	10.32	9.4	10.34	8.42	9.22	7.16	5.98
4	26.0	23.21	20.64	18.8	16.88	16.01	14.64	14.32	12.2
6	39.0	36.65	32.98	28.2	23.57	23.82	24.54	21.48	22.4
8	52.0	49.0	41.28	32.6	34.38	33.48	29.28	28.64	27.6
10	62.76	58.01	49.58	47.0	45.86	40.05	38.57	35.8	35.73
12	79.0	71.0	61.92	56.45	53.46	47.84	45.87	46.96	42.18
14	91.0	80.0	69.14	62.31	56.91	56.93	51.24	50.12	49.9
16		90.34	80.45	74.23	65.39	64.03	61.79	57.28	55.2
18			90	82.38	74.1	71.87	65.29	64.44	62.8
20				86	84.36	77.1	73.98	71.6	71.0
22					91	85.34	79.12	78.76	75.9
24						92.74	88	86	83

**TABLE 3: RESULT OF FORMULATION F OF FLURBIPROFEN CHITOSAN ALGINATE MICROSPHERES**

S. no.	Batch Code	% Drug content	% Entrapment	% Swelling Index	Mean Size ( $\mu\text{m}$ )	Sphericity
1	A	26.85 $\pm$ 0.28	67.10 $\pm$ 0.97	812.5 $\pm$ 2.07	812.5 $\pm$ 2.93	Irregular spherical
2	B	27.71 $\pm$ 0.19	69.25 $\pm$ 0.76	850.0 $\pm$ 1.62	850.0 $\pm$ 1.23	Irregular spherical
3	C	28.00 $\pm$ 0.15	70.00 $\pm$ 0.65	812.5 $\pm$ 1.51	812.5 $\pm$ 2.93	Spherical
4	D	20.50 $\pm$ 0.99	75.13 $\pm$ 0.08	837.5 $\pm$ 0.62	837.5 $\pm$ 0.15	Spherical
5	E	29.71 $\pm$ 0.02	75.75 $\pm$ 0.01	800.0 $\pm$ 0.40	800.0 $\pm$ 0.37	Spherical
6	F	37.14 $\pm$ 0.85	83.25 $\pm$ 0.81	837.5 $\pm$ 1.37	837.5 $\pm$ 0.15	Spherical
7	G	31.71 $\pm$ 0.25	77.65 $\pm$ 0.19	675.0 $\pm$ 2.37	875.5 $\pm$ 0.06	Irregular spherical
8	H	31.14 $\pm$ 0.18	80.96 $\pm$ 0.56	750.0 $\pm$ 0.70	850.0 $\pm$ 1.23	Irregular spherical
9	I	32.28 $\pm$ 0.31	83.90 $\pm$ 0.89	775.0 $\pm$ 1.81	875.0 $\pm$ 1.01	Irregular spherical

One formulation, chosen as optimal from A to I batches, were also evaluated for % drug content, equilibrium % swelling index, sphericity. The formulation that fulfilled maximum requisites because of better drug entrapment efficiency, microspheres size and controlled release of the drug was F.

**Morphology:** Morphology of microspheres was examined by using scanning electron microscopy. The Fig. 2 shows the top view of chitosan microspheres. The top view of the microspheres showed a spherical structure.

**FIG. 2: MORPHOLOGY OF MICROSPHERES BY SCANNING ELECTRON MICROSCOPY**

**DISCUSSION:** Optimal formulation of chitosan alginate microspheres were selected by results like % entrapment efficiency, size of microspheres, shape, and % drug release from nine experiments. The concentration of sodium alginate had significant impact on drug entrapment efficiency and particle size.

However, the drug release was greatly retarded at higher concentration of sodium alginate as the concentration increases from 2.0% w/v to 3.0% w/v. Above 4% w/v sodium alginate polymeric solution was too viscous to pass through needle therefore microspheres could not formed. As the concentration increases from 0.5% w/v to 1.5% w/v, (sodium alginate 3 - 4% v) drug release decreases from 88.00% to 83.00% and % entrapment efficiency increases from 77.65% to 80.90%.

And controlled the release from 86.79% to 70.76 % but at the same time drug entrapment efficiency of microspheres increases drug: polymer ratio also showed significant effect on drug entrapment efficiency, drug release and particle size of microspheres. As drug: polymer (sodium alginate)



ratio increases from 1.5:3 to 1.50:4 the % drug release decreases from 92.74 % to 83.00% due to leaching of drug in to counterion solution. Chitosan, a natural polymer which get degraded in acidic environment, non toxic. Flurbiprofen loaded chitosan microspheres were prepared by using ionotropic gelation technique.

Prepared flurbiprofen loaded chitosan alginate microspheres evaluated for size, shape, % entrapment efficiency, % drug content and % drug release. The concentration of chitosan had significant impact on drug entrapment efficiency and particle size. However the drug release was greatly retarded at higher concentration of chitosan as the concentration increases from 0.5% w/v to 1.0% w/v. 1.5% w/v chitosan polymeric solution was too viscous to pass through needle therefore microspheres could not formed. As the concentration increases from 1.0% w/v to 1.5% w/v, drug release decreases and % entrapment efficiency increases. Drug: polymer ratio also showed significant effect on drug entrapment efficiency, drug release and particle size of microspheres, as drug: polymer ratio increases from 1.5:4 to 1.5:3 the % entrapment efficiency increases from 75.13% to 83.90% and % release of drug also decreased from 94.24% to 83.43%. As drug: polymer ratio increases from 0.33:1 to 0.50:1 the % entrapment efficiency decreases from 91.34 % to 59.81% due to leaching of drug in to counter ion solution.

The demonstrated higher values of R<sup>2</sup> (0.996 to 0.998), indicating excellent fitting of model. Evaluation of formulations, chosen as optimal from A to I, indicated that the formulation F fulfilled maximum requisites because of better drug entrapment efficiency and % controlled release of the drug. After comparing the evaluation parameter of chitosan alginate formulations optimized microspheres formulation (F) was selected because of better drug entrapment efficiency, and controlled release of the drug. Chitosan alginate optimized formulation (F) was evaluated for SEM, *in-vitro* drug release.

**CONCLUSION:** The sodium alginate and chitosan microspheres of flurbiprofen prepared by ionotropic gelation method. Optimization helped to predict the best possible formulation. *In-vitro*

release study of F indicated that flurbiprofen was released in controlled manner up to 24 h.

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**CONFLICT OF INTEREST:** Nil

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