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Formulation and evaluation of sustained release microbeads of mefenamic acid

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ABSTRACT

Sustained release microbeads of mefenamic acid were successfully prepared by ionotropic gelation technique. The prepared all formulations were evaluated for Percentage yield, %Entrapment efficiency, Bulk and Tapped density, Hausner ratio, SEM analysis, Swelling index(%), *In vitro* drug release studies and stability studies. Results from Hausner ratio of prepared formulations F4 showed good to excellent flow property. It is found to be (1.154). The percentage yield of formulation F4 was found to be 97%. Bulk density of formulation F4 was found to be 0.652 gm/ml, and Tapped density of formulation F4 was found to be 0.772 gm/ml. Drug entrapment efficiency (%) of Mefenamic acid alginate microbeads increased with increase in concentration of sodium alginate in formulation F4. The entrapment efficiency was found to be (97.01%). Swelling of the dry beads is mainly attributed to the hydration of the hydrophilic groups of alginate, HPMC E3. Formulations F4 exhibited significant swelling rates when exposed to the alkaline medium (pH 7.4). The swelling index was found to be (89.31%). The *in- vitro* dissolution studies using two different dissolution media pH 1.2 and pH 7.4 performed for 12 h. Formulation F4 was showed exellent *in - vitro* drug release. It is found to be (98.33±0.12%). The formulation F4 showed more sustained release. This indicates that the release rate was retarded due to increase in percentage of Polymers (sodium alginate & pectin) and cross linking agents because of strong bonds between sodium alginate and divalent ions. Also the results revealed that the increase in the sodium alginate concentration, diminished the drug release profile. According to stability study it was found that there was no variation in percentage yield, Entrapment efficiency,and *In-vitro* drug release profile of optimized formulation F4 for 1 month periods. From the overall studies it can be concluded that the formulation F4 considered as the best formulation amoung Five formulation by comparing all the evaluated parameters. Therefore mucoadhesive microbeads could be a feasible approach to achieve sustained release profile of mefenamic acid by reducing its serious side effects, and to improve the bioavailability and patient compliance.

Keywords: Mefenamic acid, HPMC, calcium carbonate, spectrum reagents.

INTRODUCTION

Multiparticulate systems have been paid considerable attention since several years in controlling and sustaining of release rate of many active pharmaceutical ingredients. And use of natural biodegradable polymers as rate controlling agents also has been enormously increased. [1] Recently, dosage forms that can precisely control the release rates and targets drugs to a specific body site have made enormous impact in the formulation and development of novel drug delivery systems. Oral multiunit dosage forms such as microcapsules and microspheres have received much attention as modified/ controlled drug delivery systems for the treatment of various diseases without major side effects. [2] Additionally, the beads maintain functionality under physiological conditions, can incorporate drug to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. It will therefore be advantageous to have means for providing an intimate contact of the drug delivery system with microbeads. [3]

Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. [4] The literature review discussed reveals the research work done to develop microparticulate drug delivery system containing anti-diabetic, anti-hypertensive and NSAIDS drugs by ionotropic gelation method. Significant work has been done on mucoadhesive hydrogel based microbeads for various drugs such as nizatidine [5], candesartan cilexetil [6], etodolac [7], nifedipine [8], diclofenac sodium [9], aceclofenac [10], prazosin [11], gliclazide [12], metformin [13], ampicillin [14]. The aim of the present study was to formulate and evaluate sustained release microbeads of mefenamic acid using combination of sodium alginate, pectin, and HPMC E3**.**

MATERIALS AND METHODS

Mefenamic acid was gift sample from Micro labs, Bangalore. Sodium alginate and Potassium dihydrogen phosphate were purchased from Himedia Lab, Mumbai. Hydroxy propyl methyl cellulose E3 from Nice Chemicals, Kerala, calcium carbonate from Loba Chemie, Mumbai, pectin from Chem Industries, Mumbai, Methanol Fine Chem Industries, Mumbai Calcium chloride from Merck Specialities, Mumbai were procured. Sodium hydroxide and lead nitrate were obtained from Spectrum reagent and chemicals, Cochin.

