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Preparation and Evaluation of *Acacia nilotica* Gum Microsphere Using Various Cross-Linking Agents

Vandana Chaudhary*, Dr Ravi Kumar Patel

1. Assistant Professor in Shree Swaminarayan College of Pharmacy, saij, Kalol, Ahmedabad (Gujrat) India.
2. Professor in Shree Swaminarayan College of Pharmacy, saij, Kalol, Ahmedabad (Gujrat) India.

Shree Swaminarayan College of Pharmacy, Department of Pharmaceutics, Ahmedabad Gujrat, India

ABSTRACT

Objective: The aim of present study was to formulate natural polymer *Acacia nilotica* gum based Famotidine microsphere which is improve its therapeutic efficacy, patient compliance and reduce the dosing frequency and adverse effects.

Methods: Different batches of microspheres were prepared by ionotropic gelation technique. The physicochemical parameters like drug content, particle size measurement, swelling index and percentage yield as well as *in vitro* drug release were determined using USP Type 1 apparatus. SEM study was done for the optimized microspheres.

Result: Eighteen batches of microspheres were prepared by natural polymer *Acacia nilotica* gum and drug loaded Famotidine. All prepared batches of microspheres evaluated different parameters like particle size is having 846.21 to 989.04µm, F5 shows highest particle size. Micromeritics properties that are bulk density tapped density, carr, s index, hausner ratio, angle of repose and found excellent flow and packaging properties. Percentage yield of microsphere has well. Formulation F1 shows maximum % yield of microspheres. Drug content % was found 98% F1 batch. Swelling % formulation F5 shows maximum swelling property. Drug and polymer is compatible to each other. Percent release of drug is 98% in 8 hours. Conclusion: This study final from the obtained results, it could be concluded that Famotidine natural polymer microspheres can be formulated as controlled and sustained release of drug for several hours.

Key words: *Acacia nilotica*, Natural Polymer, Microsphere, Famotidine, Ionotropic Gelation.

INTRODUCTION

Microspheres are characteristically free flowing powders consisting of protein or natural, synthetic polymers which are biodegradable in nature and ideally having particle size less than 1000µm [1, 2]. Natural polymers are the widely used in Pharmaceutical preparation. While obtained by the any plant parts that called natural polymers. Natural polymers are extracted and obtained from natural source as plant and animal kingdom [3, 4]. Natural polymers are easily available and non toxic than synthetic polymers. Most of the polymers

highly molecular weight and which are soluble in water. Gummy exudates of natural polymers such as protein, enzyme, muscle, fibre, and polysaccharide have been used to formulate various pharmaceutical products [5]. Natural polymers that is Aloe mucilage, Guar gum, Agar gum, Karaya gum, Kheri gum, *Acacia nilotica* gum, Locust bean gum, Sodium alginate, Okra gum, Linseed gum etc. [6]. These polymers are used in natural pharmaceutical products and many pharmaceutical dosage forms likes nanoparticle, nanospheres, microspheres, buccal films, patches, microparticles, for controlled drug delivery [7]. Polymers have property of mucoadhesion and controlled release of the mucus gastric layer. The special application of natural polymers in pharmaceutical preparation is to help in the processing of drug delivery systems during its manufacturing, protection, enhancement of stability, bioavailability, patient acceptability and patient compliance, easy to use [8, 9].

*Acacia nilotica*is is a large tree. Botanical name of babool is *Acacia nilotica,* family Fabaceae. Many species of found of *Acacia* tree that is *Acacia arabica, Acacia adstringens, Acacia leiocarpa, Acacia subalata, Acacia kraussiana* etc. composed of *Acacia*is D Rhamnose. *Acacia nilotica* is widely found in African countries mainly in Sudan [10]. *Acacia nilotica* gum is providing in matrix controlled release of drug more than 5 hour. The same study indicates that *Acacia nilotica* gum matrices were useful in the formulation of sustained and controlled release microspheres for up to 5 h.

