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Research Article

FORMULATION AND EVALUATION OF MEFENAMIC ACID MICROSPHERES BY IONIC GELATION TECHNIQUE

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ABSTRACT

The aim of the present investigation is to prepare mefenamic acid microspheres by ionic gelation technique. A total of three formulations were prepared by altering the polymer ratio. The obtained microspheres were evaluated for drug entrapment efficiency, swelling index, and *in vitro* drug release. Out of three formulation F3 formulation i.e., (1:2) drug: polymer ratio was found to best formulation with high product yield, Drug entrapment efficiency, Swelling index, and *in vitro* drug release.

Keywords: Mefenamic acid, ionic gelation, Microspheres, Drug entrapment efficiency, swelling index and *in vitro* drug release.

INTRODUCTION

The development of innovative dosage forms that can regulate the rate of release and direct the active drug molecule to a specific spot has recently attracted a lot of attention. Microspheres are cutting-edge medication delivery devices with a variety of uses and compositions of different polymers.

Microspheres are tiny, spherical particles that can range in size from 1µm to 1000 µm. Natural or manmade polymers may be used to create microspheres. The addition of mucoadhesive properties to microspheres will further increase the absorption and bioavailability of the drugs. Microspheres can generally be used for targeted, controlled, or extended drug release.

By securing the medicine to the absorption site, mucoadhesive microspheres improve the close contact with the mucus layer.

Mefenamic acid (MA) [(2-[(2,3dimethylphenyl) amino] benzoic acid], an anthranilic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) that is widely used for the Mefenamic treatment of mild-to-moderate pain. Acid belongs to the Biopharmaceutical Classification System (BCS) class Il drug which has lower water solubility but high permeability. Sustained-release MA microspheres, MA matrix tablets, and controlled-release MA-loaded alginate beads have been reported in the literature. Recently, it has been reported that MA could be used as a therapeutic agent in Alzheimer's disease since it improves learning and memory impairment in an amyloid ß peptide (Aßl -42)-infused Alzheimer's disease rat model. The usual oral dose is 250 or 500 mg and is administered three times daily. The formulation of MA as a modified release dosage form of microsphere seems to be an alternative approach to overcome the potential problems in the gastrointestinal tract, as it reduces the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs). Ionotropic gelation is a quick, easy, and affordable process that can crosslink opposing ions to create hydrogel through drop or aerosolization. L-Glucuronic (G) and D-mannuronic acid (M) subunits make up the anionic, biocompatible, and biodegradable polysaccharide is known as alginate. With a divalent cation like Ca2+, alginate creates egg box gels.[1,2,3]

MATERIALS AND METHODS

Collection of Materials: All the chemicals used were of standard pharmaceutical grade. Mefenamic acid was received as a gift sample from VerGO Pharma Research Laboratories Pvt. Ltd., Goa, India. Sodium Alginate was procured from Burogyne Burbidge and Co. Mumbai, India. HPMC and Calcium Chloride were obtained from Molychem, Mumbai.

Preparation of Mefenamic acid microspheres by ionic gelation technique: Mucoadhesive microspheres containing non-steroid anti-inflammatory drugs as a core material were prepared by orifice ionic gelation technique. Sodium alginate and the mucoadhesive polymer HPMC were dissolved in 40mL purified water to form a homogeneous polymer solution. The active substance, Mefenamic acid (1000mg) was added to the polymeric solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually dropwise into 10 % w / v calcium chloride solution (40 mL) through a syringe (no.20). The added droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and produced spherical rigid microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with water and dried at 40 for the study of °C for 3 h in a hot air oven. Stored in a desiccator over fused $CaCl_2$ until further study. The prepared batches of mucoadhesive microsphere are as shown in the following Table 1.

EVALUATION PARAMETER

Estimation of Mefenamic acid: Estimation of mefenamic acid was carried out using a spectrophotometric method based on the

measurement of absorbance at 279nm in 7.4pH buffer. An absorption maximum of mefenamic acid was determined using 7.4pH buffer. Beer's range was found to be in the range from 0-20 µg/ml. The absorbance of these solutions was measured at 279 nm by UV spectrophotometer, using 7.4pH buffer as blank. The absorbance values were plotted against concentration to obtain the standard.