Preformulation Studies

Before the formulation of a product it should be investigation of physical and chemical properties of a drug substance alone to find effective, stable and safe dosage form. It is the first step in rational development of dosage form.

Organoleptic properties of drug

The organoleptic properties like physical state, colour, taste, odour, etc., of the drug was reported with help of the descriptive terminology. It helps to identify the drug.

Melting point

In this method a small amount of drug was filled in a capillary tube of open both the ends and it was placed along with thermometer in melting point apparatus.

Solubility profile

It is important to know about solubility characteristics of a drug in aqueous system, since they must posses some limited aqueous solubility to elicit a therapeutic response. The solubility of drug substance was recorded by using various descriptive terminology specified in Indian Pharmacopeia, 2007.

Standard curve preparation for mefenamic acid

Phosphate buffer solution (pH 7.4) was prepared as per the standard protocol. 40 Mefenamic acid (100 mg) is accurately weighed, dissolved in 5 ml methanol and diluted with pH 7.4 phosphate buffer to form a stock solution. The stock solution is further diluted suitably with pH 7.4 phosphate buffer to get a working standard solution of concentration 100 µg/ml. This working standard solution is suitably diluted to get a concentration of 10 µg/ml and the resultant solution is scanned in the range of 200 – 400 nm in UV Spectrophotometer to get absorption maximum. From the working standard solution, 2, 4, 6, 8, 10 and 12 ml are taken separately and diluted to 100ml with the same pH 7.4 buffer solution, so that the final concentrations of 2-12 µg/ml solutions are obtained. The above solutions are analyzed by Ultraviolet (UV) spectrophotometer at λmax. The calibration graph is drawn by taking the concentration on X axis and respective absorbance in Y axis, to get a straight line as per Beer's law. This standard curve is used to estimate the concentration of the drug release from the formulation during the *in vitro* dissolution studies. [15]

FTIR studies

Drug polymer interactions are studied by FT-IR spectroscopy. FT-IR spectra (Shimadzsu) for the drug and various physical mixtures are obtained in a FT-IR spectroscopy in the transmission mode with the wave number region 4000-500 cm^{-1}. KBr pellets are prepared by gently mixing 1mg sample powder with 100mg KBr. [16]

Formulation of microbeads of mefenamic acid

The alginate microbeads are prepared by using ionotropic gelation method as per the composition shown in Table 1. An aqueous solution of different concentrations of sodium alginate and add calcium carbonate is prepared with continuous stirring to form a uniform dispersion. To this appropriate concentration of pectin and drug are incorporated slowly and stirred continuously until a uniform dispersion is obtained. The resultant bubble free, homogenous dispersion is extruded into ($CaCl_2$) polyvalent ion solutions (100 ml) containing HPMC E3 using a hypodermic syringe with 21 gauge needle and stirred at 100 rpm in a Remi stirrer. The gel beads are cured in gelation medium for 30 minutes and then collected by decantation technique and the product thus separated is dried at room temperature for 24 h. [17]

Table 1: Composition of sustained release microbeads of mefenamic acid

Formula code	Drug (gm)	Sodium alginate (% w/v)	Pectin (%w/v)	HPMC E3 (%w/v)	Calcium carbonate	Calcium chloride (%w/v)
F1	1	2	0.5	2	0.5	5
F2	1	2	0.5	3	0.5	5
F3	1	2	0.5	4	0.5	5
F4	1	3	0.5	2	0.5	5
F5	1	4	0.5	2	0.5	5

Characterization of microbeads of mefenamic acid [12]

Determination of Percentage yield

The % yield of all the formulations of alginate microbeads are calculated using the formula,

$$\% \text{ Yield} = \frac{\text{Total weight of dried alginate beads}}{\text{Total weight of polymer + drug}} \times 100$$

