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Original Article

Metal Ion Induced Sodium Alginate-Gellan Gum Microspheres of Ofloxacin

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ABSTRACT

Objective: The objective of the present study was formulation and evaluation of metal ion induced sodium alginate-gellan gum microspheres for oral drug delivery of ofloxacin. **Methodology:** In this study, the microsphere containing ofloxacin were prepared by using sodium alginate and gellan gum and cross-linked by metal ion like calcium chloride, aluminium chloride and maleic anhydride. The prepared microspheres were evaluated for in-vitro release study, swelling index, particle size determination, entrapment efficiency and percentage yield. **Results**: Entrapment was found good in all the formulation while the maximum entrapment (97.1%) was recorded in formulation cross-linked by aluminium chloride and maleic anhydride and their average particle size were 60 µm to 90 µm. From the in-vitro release study, 24.98% of drug was release by the formulation cross-linked by aluminium chloride over a period of 3 hours. **Conclusion**: From all the experiment, it is observed that formulations which are cross-linked by aluminium chloride is the better formulation among other due to good release profile and entrapment efficiency.

Keywords: Microspheres, Ofloxacin, Gellan Gum, Drug Release.

1. INTRODUCTION

Microspheres are free flowing small spherical particles, with diameters in the micrometer or nanometer range (topically 1 µm to 1000 µm) [1]. It is sometime referred to as microparticles [2]. It is defined as a monolithic sphere with therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles or as a structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at molecular or macroscopic level [3].

Generally in pharmaceutics industry, microspheres can be applied to encapsulate drugs, in order to attain sustained-release, protect sensible drug or special delivery methods [2]. It

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is a first order release system. When the optimal amount of agent is deliver to the target tissue in the right period of time it show maximum therapeutic efficacy, it causing little toxicity and side effects. They are novel drug delivery systems formulated to obtained sustained drugs therapy to prolong the residence time of drug in plasma [4].

Microspheres are generally made up of polymeric, waxy, or other protective materials such as starches, gums, proteins, fats, and waxes and used as drug carrier matrices for drug delivery. Natural polymer can also be used form microspheres preparation like Albumin, Gelatin etc. Various naturally occurring biodegradable polymers are used like, sodium alginate, gellan gum etc. They are widely used polymer for the designing and development of drug delivery system [5].

Alginates are established among the most versatile biopolymers, used in a wide range of applications. Alginate is known as a family of liner copolymers containing blocks of (1, 4)-linked β-D-mannuronte(M) and α-L-guluronate(G) residues [6]. It is also a significant component of the biofilms produced by the bacterium Pseudomonas aeruginosa, the major pathogen in cystic fibrosis, that confer it a high resistance to antibiotics and killing by macrophages. Hydrocolloids like alginate can play a significant role in the design of a controlled-release product. The conventional used of alginate as an excipient in drug products generally depends on the thickening, gel-forming, and stabilizing properties [7]. The method is based on control of the gelification phenomenon of alginate by calcium ions, and it leads to small particles of a wide range of very well-defined sizes (250–850 nm) depending on the alginate concentration [8]. Alginate is also easily gelled in the presence of a divalent cation as the calcium ion [9].

Gellan Gum is a kind of extra cellular and anionic microbial polysaccharide excreted by microorganism Pseudomonas elodea. It is a linear structure with a repeating unit of tetrasaccharide. It is used as emulsifier, suspension agent, thickener, stabilizer, gelling agent, film former and lubricant. The physical gelation properties make this polysaccharide suitable as a structuring and gelling agent in food industries. Gellan is also exploited in the field of modified release of bioactive molecules. Aqueous solutions of Gellan are used as in situ gelling systems, mainly for ophthalmic preparation and for oral drug delivery [10]. Physical Gellan hydrogels, prepared with mono or divalent cations, are used also for the preparation of tablets, beads or microspheres. Interpenetrating polymer networks or co-crosslinked polymer networks based on Gellan and other polysaccharide systems have also been developed as drug delivery matrices. Chemical hydrogels of Gellan are usually prepared via chemical crosslinking of preformed physical networks, in order to enhance their mechanical properties, and to obtain slower drug release profiles [11].

Ofloxacin is an antibiotic useful for the treatment of a number of bacterial infections[12]. It is a racemic mixture, which consists of 50% levofloxacin and 50% of its “mirror image” or enantiomer dextrofloxacin [13]. When taken by mouth or injection into a vein this includes pneumonia, cellulitis, urinary tract infections, prostatitis, plague and certain types of infectious diarrhea. It is a synthetic fluoroquinolone [14] (fluoroquinolones) antibacterial agent that inhibits the supercoiling activity of bacterial DNA gyrase, halting DNA replications, that has a broad spectrum of activity against both gram-negative and gram-positive bacteria [15], with half life 8 - 9 hours.