Acacia nilotica gum are used in treatment of eczema, it is used in skin irritations problem, *Acacia nilotica* leaves is help in rejuvenating the skin and keeping infections and rashes at bay [11].

Natural polymers such as Chitosan, Gelatin, *Acacia nilotica*, Sodium aliginate and their derivatives have been widely studied for their ability to form microspheres [12, 13]. These polymer-based materials are oriented to prepare microspheres and microbeads. So far, various studies have been reported on the development of these carriers which have been used in the preparation of microspheres. Recently, dosage forms that can easily and accurately control release rate and target the drug to specific site have made great influence for the formulation and improvement of novel drug delivery systems. Microspheres have given a significant role in novel drug delivery systems [14]. Multi-particulate drug delivery systems are mainly oral dosage forms which consist of multiplicity of small discrete units, each exhibit some desired characteristics. To deliver the recommended total dose, these subunits are encapsulated and compressed into a tablet. For the development of multi-particulate dosage forms in preference to single unit systems because of their benefits such as increased bioavailability, long effect,

reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying, patient compliance, easy to use, minimize side effects etc [15,16].

Famotidine is an antiulcer drug. It is inhibit secretion of gastric fluid, prevent ulcer in mucus membrane of stomach and intestine.

The objective of the present study was to develop microspheres of Famotidine by Ionotropic Gelation Technique using *Acacia nilotica* gum to sustained and controlled release so as to reduce the frequency of dosing and to improve patient compliance.

MATERIALS AND METHODS

Chemicals: Crude *Acacia nilotica* gum was obtained from the plant situated in university by making incision on the bark of plant gum extrudes out and was kept under sunlight for two months for variably drying and then gum (material) was collected by shedding them from the bark. Plant leaves and bark were identified and authenticated Gautam Buddha University (State Govt. University) Greater Noida. Famotidine was used as model drug and it was obtained as a gift sample from GlaxoSmithKline Pharmaceuticals limited Mumbai. All the other materials such as Sodium alginate, Aluminium chloride, Calcium chloride, Barium chloride purchase from CDH Laboratory Reagent, Central Drug House (P) LTD New Delhi.

Preparation of Microspheres:

Ionotrpic gelation method: The microspheres of Famotidine were prepared by ionotropic gelation technique. Firstly, in this method, sodium alginate and *Acacia nilotica* gum were weighed in a required quantity. Make a solution up to 30 ml with distilled water. With the help of magnetic stirrer, this solution mixed for 1 hour. Then required quantity of Famotidine was weighed and mixed in above solution, stirred well continuously for 3 hour. Resultant solution was extruded drop wise with the help of syringe and needle into 50 ml of different cross linking solution of Aluminium chloride, Barium chloride, Calcium chloride and stirred well at 100 rpm for 1 hr. Obtained microspheres were washed with distilled water and dried at 50ºC for 6 h in an oven. Eighteen batches of microspheres were prepared. Increasing the concentration of *Acacia nilotica* gum and keeping the concentration of Sodium alginate and Famotidine constant [17].

Table 1. Composition of Microspheres of Famotidine

Ingredients	Formulations					
	F1	F2	F3	F4	F5	F6
Sodium alginate (mg)	1000	1000	1000	1000	1000	1000
***Acacia nilotica* (mg)**	500	750	1000	1250	1500	1750
Drug (mg)	100	100	100	100	100	100
$AlCl_3$,/$BaCl_2$, $CaCl_2$ %	10%	10%	10%	10%	10%	10%

Evaluation of Microspheres:

Prepared Microspheres were evaluated and characterized for the following parameters:

Compatibility study: Compatibility study of drug and polymer analyzed by UV spectrophotometer.

SEM: Morphology characters of prepared microspheres were done by Scanning Electron Microscope (SEM) photographs. SEM study was done Nanotechnology Department of Jamia Miliya Islamiya University in Delhi [3].