Determination of Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It is measured by pouring the alginate microbeads into a measuring cylinder and initial weight is noted. This initial volume is called the bulk volume. From this the bulk density is calculated using the formula mentioned below, it is expressed in gm/ml and is given by,

$$\mathbf{Db = M / Vb}$$

Where, M - Mass, Vb - bulk volume, Db – bulk density.49

Determination of Tapped Density (Dt)

Tapped density is determined by placing a graduated cylinder, containing a known mass of microbeads. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 seconds intervals. The tapping is continued until no further change in volume is noted.

$$\textit{Tapped density (Dt)} = \frac{\text{Weight of powder blend}}{\text{Tapped volume of powder blend}}$$

Determination of Hausner ratio

It is an another parameter for measuring the flowability of prepared alginate micro beads and is calculated using the formula,

$$\textit{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Determination of Particle size

For size distribution analysis was determined using an optical microscopy method. Approximately 100 microparticles were counted for particle size using a calibrated optical microscope.44

Morphology Analysis

Surface morphology of microbeads was determined by scanning electron microscopes (SEM). The microbeads were coated uniformly with gold - palladium by using a sputter coater, After the sample in individually stabs and were analyzed by using ZEISS.

Determination of Entrapment efficiency

Accurately weighed 100 mg equivalent of alginate beads are suspended in 100ml of pH 7.4 phosphate buffer solution for 24 h. Then it is stirred for 15 minutes. After suitable dilution, drug content in the filtrate is analyzed spectrophotometrically at λmax by UV spectrophotometer. The encapsulation efficiency is calculated according to the following equation.

$$\textit{\% Entrapment efficiency} = \frac{\text{actual drug content(\%)}}{\text{Theoretical drug content(\%)}} \times 100$$

$$\textit{Drug content (\%)} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

Determination of Swelling Index

The swelling properties of alginate beads are studied by measuring the % water uptake by the beads. About 100mg of beads are accurately weighed and placed in 100 ml of buffer solution. Then, the beads are removed from the respective swelling media after 6 h and weighed after drying the surface water using filter paper. The water uptake is calculated as the ratio of the increase in weight of beads after swelling to the dry weight. The percentage of swelling of the beads can be calculated using the formula.15

$$\textit{Swelling Index (\%)} = \frac{\text{Final weight of beads – initial weight of beads}}{\text{Initial weight of beads}} \times 100$$

In vitro drug release studies

In vitro dissolution studies are performed for all the formulations using USP type I (Basket) apparatus. An accurately weighed amount of drug loaded alginate beads equivalent to 100 mg are filled into hard gelatin capsules. The study is carried out using 900ml of buffer solution as dissolution medium. The rotating speed of basket is maintained at 50 rpm at 37 ± 0.5° C. First 2 h study is carried out in pH 1.2 and next 10 h study is carried out in Phosphate buffer pH 7.4. Samples are withdrawn for every 30 minutes. 10 ml of sample is withdrawn from dissolution jar, diluted with fresh medium and make up to 100ml. At the same time 10ml of fresh medium is added to the dissolution medium to maintain the sink condition. The collected samples are analysed by using UV spectrophotometry at λ_{max}.

Stability studies

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity was not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously. The stability studies were carried out at optimized formulations as per ICH guidelines [18]. The formulation was store at (40±2 °C at 75% RH ±5%) for 1 month. Sample were withdrawn and retested for drug release and was compare with the formulation diffusion profile.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies using FTIR

The FTIR spectra of mefenamic acid and its binary systems with different polymers were shown in **Fig. 2** To check the compatibility of drug with various polymers, FTIR spectra of drug, polymers and combination of the drug and polymers were taken**.** Mefenamic acid spectra showed sharp characteristic peaks at 3291, 2928.38, 1832.14, 1707.78, and 762.43 cm^{-1} All the above characteristic major peaks were appeared in the spectra of physical mixture of sodium alginate, pectin, and HPMC E3, suggesting that there was no interaction between the polymers and drug used in the present study

