Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Formulation and Evaluation of FSM-Alginate Beads of Vildagliptin

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ABSTRACT

Many approaches have been immerged to prolong the residence time of the dosage forms at the absorption site .One among them is the development of oral controlled release mucoadhesive system. The present study aims to formulate and evaluate the effectiveness of FSM-Alginate beads of Vildagliptin in streptozotocin induced diabetic rats. In the present work, 6 formulations of Vildagliptin mucoadhesive beads (F1 to F6) were prepared by ionotropic gelation method. Fenugreek seed mucilage and sodium alginate was used as polymers and calcium chloride as cross linking agent. The beads containing drugs and excipients were subjected to various evaluation test such as Particle size distribution, Swelling index, Mucoadhesivity and Dissolution studies. Among all the formulations, F3 containing FSM and sodium alginate in the concentration of 0.6g and % DEE of 97.89 resulting in the highest drug release rate of 97.86% at the end of 10 h. Hence, it was considered as the optimized formulation.

Keywords: Mucoadhesion, Fenugreek Seed Mucilage, Sodium Alginate, Diabetes. Ionotropic Gelation.

Article Info: Received 14 July 2019; Review Completed 23 Aug 2019; Accepted 27 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Cherian AS, Boby Johns G, Praveen Raj R, Daisy P.A, Jeny S, Formulation and Evaluation of FSM-Alginate Beads of Vildagliptin, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):246-251 **http://dx.doi.org/10.22270/jddt.v9i4-A.3289**

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1. INTRODUCTION:

Over the previous few decades, a great deal of interest has been paid to the development of polysaccharide-based hydrogel beads thru ionotropic gelation technique, which are useful as achievable carriers in controlled drug delivery. The benefit of physical cross-linking by way of ionotropic gelation is that the drug encapsulation in the beads could be carried out in an eco-friendly environment avoiding the feasible toxicity of reagents associated with chemical cross-linking. To formulate numerous cross-linked alginate mucoadhesive systems for controlled-release drug delivery, use of mucoadhesive polymer-blend with alginate is one of the generally accepted approaches. Again, blending with suitable polymer can enhance drug encapsulation and stability, which are found lower in cross-linked alginate hydrogel beads processed by ionotropic gelation.

FSM was obtained from *Trigonella foenum-graecum L*. seeds known as Methi and is a commonly reachable material in nature. Fenugreek seeds comprise a high percentage of mucilage. The pharmaceutical utility of FSM is already established as mucoadhesive gelling agent, binding agent, and disintegrating agent. It is additionally suggested that the FSM has antidiabetic property .In the present study, the utility of FSM, as a possible herbal mucoadhesive polymeric-blend with sodium alginate for the development of a novel mucoadhesive beads through ionotropic gelation technique for the use in oral delivery was evaluated using Vildagliptin as model drug. [1, 2, 3]

Vildagliptin is a new oral antidiabetic drug that enhances pancreatic islet cell responsiveness to glucose. Vildagliptin trade names Galvus, Zomelis,) is an oral anti-hyperglycemic agent (anti-diabetic drug) of the dipeptidyl peptidase-4 (DPP- 4) inhibitor classification of drugs. Vildagliptin inhibits the inactivation of GLP-1and GIP via DPP-4, permitting GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by using the alpha cells of the islets of Langerhans in the pancreas. Vildagliptin has been shown to limit hyperglycemia in type 2 diabetes mellitus. Biological half-life 2-4 hrs. Main site of absorption is at small intestine. Therefore, the study used to be planned with an aim of developing a herbal polysaccharide-based more than one unit mucoadhesive system of Vildagliptin by the use of sodium alginate-FSM polymer-blend for controlled-release oral drug delivery [4,5].

2. MATERIALS AND METHODS

2.1 Materials

Vildagliptin (Yarrow Chem Products, Mumbai), Sodium Alginate (Loba Chemi India), Calcium Chloride (Nice

Chemicals) and Fenugreek seeds were collected from Chertahla in the month of February 2019. All the reagents and chemicals are of analytical grade.