Physical appearance: All the prepared microspheres were observed visually for colour, uniformity of size [11].

Micromeritic Properties:

Bulk density and bulkiness: The inverse of bulk density is known as bulkiness. Firstly accurately weighed quantity of microspheres and placed in measuring cylinder. The measuring cylinder was fixed on the bulk density apparatus and the volume occupied by the powder was noted. Then the powder was tapping in a bulk apparatus until constant volume was obtained. The final volume was calculated by using bulk density formula [18].

$$Bulk\ density = \frac{Weight\ of\ microsphere}{Weight\ of\ apparent\ volume} \text{.....Equation 1}$$

$$\text{Tapped density} = \frac{weightofMicrosphere}{WeightofTappedvolume} \text{.....Equation2}$$

$$\text{Bulkiness} = \frac{1}{Bulkiness} \text{.....Equation3}$$

Flow property: Flow characteristics were measured by angle of repose. Using the formula and calculated the angle of repose [18].

$$\tan\theta = h/r \text{.....Equation4}$$

Where

Θ = angle of repose

h = height

r = radius

Compressibility index: This is also known as Carr's Consolidation Index. Compressibility index was calculated using this equation [18].

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100 \text{.....Equation5}$$

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density} \text{.....Equation6}$$

Percent yield: The dried microspheres were weighed and % yield was calculated by this formula [19].

$$\%\ \text{Yield} = \frac{weight\ of\ dried\ microspheres}{Amount\ of\ drug + Amount\ of\ polymer} \text{.....Equation 7}$$

Swelling index: Swelling index of dried microspheres was calculated. For different time intervals that are 0, 30, 60, 120, 240, 480, 960 min. Make 0.1N HCL. The microspheres were removed periodically from the stomach pH solution and remove excess surface liquid and weighed on balance calculated by this formula [20].

$$Swelling\ index = \frac{Intial\ weight - Final\ weight}{Initial\ weight} \times 100 \text{.....Equation8}$$

Particle size: Dried microspheres particle size determined by optical microscope. Particle size of microspheres analyzed all batch by optical microscopy method. In microscope fitted ocular lenceand stage micrometer than 50 individual microspheres analyzed each batch [17].

$$\text{Mean Particle size} = \frac{\Sigma(mean\ particle\ size\ of\ the\ fraction \times weight\ fraction)}{\Sigma(mean\ Fraction)} \text{.....Equation9}$$

Drug content: Each batches of dried microspheres checked out of drug content uniformity. Each batches weighed accurate quantity of dried microspheres then makes powder by the help of mortar pestle, then powder of microspheres dissolve 1.2 pH buffer solutions and kept 24 hours. Determined drug content by Shimadzu UV spectrophotometer 267nm [11].

$$\%\ \text{Drug content} = \frac{absorbance \times dilution\ factor \times bath\ volume}{1000} \times 100 \text{ .....Equation10}$$

***In-vitro* drug release:** Also known as dissolution study. It helps to evaluate the ability of the formulation to release the dose in expected time. *In vitro* studies of all batches were done. *In*

vitro release was determined by USP type I dissolution apparatus for a period of 8 hours. Make 1000 ml 1.2 pH buffer then 900 ml entered in type I dissolution apparatus after different time intervals 15, 30, 60, 120 min withdrawn 5ml solution and makeup up to 10 ml fresh buffer solution and spectra observed. Added fresh 5 ml solution in dissolution apparatus, this process continue for 2 hours. Then replaced of above solution and 7.4 pH buffer in type I dissolution apparatus entered, different time intervals that is 30, 60, 120, 240, 360 this process continue for 6 hours. Samples were analyzed for drug content at 267 nm using UV-Visible spectrophotometer [11].

Results and discussions:

Compatibility study result was found to be drug and polymer compatible with each other. The natural polymer microspheres were prepared by inotropic gelation technique. Ingredients were used Sodium alginate natural polymer *Acacia nilotica* gum obtained by natural source and drug Famotidine.