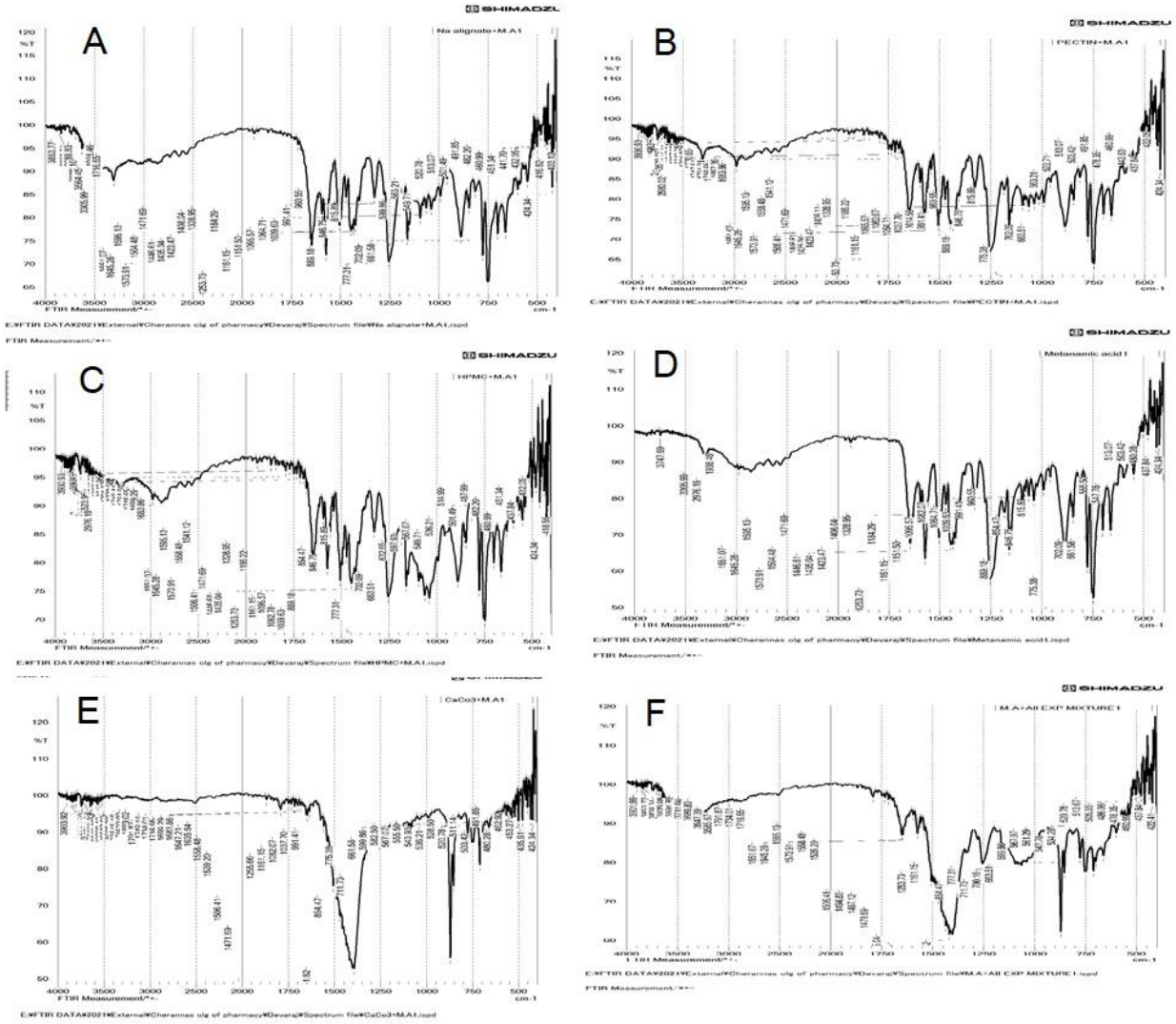

Fig. 2: FTIR Spectra of (A) sodium alginate, (B) pectin, (C) HPMC E3, (D) mefenamic acid, (E) calcium carbonate and (F) their combination

Formulation and evaluation of microbeads of mefenamic acid

The mucoadhesive alginate beads were prepared according to the formulations shown in **Table 2.** The beads were prepared by extruding of dispersion drug sodium alginate and pectin as droplets into a divalent cross linking agents such as calcium chloride and zinc chloride, can able to form uniform rigid beads. The needle size of 21G produced big size, rigid, uniform and porous beads. The shapes of all the beads were almost spherical.