2.2 **Extraction and purification of Fenugreek Seed Mucilage**:

Seeds are washed to get rid of dirt and particles. The fenugreek seeds (250 g) had been soaked in distilled water (500ml) overnight time and heated at 50ºC for 2 hours. The mucilage is extracted using multilayer material bag to take away the mare from the solution. Acetone was added to the above filtrate to precipitate the mucilage and therefor the mucilage was separated, dried in an oven at 50ºC, keep in desiccator until use. The acquired powder was re-dissolved in a hundred ml of water, filtered and centrifuged for 20 minutes at 3000rpm.The supernatant clear answer was evaporated and dried. The purified stable mass was dried and saved in an air tight container.[1,17]

2.3 **Preparation of FSM –alginate beads containing Vildagliptin**

The mucoadhesive beads could be prepared via Ionotropic Gelation Method (IG). Sodium alginate and FSM aqueous dispersions were organized separately by using of distilled water. With a magnetic stirrer, these dispersions were well blended with stirring at 200-400 rpm for 10 min. Vildagliptin was then added to the dispersion aggregate. Using magnetic stirrer, drug and polymers will be dissolved entirely in water. The stirring is sustained until clear dispersion is formed, then this dispersion is dropped through a satisfactory needle 21-G in to calcium chloride (CaCl2) solution. In the CaCl2 solution, the added droplets were retained for 15 min to complete the healing reaction and to produce rigid beads. The beads was filtered, washed with distilled water and dried at room temperature.

Table 1 Formulation Chart.

INGREDIENTS(mg)	F1	F2	F3	F4	F5	F6
VILDAGLIPTIN	500	500	500	500	500	500
SODIUM ALGINATE	100	200	300	400	500	600
FSM MUCILAGE	100	200	300	400	500	600
CALCIUM CHLORIDE	2	2	2	2	2	2

2.4 CHARECTERIZATION METHODS

2.4.1 Fourier Transform Infra-Red Spectroscopy:

The compatibility between pure drug and polymer was detected by FT-IR spectra obtained. Samples were reduced to powder and analyzed as KBr pellets by employing a Fourier transform-infrared (FTIR) spectroscope (Perkin Elmer Spectrum RX I, USA). The pellet was placed within the sample holder. Spectral scanning was taken within the wavelength region between 4000 and 400 cm−1 at a resolution of 4 cm−1 with scan speed of 1 cm/s.

2.4.2 Surface Morphology Analysis by Scanning Electron Microscopy (SEM):

Beads having drug were gold coated by mounted on a brass stub using double-sided adhesive tape and under vacuum in an ion sputter with a tiny layer of gold (3–5 nm) for 75 s and at 20 kV to make them electrically conductive and their morphology was observed by scanning electron microscope (ZEISS EVO 40, Japan).

2.4.3 Bead Size Measurement

Particle size of 100 dried beads from every batch was measured by optical microscopic technique for average particle size using an optical microscope (Olympus). The ocular micrometer was formerly calibrated by stage micrometer.

2.4.4 Determination of DEE

100 mg of beads were taken and were crushed using pestle and mortar. The crushed powders of drug containing beads were placed in a very 250 ml volumetric flask and the volume was made up to 250 ml by phosphate buffer, pH 7.4, and kept for 24 h with infrequently shaking at 37 ± 0.5 ◦ C. After the specified time, the mixture was stirred at 500 rpm for 20 min by means of a magnetic stirrer (Remi Motors, India). The polymer debris fashioned after disintegration of bead was removed by filtering through Whatman® filter paper (No. 40). The drug content within the filtrate was determined using a UV–vis spectrophotometer (Shimadzu, Japan) at 233 nm against acceptable blank. The DEE (%) of these prepared beads was calculated by the subsequent formula.

$$\text{DEE (\%)} = \ : \frac{\text{Actual drug content in beads}}{\text{Theoritical drug content in } \textbf{beads}} * 100$$