Prepared *Acacia nilotica* gum microspheres was having equal amount of sodium alginate and drug Famotidine in all batches, but of all batches in different concentration.

Physical appearance of prepared microspheres were found to colour is dark brownish, and mostly uniform in size but F3, F5 was fully uniform in size and spherical in shape.

All prepared microspheres were evaluated % yield, micromeritics characters, swelling studies of drug content %, particle size, *in vitro* drug release.

By the Scanning electron microscopy observed drug loaded F3 batch microspheres, sphere in shape and rough surface comparision to other batches of microspheres. So it is acceptable. SEM photographs are shown in figure 1.

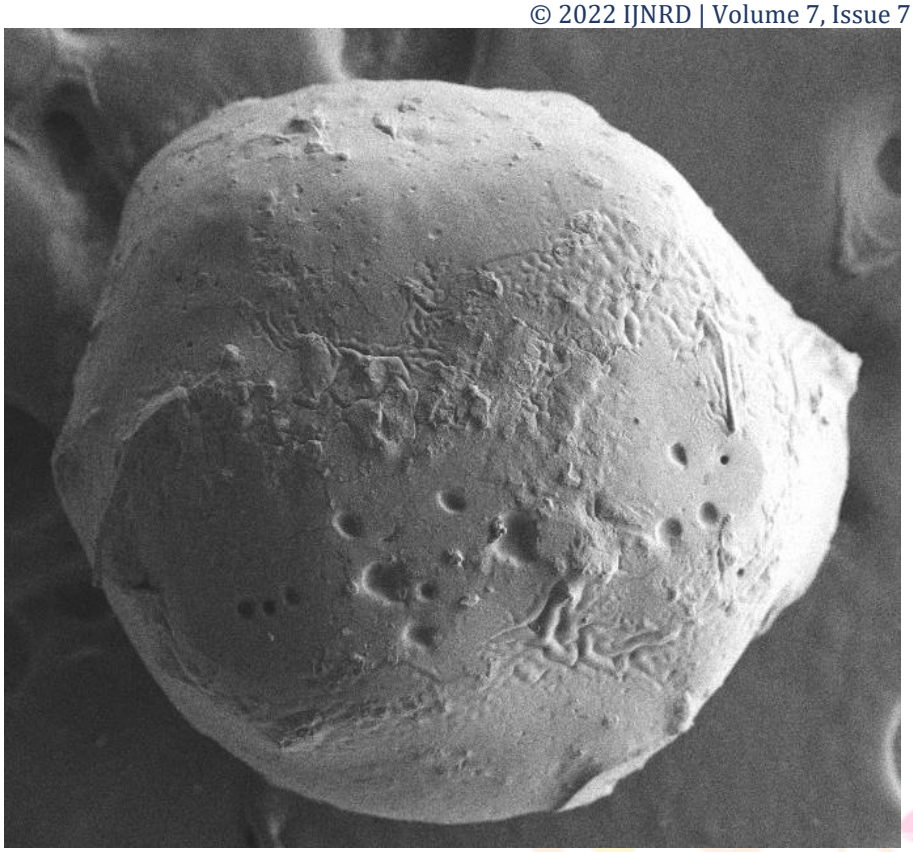

Fig 1.SEM photograph of microsphere

Micromeritics evaluation was done of natural polymer microspheres. The micromeritics parameters like bulk density, tapped desity, bulkiness, compressibility index hausner ratio and angle of repose better flow and has good packaging properties. Micromeritics studies have good acceptable flow properties. Comparative study has shown all batches formulation F5 higher bulk density. Formulation F1 has shown maximum tapped density. Percentage yield dried natural polymer microspheres was found the fluctuated yield. Flow properties, % yield, Particle size result shown in table 2, 3, 4.