Angle of Repose: The powder mass was allowed to flow out of the funnel orifice on a plane of paper kept on the horizontal surface. This forms a pile of the angle of powder on the paper. The angle of repose was calculated by substituting the values of base radius "R" and pile height "H" in the following equation:

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

Bulk Density: Accurately weighed quantities of powder mixture were poured into a graduated measuring cylinder through a large funnel and volume was measured. The measuring cylinder was then tapped 3 times on a hard surface from a height of 2-3 inches at 2-second intervals till a constant volume was obtained.
It was expressed in gm/ml and given by

$$BD = Wp/Bp$$

Carr's Consolidation Index (%Compressibility): The % compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr,s Index of each formulation was calculated according to the equation given below.[5]

$$\text{consolidation Index} = \text{Tapped density} - \text{Untapped density} / \text{Tapped density} \times 100$$

Hausner's ratio: Hausner's ratio is a number that correlated to the flowability of a powder or a granular material. It is calculated by the formula

$$H = Dt/Du$$

Percentage yield: The % yield of all the formulations of alginate microbeads was calculated using the formula,[4]

$$\% \text{ yield} = \text{Total weight of dried alginate beads} / \text{total weight of polymer + drug + sodium alginate} \times 100$$

Drug content and Drug Entrapment Efficiency (DEE): Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 7.4 Ph buffer repeatedly. The extract was transferred to a 50 ml volumetric flask and the volume was made up using 7.4 ph buffer. The solution was filtered, and the absorbance was measured after suitable dilution spectrophotometrically at 279 nm against the appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula.[6]

$$\% \text{ DEE} = (\text{Amount of drug present} / \text{Theoretical drug load expected}) \times 100$$

Swelling index: The swelling index was determined by measuring the extent of swelling of microspheres in a 7.4 pH buffer. To ensure complete equilibrium, an exactly weighed amount of microspheres were allowed to swell in a 7.4 pH buffer. The excess surface-adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using a microbalance. The microspheres were then dried in an oven at 60°C for 5 hr until there was no change in the dried mass of a sample. The swelling index of the microsphere was calculated by using the formula.[7,8]

$$\% \text{ Swelling index} = (\text{mass of swollen microspheres} - \text{Mass of dried Microspheres}) / \text{Mass of dried microspheres} \times 100$$

***In vitro* drug release:** Dissolution studies on both the formulations of Mefenamic acid microspheres were carried out using a USP dissolution apparatus Type II (paddle- Electro labs, TDT- 08 L). 7.4 pH buffer was used as the dissolution medium. To carry out *In-vitro* drug release, accurately weighed 25mg of loaded microspheres were dispersed in dissolution fluid in a dissolution jar and maintained at 37±2 °C under continuous stirring at 100 rpm. The samples were analysed spectrophotometrically after suitable dilution. The released drug content was determined from the standard calibration curve of a given drug. [9,10]

Table 1: Compositions of muco-adhesive microspheres

FORMULATION CODE	DRUG (g)	SODIUM ALGINATE(g)	HPMC(g)
F1	1	1	1
F2	1	1.5	1.5
F3	1	2	2

Table 2: Flow properties, percentage yield, and drug entrapment efficiency of microspheres

FORMULATION CODE	ANGLE OF REPOSE (θ)	BULK DENSITY (g/cc)	HAUSNER'S RATIO	% COMPRESSIBILITY	% YIELD	% DEE
F1	19	22	1.10	9	90.66%	84.15±0.01
F2	20	19	1.20	13	87.34%	69.20±0.10
F3	22	19	1.16	11	91.22%	86.25±0.01

Table 3: Percentage swelling index

FORMULATION CODE	SWELLING INDEX (%)				
TIME	1 hr	2hr	4hr	8hr	10hr
F1	0.370±0.13	0.486±0.45	0.673±0.26	0.911±0.10	0.988±0.0190
F2	0.314±0.22	0.436±0.34	0.634±0.31	0.996±0.20	1.039±0.23
F3	0.386±0.34	0.439±0.1	0.512±0.31	0.897±0.56	1.116±0.54

Table 4: Release kinetics of microspheres

FORMULATION CODE	ZERO-ORDER		FIRST ORDER	
	K_{slope}	Regression	K_{slope}	Regression
F1	0.2165	0.6813	-0.002	0.8028
F2	0.2552	0.7118	-0.003	0.9015
F3	0.2694	0.7277	-0.003	0.9069