2.4.5 Evaluation of Swelling Behavior

Swelling behavior analysis of beads containing drug were carried out in two different aqueous media: 0.1 N HCl (pH 1.2), and phosphate buffer (pH 7.4). 100 mg beads were placed in vessels of dissolution equipment (Campbell Electronics, India) containing 500 ml corresponding media. The experiment was carried out at 37 ± 1 ◦ C under 50 rpm paddle speed. The swelled beads were removed at scheduled time interval and weighed after drying the surface, by using a tissue paper. Swelling index was resolved by using the following formula:

$$\text{Swelling index (\%)} = \frac{\text{Weight of beads after swelling} - \text{Dry weight of bead}}{\text{Dry weight of beads}} * 100$$

2.4.6 Ex- vivo Mucoadhesion Testing

The mucoadhesive properties of beads containing drug were evaluated by ex vivo wash-off methodology. Freshly excised pieces of goat intestinal mucosa (2 cm × 2 cm) (collected from slaughterhouse) were mounted on glass slide (7.5 cm × 2.5 cm) using thread. About 50 beads were unfold onto the wet tissue specimen, and the prepared slide was slung onto a groove of disintegration test apparatus. The tissue specimen was given a even up and down movement in a vessel containing 900 ml of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4), separately, at 37 ± 0.5 ◦ C. After regular time intervals, the machine was stopped and therefore the range of beads still adhering to the tissue was counted.

2.4.7 In Vitro Drug Release Studies.

The release of drug from numerous beads was tested using dissolution equipment USP (Campbell Electronics, India). The baskets were enclosed with 100-mesh nylon cloth to

stop the seepage of the beads. The dissolution rates were measured at 37 ± 1 ◦ C under 50 rpm speed. Accurately weighed quantities of beads containing Vildagliptin equivalent to 100 mg were added to 900 ml of 0.1 N HCl (pH 1.2). The test was carried out for 2 h and then continued in phosphate buffer (pH 7.4) for next 8 h. 5 ml of aliquots was collected at regular time intervals, and therefore the same quantity of fresh dissolution medium was replaced into dissolution vessel to keep the sink condition throughout the experiment. The collected aliquots were filtered, and suitably diluted to determine the absorbance using a UV–vis spectrophotometer (Shimadzu, Japan) at 233 nm against suitable blank.

2.4.8 Drug Release Kinetic Data

In order to understand the kinetics and mechanism of drug release, the result of in-vitro drug release study of beads were fitted with various kinetic equation like zero order (cumulative % release vs. time), Kosmeyer Peppas model ,Higuchi's model (cumulative % drug release vs. square root of time). R^2 values were calculated for the linear curve obtained by regression analysis of the above plots.

Table 2: Results of various studies like particle size determination, %DEE and in-vitro drug release

SI NO	FORMULATION CODE	MEAN PARTICLE SIZE(mm)	%DEE	%DRUG RELEASE
1	F1	1.37	96.45	96.42
2	F2	1.35	95.29	94.20
3	F3	1.28	97.89	97.86
4	F4	1.36	96.65	96.49
5	F5	1.37	95.49	94.74
6	F6	1.39	95.86	95.76

3. RESULTS AND DISCUSSION

3.1 Fourier Transform Infra-Red Spectroscopy:

The FTIR spectra of Sodium alginate, FSM, Vildagliptin and FSM alginate bead contain Vildagliptin were shown in the figure 1. The FTIR spectra of sodium alginate showed the band around 3440.92, 2931.73, 2160.23, 1620.18, 1419.59, and 1033.84cm^{-1} which are due to the stretching of OH ,CH,C=C,CF,CBr,=C-H respectively. FTIR spectrum of isolated FSM showed characteristic peaks of –OH between 3511.6 and 3154.3 cm−1, –CH3 at 2925.48 cm−1,–CH stretching between 2920.0 and 2854.1cm−1, ether linkage at 1455–1400 cm−1 and–CO stretching at 1017.7 cm−1.Absence of peaks indicates that there were no interaction among the polymers.