Physical evaluation of microbeads of mefenamic acid

As shown in Table 2 and Fig. 2 the percentage yield of alginate beads prepared by ionotropic gelation method were found to be between 81% and 97.01 %. The spherical shape of the beads in wet state was usually lost after drying especially for beads prepared with low concentration of sodium alginate and cross linking agent. With the increase in the concentration of sodium alginate the shape of the beads retained considerably. The Bulk density of all the formulations was in the range of 0.652 gm/ml to 0.772 gm/ml. The Hausner ratio of all the formulations was in the range of 1.102 to 1.211% which exhibited good flow property.

Table 2: Results of various parameters studied for sustained release microbeads of mefenamic acid

Formula code	Percentage yield (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%) Hausner ratio	
F1	81	0.772	0.831	1.102	10.71
F2	86	0.667	0.852	1.112	11.15

F3	90	0.703	0.751	1.211	13.12
F4	97	0.652	0.772	1.154	14.15
F5	97.01	0.652	0.764	1.151	14.21

The surface morphology and shape characteristics of microbeads were evaluated by means of scanning electron microscopy. The SEM Photographs of the microbeads revealed that the microbeads were spherical and discrete shown Fig. 3.

The particle size of the prepared microbeads was determined using optical microscopic technique. The prepared formulations F1 to F5 were in the size range of 1056, 1097, 1345, 1387, 1478µm respectively **Table 3.** Increase in Bead size was observed on increasing the concentration of sodium alginate.

Table 3: Particle size, Entrapment Efficiency, Swelling index, Percentage yield of sustained release microbeads of mefenamic acid

Formula code	Particle size (µm)	Entrapment Efficiency (%)	Swelling Index (%)
F1	1056	86.71	68.28
F2	1097	87.20	70.01
F3	1345	88.10	75.02
F4	1387	97.01	89.31
F5	1478	96.68	88.91