Table 2.Characterization parameters of *Acacia nilotica* microspheres cross linked with Aluminium chloride

Formulations	**Bulk density (g/ml)**	**Tapped density (g/ml)**	**Bulkiness ($cm^{3/g}$)**	**Carr's index (%)**	**Hausner's ratio**	**Angle of repose (º)**	**Percent Yield (%)**	**Particle size (µm)**
F1	0.57 ± 0.02	0.56 ± 0.04	1.75 ± 0.20	1.78 ±0.08	0.98 ±0.01	19.64 ±.01	85.00 ±0.02	980.42 ±0.02
F2	0.56 ± 0.01	0.54 ± 0.00	1.78 ± 0.22	3.70 ±0.14	0.96 ±0.02	18.98 ±.02	75.67 ±0.01	931.56 ±0.01
F3	0.54 ± 0.04	0.53 ± 0.02	1.82 ±0.30	1.88 ±0.00	0.98 ±0.02	20.55 ±.02	80.5 ±0.05	864.31 ±0.02
F4	0.56 ± 0.01	0.55 ± 0.10	1.78 ±0.24	1.81 ±0.22	0.98 ±0.01	24.56 ±.02	73.19 ±0.02	925.04 ±0.03
F5	0.57 ± 0.02	0.58 ± 0.04	1.75 ±0.26	1.72 ±0.16	1.01 ±0.02	26.29 ±.01	83.46 ±0.01	992.04 ±0.04
F6	0.55 ± 0.01	0.56 ± 0.02	1.70 ±0.32	1.78 ±0.08	1.01 ±0.06	26.24 ±.02	78.24 ±0.12	968.98 ±0.02

Table 3.Characterization parameters of *Acacia nilotica* microspheres cross linked with Barium chloride

Formulations	**Bulk density (g/ml)**	**Tapped density (g/ml)**	**Bulkiness ($cm^{3/g}$)**	**Carr's index (%)**	**Hausner's ratio**	**Angle of repose (º)**	**Percent Yield (%)**	**Particle size (µm)**
F1	0.57 ±0.04	0.55 ±0.03	1.75 ± 0.20	3.63 ±0.08	0.97 ±0.01	19.65 ±.02	85.44 ±0.02	968.54 ±0.02
F2	0.58 ±0.01	0.57 ±0.02	1.73 ±0.12	1.75 ±0.10	0.98 ±0.03	18.99 ±.04	77.69 ±0.01	943.58 ±0.01
F3	0.55 ±0.04	0.54 ±0.02	1.70 ±0.10	1.85 ±0.01	0.98 ±0.02	20.57 ±.01	80.5 ±0.05	847.33 ±0.02
F4	0.60 ±0.02	0.57 ± 0.10	1.67 ±0.24	5.26 ±0.22	0.95 ±0.01	24.52 ±.02	73.19 ±0.02	981.04 ±0.03
F5	0.59 ±0.02	0.58 ±0.04	1.70 ±0.02	1.72 ±0.16	0.98 ±0.04	27.39 ±.04	83.48 ±0.01	989.04 ±0.04
F6	0.56 ±0.04	0.55 ±0.02	1.78 ±0.32	1.82 ±0.08	0.98 ±0.06	26.28 ±.04	79.34 ±0.12	924.97 ±0.02

Table 4.Characterization parameters of *Acacia nilotica* microspheres cross linked with Calcium chloride