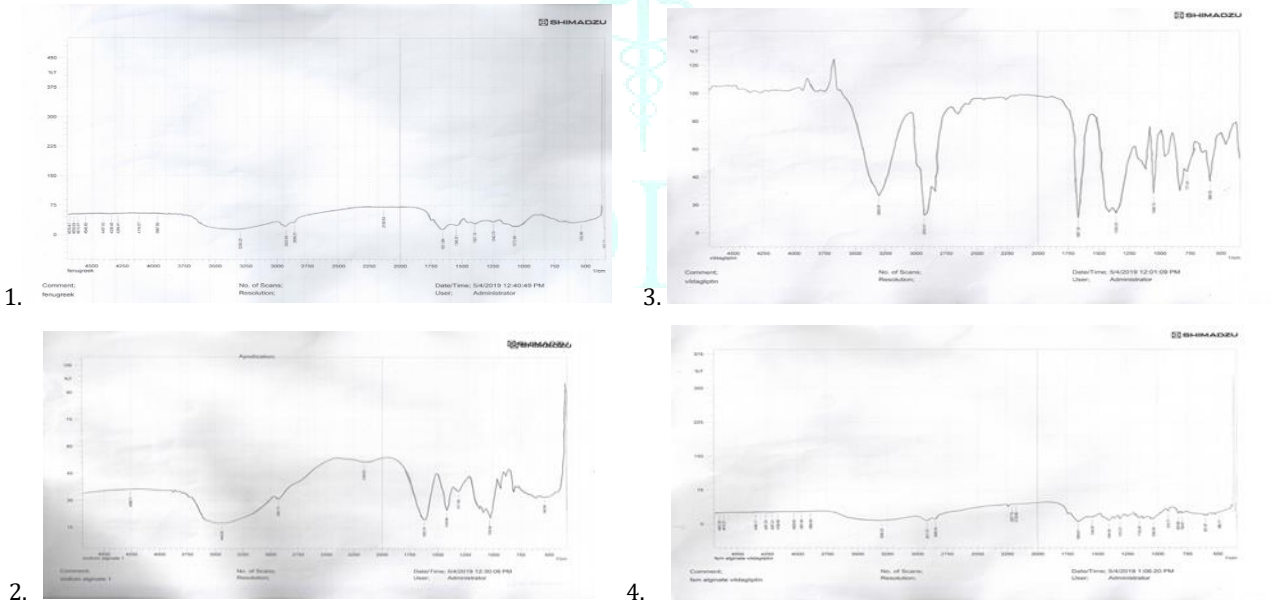

Fig:1 FTIR Spectrum 1: Vildagliptin,2:Sodim Alginate,3:FSM,4: Drug Polymer Mixture.

3.2 Surface Morphology Analysis by Scanning Electron Microscopy (SEM Analysis)

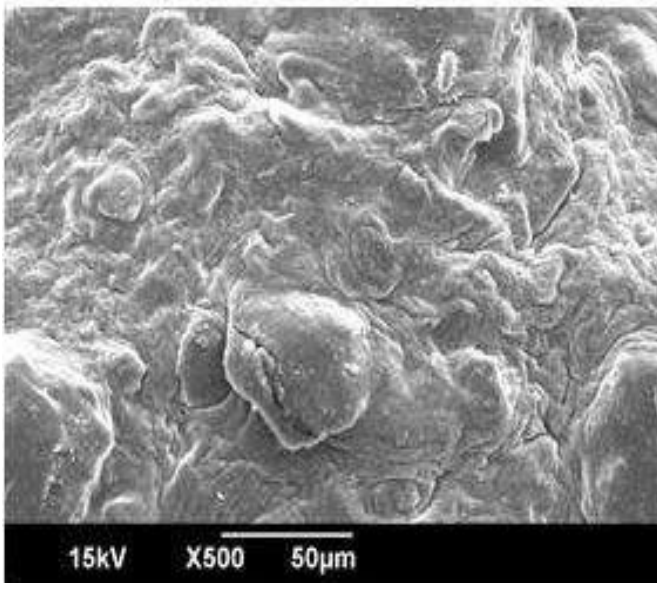

Fig.2 Scanning electron photograph of optimized FSM-Alginate bead containing Vildagliptin.