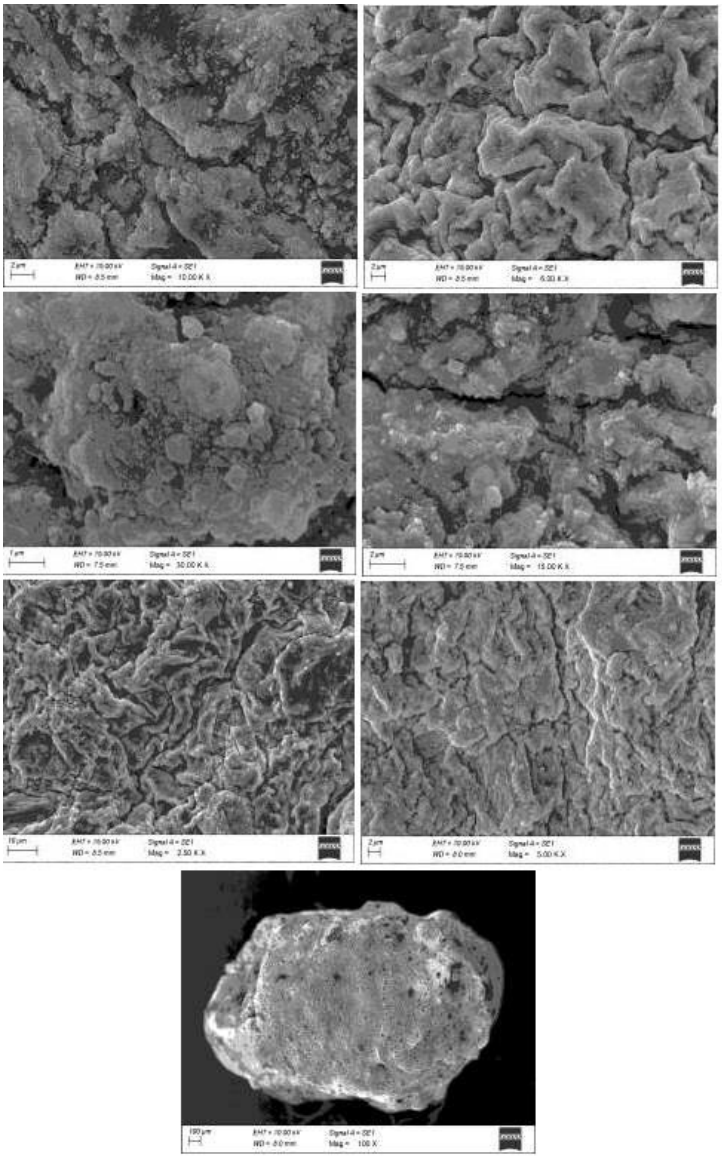

Fig. 3: SEM photographs of prepared microbeads at various magnifications

The drug entrapment efficiency of all formulations were in the range between 86.71% and 97.01% shown in **Table 3.** Drug entrapment efficiency of alginate beads increased with increase in concentration of polymers. The higher viscosity of the polymer solution at the highest polymer proportion would be expected to decrease the diffusion of the drug into the external phase which would result higher entrapment efficiency. This may be attributed to the greater availability of active binding sites in polymeric chains and consequently the greater degree of cross linking as the quantity of alginate increased.

Swelling of the dry beads is mainly attributed to the hydration of the hydrophilic groups of alginate, HPMC E3. In this case free water penetrates inside the beads in order to fill the inert pores among polymer chains, contributing to a greater swelling degree. All the formulations exhibited significant swelling rates when exposed to the alkaline medium (pH 7.4). In pH 7.4, the alginate beads swelled and they were not broken in these pH values after 8 h. These results suggested that alginate beads do not disintegrate in the stomach and thus resulted in release of mefenamic acid in intestinal fluids. **Table 3** showed the swelling behaviour of microbeads, as a function of pH. The swelling degree of calcium-alginate beads was lower than that of zinc-alginate, beads. The increase in concentration of ca2+ ions in the gelation medium increases the availability of Ca^{2+} ions which increase the number of interactions with coo-groups present in alginate. This resulted in increased cross linking density which hindered inward diffusion of swelling medium.

In vitro drug release studies

The results of *in vitro* drug release studies from the mucoadhesive alginate beads were shown in the **Fig. 4**. The *in vitro* dissolution studies of all formulations were carried out by USP type I method by using two different dissolution media pH 1.2 and pH 7.4. The studies were performed in all the formulations for 12 h. Sampling was done every one hour and absorbance was determined using UV spectrophotometer at 284 nm. The beads did not show any drug release at pH 1.2 and it released the drug at pH 7.4. So it protected the release of drug from the acidic medium to minimize the side effects.

As increasing the percentage of sodium alginate in formulation could led to a greater viscosity of the solution, and hence large drops needs to be dripped out of the needle. As a result, larger beads were formed and diffusivity decreased. This indicates that the release rate was retarded due to increase in percentage of Polymers (sodium alginate & pectin) and cross linking agents because of strong bonds between sodium alginate and divalent ions. As the polymer to the drug ratio was increased the extent of drug release decreases. The decrease in the rate and extent of the drug release is due to the higher density of polymer matrix that results in increased diffusion pathlength through which the drug molecule have to traverse.