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Bulkiness ($cm^{3/g}$)	Carr's index (%)	Hausner's ratio	Angle of reose (º)	Percent Yield (%)	Particle size (µm)
F1	0.59 ±0.04	0.58 ±0.03	1.69 ±0.20	1.72 ±0.08	0.98 ±0.01	19.65 ±.02	85.44 ±0.02	958.54 ±0.02
F2	0.60 ±0.01	0.58 ±0.02	1.67 ±0.12	3.45 ±0.10	0.96 ±0.03	18.99 ±.01	77.69 ±0.01	943.58 ±0.01
F3	0.55 ±0.04	0.54 ±0.02	1.82 ±0.10	1.85 ±0.02	0.98 ±0.02	20.57 ±.04	80.5 ±0.05	847.33 ±0.02
F4	0.58 ±0.02	0.56 ± 0.10	1.72 ±0.24	3.57 ±0.12	0.96 ±0.01	24.52 .03	73.19 ±0.02	981.04 ±0.03
F5	0.57 ±0.03	0.56 ±0.04	1.75 ±0.02	1.78 ±0.04	0.98 ±0.04	27.39 ±.04	83.48 ±0.01	989.04 ±0.04
F6	0.56 ±0.04	0.55 ±0.02	1.78 ±0.32	1.81 ±0.08	0.98 ±0.06	26.28 ±.02	79.34 ±0.12	924.97 ±0.02

Swelling index % of all the batches was found to be excellent range. Formulation F5 having highest swelling property. This Swelling % result shown in figure 2.

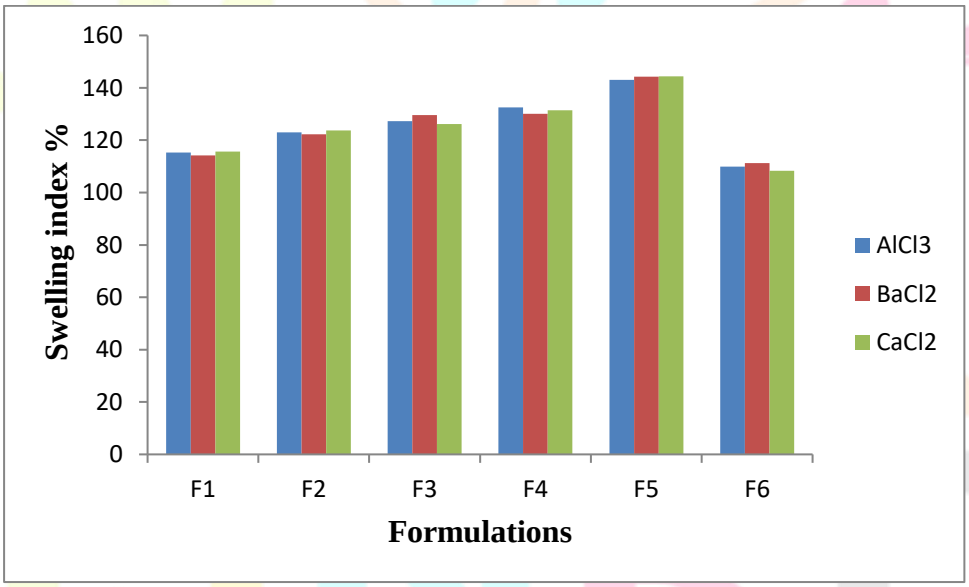

Fig 2.Swelling (%) of $AlCl_3$, $BaCl_2$, and $CaCl_2$ cross linked agent

Present study found highest drug content % F1 formulation of all batch comparative other formulations. And drug content range 88.98 to 98.23 %. Result was shown all batches in figure 3.