The SEM photograph of the surface of the FSM-alginate bead of Vildagliptin (Fig. 2) exhibited very hard surface with characteristic massive wrinkles and cracks. These cracks and wrinkles may be caused via partly collapsing the polymeric gel network during drying. Due to the migration of beads along with water to the surface during drying will result in the formation of drug crystals.

3.3 Bead Size Measurement.

Particle of FSM-alginate beads of Vildagliptin was within the range of 1.28-1.39mm. Increasing the incorporation of FSM in the polymer solution with sodium alginate will increase the size of beads. Due to the increase in viscosity of the polymer blend solution with the addition of FSM in increasing ratio in turn increase the droplet size. A decrease in particle size of FSM alginate beads was seen when concentrated calcium chloride was used as cross linking agent.

3.4 Determination of DEE

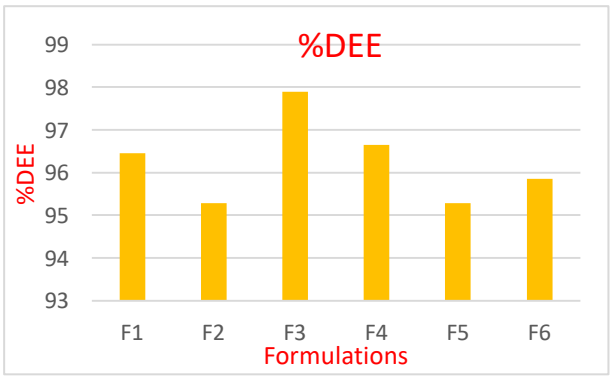

Fig.3: Drug encapsulation efficiency of F1-F6 formulations.

The drug encapsulation of beads was within the range of 95.29 - 97.89. When the sodium alginate to FSM ratio in the polymer blend decreases, DEE % was increased. This may be due to the viscosity variations in the polymer blend. Thus the leaching of the drug to the polymeric solution will be prevented during the time of cross linking.

3.5 Evaluation of Swelling Behavior.

Swelling behavior of optimized formulation F3 was carried out in 2 different medias.0.1N HCL pH1.2 and phosphate buffer pH7.4.When compared with phosphate buffer swelling behavior of FSM-alginate beads containing Vildagliptin was lower in acidic medium. This is because of the shrinkage of alginate at acidic medium.

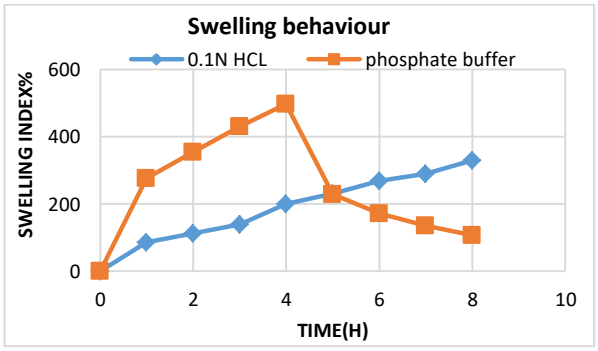

Fig.4 Swelling behavior of optimized formulation F3.

Maximum swelling was observed in 3-4 hours in phosphate medium after that erosion and dissolution takes place. It has been previously reported that the swelling of calcium alginate in presence of calcium ion capturing agent depends on the progressive displacement of calcium ions within calcium alginate-based beads. It has been also reported that the swelling of calcium alginate-based beads can be enhanced by the presence of phosphate ions (in phosphate buffer), which act as calcium sequestrant. Thus this results clearly suggest that FSM –alginate beads containing Vildagliptin may slightly swell in the stomach and move to the upper intestine and the Vildagliptin is to be absorbed.

3.6 Ex- vivo Mucoadhesion Testing

The ex vivo wash off test using goat intestinal mucosa for assessing Mucoadhesivity of FSM-alginate beads containing Vildagliptin was once performed at each gastric pH (0.1 N HCl, pH1.2) and intestinal pH (phosphate buffer, pH 7.4) for eight h. The wash off used to be faster at intestinal pH than at gastric pH. In acidic pH the percentage of beads adhere to the mucosal tissue varied from 70-87% in acidic buffer and 90-50% in alkaline buffer. The decreased Mucoadhesion of FSM-alginate beads containing Vildagliptin in phosphate buffer may be resulted due to the erosion of calcium ion. Therefore, the results of the wash off test indicated that the FSM-alginate beads containing Vildagliptin possessed good mucoadhesivity.