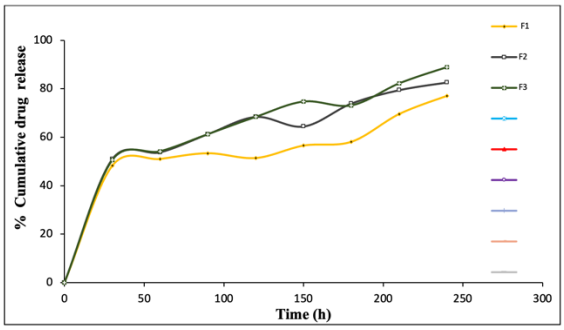

Figure 1: *In-vitro* drug release

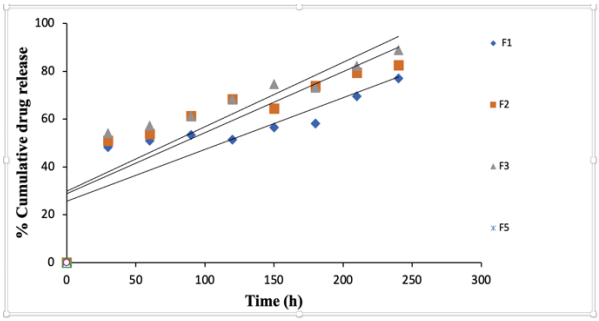

Figure 2: Zero-order kinetics

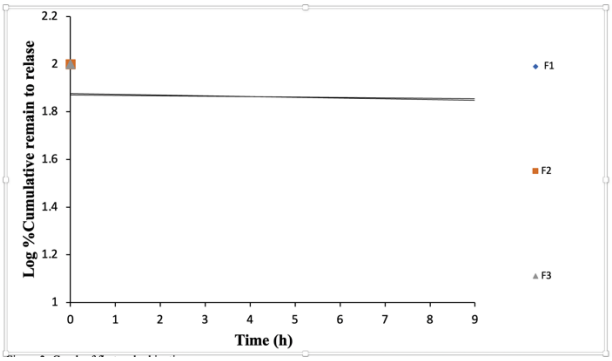

Figure 3: First-order kinetics

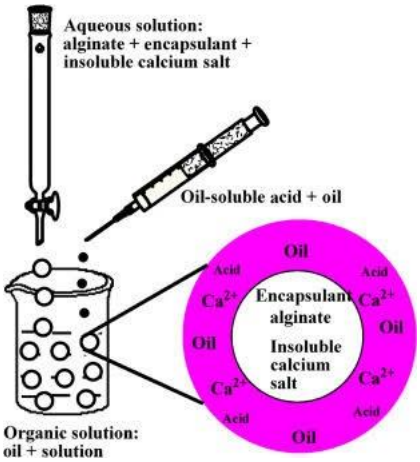

Figure 4: Ionic gelation tachnique

Figure 5: Microspheres

RESULTS AND DISCUSSION

Standard graph of mefenamic acid by UV – Visible spectrophotometry: A simple, fast and precise UV spectrophotometric method for the estimation of mefenamic acid was carried out. Absorbance was read at 279nm using a 7.4 pH buffer as blank. Beer, s range was obeyed between 0-20µg/ml. Given in Figure 1.

Flow properties: Flow properties play an important role in pharmaceuticals, especially in microspheres formulation. The bulk density of the powder blend was found to be in the range of 22 and 19 g/cc respectively. The angle of repose was found to be in the range of 22° and 19° which indicates good flowability. The % compressibility and Hausner's ratio were between 5 to 15 % and 1.10 to 1.20respectively which indicates excellent flow properties.

Percentage yield: The percentage yield of microspheres of all the formulations is shown in Table 2.

Drug content and drug entrapment efficiency (%DEE): The drug content and drug entrapment efficiency of the dried microspheres of all the formulations are shown in Table 2.

Swelling Index: Swelling properties of different formulation depends upon the viscosity of the polymer used. The swelling index is shown in Table 3.

***In-vitro* drug release:** HPMC is a cross-linked polymer with high molecular weight and viscosity. These properties are responsible for retarding drug release. As a polymer concentration increase exhibits good *in-vitro* release which is shown in Figure 1.

CONCLUSION

Mefenamic acid microspheres were successfully prepared by ionic gelation technique by altering the polymer ratio. F3 formulation had good flow properties, a Swelling index, and a high retarded or sustained drug release.

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