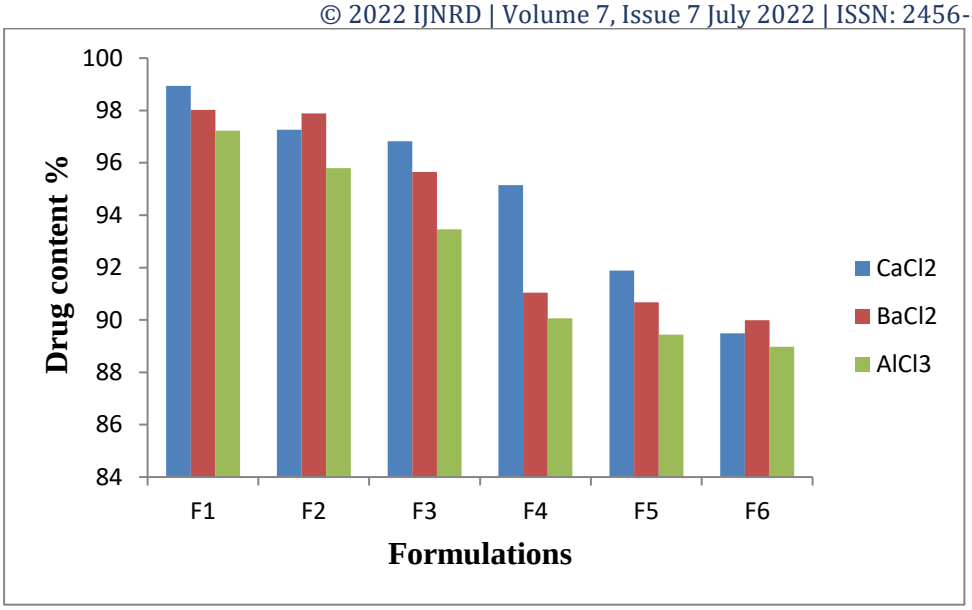

Fig3. Drug content (%) $AlCl_3$, $BaCl_2$, $CaCl_2$ cross linked agent

In vitro drug release % studies in this paper of all batches were done. Batch F1showed maximum% release of drug and F6 batch shows minimum % release of drug. In 480 mins more than 98 % drug is released.