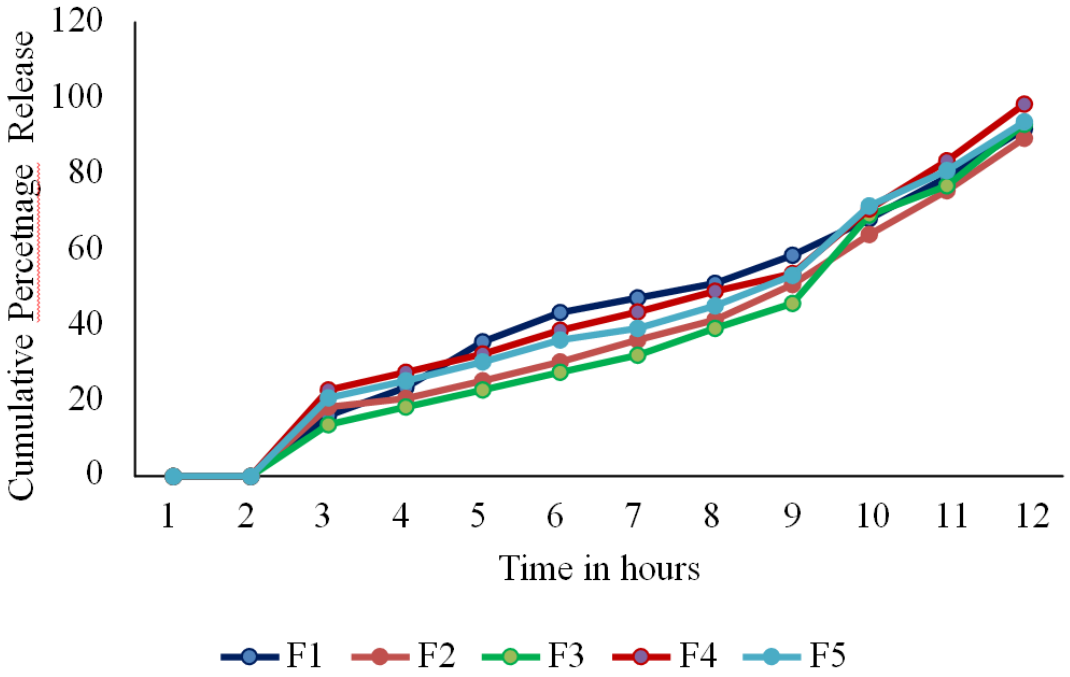

Fig. 4*: In vitro* drug release of sustained release microbeads of mefenamic acid

Stability studies

The stability studies indicated that there exists significant difference between the release pattern of microbeads at 40°C and RH and at room temperature for one month. The stability studies were carried out at optimized formulation **F4.** The formulation was stored at (40° C at 75 % RH ±5%) for 1 month. Sample were withdrawn and rested for drug release and the results were compared with the formulation diffusion profile as shown in **Table 4.**

Table 4: Stability studies for formulated microbeads of mefenamic acid

Characters		**Initial month**	**After 1 month**
Appearance		Spherical	Spherical
Solubility		soluble in organic solvent	Soluble in organic solvent
Colour		white	white
Particle size		1387 ±0.5 nm	1387±0.5 nm
Swelling index		89.31 ± 0.2 %	89.29 ± 0.1%
***Invitro* drug release in hrs.**	**Theoretical drug release**	**Mean cumulative release in %**	
1	0	0	0
2	0	0	0
3	(20 - 25)	22.86±1.12	22.60±1.02
4	(25-30)	27.48±1.32	27.35±1.06
5	(30-35)	32.33±1.04	32.30±1.00
6	(35-40)	38.57±1.19	38.45±1.12
7	(40-45)	43.38±1.95	43.30±1.85
8	(45-50)	48.96±1.10	48.90±1.09
9	(50-55)	53.55±0.72	53.44±0.69
10	(55-75)	70.69±1.56	70.69±1.52
11	(75-85)	83.3±1.16	83.3±1.14
12	(85-100)	98.33±0.12	98.33±0.11

CONCLUSION

Sustained release microbeads of mefenamic acid were successfully prepared by ionotropic gelation technique. It was found that sodium alginate along with pectin substantially sustained the release of Mefenamic acid from the microbeads. The sustained release of the drug from the microbeads suggests that the frequency of administration may be reduced. From the overall studies it can be concluded that the formulation **F4** considered as the best formulation amoung Five formulation by comparing all the evaluated parameters. Therefore mucoadhesive microbeads could be a feasible approach to achieve sustained release profile of mefenamic acid by reducing its serious side effects, and to improve the bioavailability and patient compliance.

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