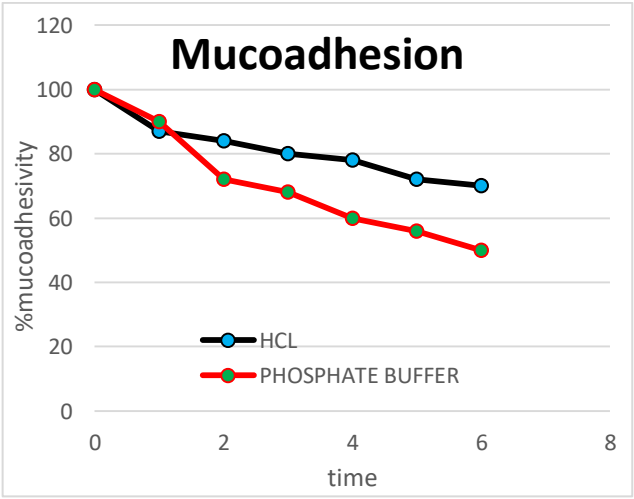

Fig.5 Mucoadhesivity of optimized formulation F3

3.7 *In Vitro* Drug Release Studies

The *In-vitro* drug release for FSM –alginate beads containing Vildagliptin was carried out in 0.1 N HCL for 1st two hours and then in phosphate buffer for 8 hours. All the 6 formulations showed prolonged release over 10 h. The drug release from the beads in acidic medium was slow due to the shrinkage of alginate in acidic pH (10.17%-20.04%). Due to the higher swelling rate in phosphate buffer drug release was found to be greater in phosphate buffer.(31.45%-97.86%).

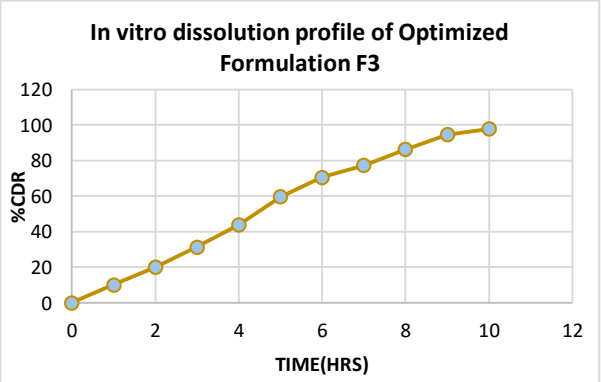

Fig.6 The *In-vitro* drug release of Optimized Formulation F3

3.8 Drug Release Kinetic Data:

FORMULATIONS	ZERO ORDER	HIGUCHI	KOSMEYER PEPPAS
F3	R^2	R^2	R^2
	0.943	0.877	0.843

The highest value of R^2 indicates that the model follows zero order kinetics .For zero order R^2 value was found to be: 0.943.

4. CONCLUSION:

Mucoadhesive beads containing Vildagliptin made of FSM-alginate polymer-blend by ionotropic gelation technique was successfully prepared and evaluated. The above studies suggested that the FSM-alginate mucoadhesive beads containing Vildagliptin swelled slowly in the stomach and accordingly adhered to the stomach mucosa allowing more drug to be absorbed minimizing the diffusion barriers to increase the absorption period by prolonging the gastric residence time. Then, these beads were subsequently move to the upper part of the intestine, where they swelled more and release the drug. The results demonstrated that the ability of the beads to maintain dense blood glucose level. Thus FSM is a potential mucoadhesive agent in the development of controlled release formulations.

ACKNOWLEDGEMENTS:

College Director: Dr Sr Betty Carla.

Principal: Dr Vinod B.

Guide: Dr Boby Jhons G.

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