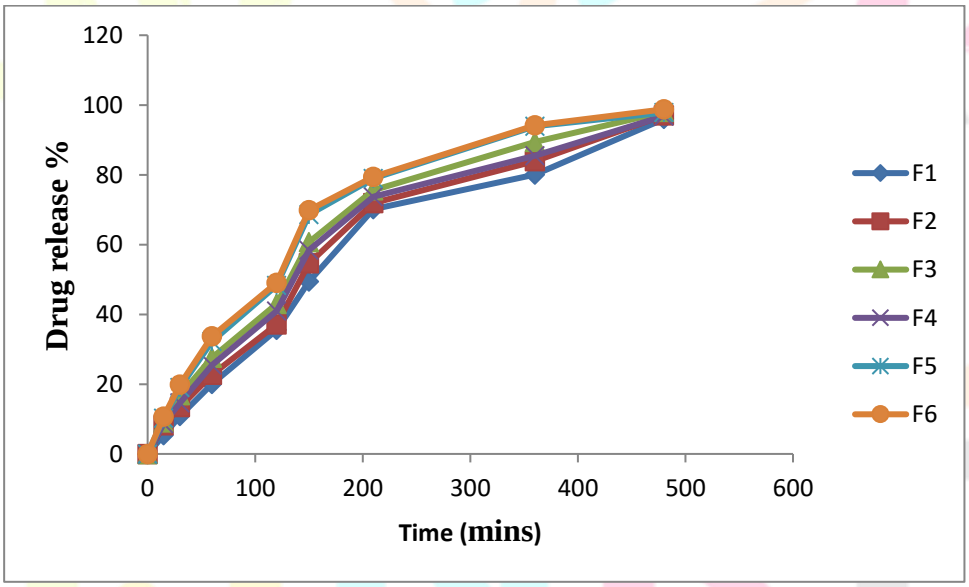

Fig4. Drug release (%) of $AlCl_3$cross linked agent

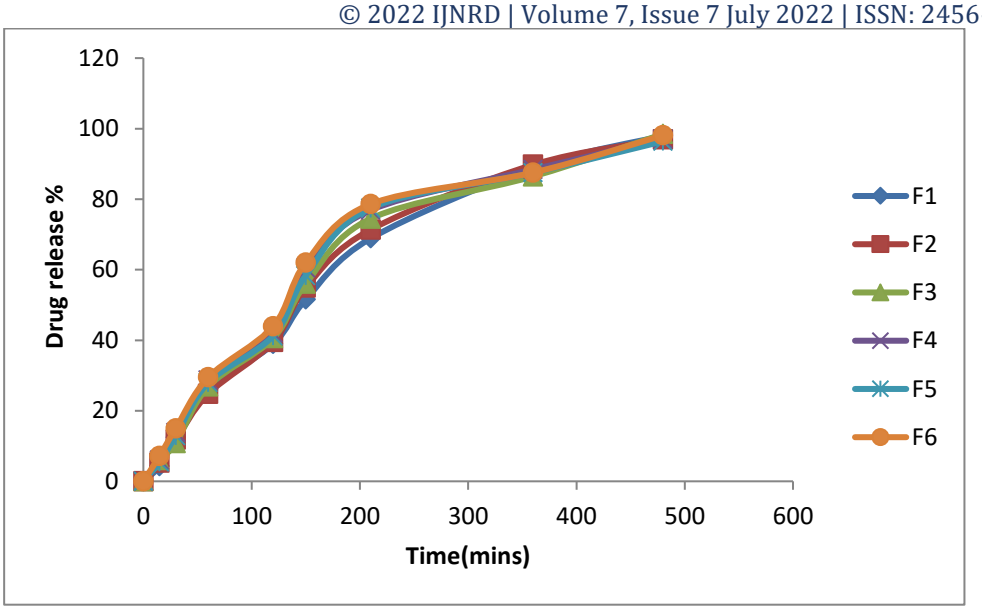

Fig 5. Drug release (%) of $BaCl_2$ cross linked agent

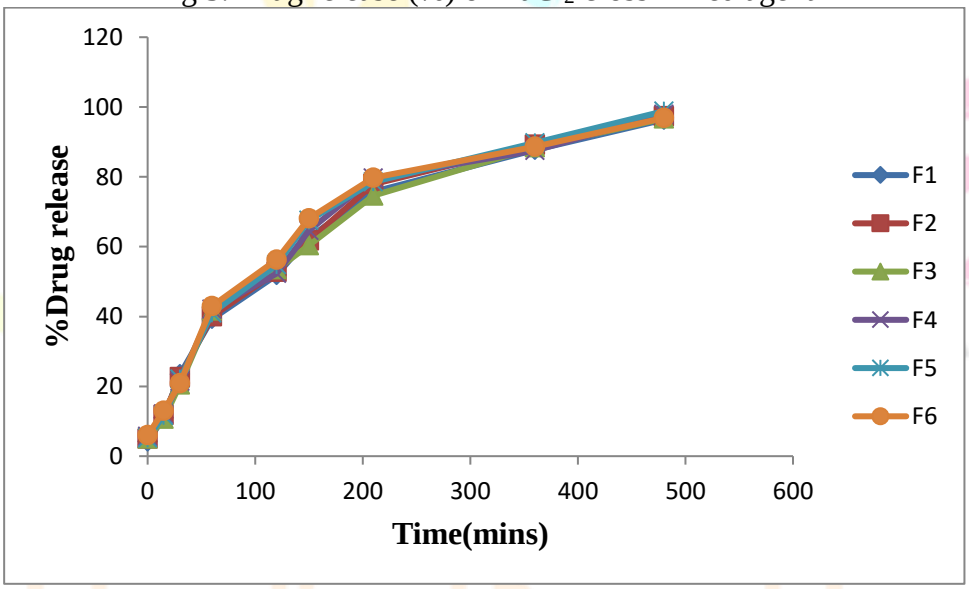

Fig 6. Drug release % of $CaCl_2$cross linked agent

CONCLUSION

In this study many attempts have been made to prepare the Famotidine microspheres using different polymers by the ionotropic gelation technique. Natural polymer microsphere was successfully prepared as controlled release formulation, which reduce the frequency of dose and gives good patient compliance. All the evaluation parameters obtained from the formulas were found to be acceptable. Based on the observation, it can be concluded that the attempt of preparation and evaluation of natural polymer microsphere with Famotidine was found to be successful in the controlled release of the drug for an extended period.

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