When it was taken by mouth common side effects include vomiting, diarrhea, headache, and rash. Other serious side effects include tendon rupture, numbness due to nerve damage, seizures, and psychosis. Use in pregnancy is typically not recommended. Including the fluoroquinolone family of medications, It works by interfering with the bacterium's DNA [16]. The bioavailability of ofloxacin in the tablet form is approximately 98% following oral administration reaching maximum serum concentrations within one to two hours. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Therefore, elimination is mainly by renal excretion [13]. Therefore, the attempt to design ofloxacin-loaded sodium alginate and gellan gum microspheres using calcium chloride, aluminium chloride and or maleic anhydride as cross-linking agent.

2. MATERIALS AND METHODS

Materials:

Ofloxacin was purchased from Yarrow Chem Pvt Ltd, Mumbai, India. Sodium alginate, calcium chloride, aluminium chloride and maleic anhydride were obtained from Loba chemine, Mumbai, India. Gellan Gum was purchased from Yarrow Chem Pvt Ltd, Mumbai, India and was used without any further purification. All chemical and reagents used were of analytical grade.

Methodology:

Preparation of ofloxacin microspheres: [17]

The ofloxacin-loaded microspheres made of sodium alginate – gellan gum were prepared through interfacial ionotropic gelation technique. The ofloxacin-loaded microspheres were prepared by mixing with different concentration of polymer matrix of sodium alginate and gellan gum. The polymer matrix was cross-linked with various combinations of metal ions like calcium chloride, aluminium chloride and or maleic anhydride.

Sodium alginate 500 mg was accurately weighed and dissolved in 40 ml of deionized water with the help of magnetic stirrer. Gellan gum also accurately weighed and dissolved in 40 ml of deionized water. The temperature of the solution maintain 50° C and was rotate at 300 rpm with the help of magnetic stirrer until dissolve. When the dissolution of two polymers are complete, they were mixed together and become bubble free or uniformly mixed.

In a separate beaker 500 mg of accurately weighed ofloxacin was taken and mixed thoroughly in 20 ml of deionized water. On complete dissolution of the drug in water, the drug solution was mixed in the polymer mix to form a drug-polymer solution. The drug-polymer was rotated at 300 rpm until it become homogenous mixture. On an another beaker, the counter ion solution was prepared by weighing calcium chloride, aluminium chloride and or malic anhydride at ratio and dissolved in 50 ml of water with the help of magnetic stirrer.

When all the mixture is complete, the drug polymer mix was pipette out and drop wise in the counter ion solution with the help of pipette maintaining a minimum distance from the tip of pipette and the surface of counter ion solution. The droplet of the drug polymer mix cross link with the counter ions and form microspheres. After 20 minutes of curing, the microspheres were strained and washed thoroughly with distilled water to remove the traces of excess counter ion solution from the surfactant of the microspheres and hardens of the microsphere. The microspheres were collected on a Petridis and kept to dry under room temperature overnight. The ingredients were taken as per the formula given in table-1.

Table 1: Compositions of different formulations of ofloxacin microspheres.

Formulation code	*Ofloxacin [%w/v]*	*Sodium alginate [%w/v]*	*Gellan gum [%w/v]*	*Calcium chloride [%w/v]*	*Aluminium chloride [%w/v]*	*Malic anhydride [%w/v]*
F1	0.5	0.5	0.5	1		
F2	0.5	0.5	0.5		1	
F3	0.5	0.5	0.5			1
F4	0.5	0.5	0.5	1	1	
F5	0.5	0.5	0.5	1		1
F6	0.5	0.5	0.5		1	1
F7	0.5	0.5	0.5	1	1	1

In-vitro release study: [18, 19]

In-vitro release studies were carried out in USP dissolution apparatus type-II which is rotating paddle type apparatus. The microspheres were placed in the basket and immersed in the dissolution media containing 900 ml of phosphate buffer, pH 6.8 at temperature of 37 ± 1^0 C under 50 rpm for a period of 3 hours. At intervals of 15 minutes, 5 ml aliquots were withdrawn and replenished by 5 ml fresh media. The same volume of dissolution medium was replenished after each sampling. The sample were diluted ten times by taking 1 ml of sample and diluting it by adding 9 ml of phosphate buffer of ph 6.8. The diluted samples were checked for absorbance using UV spectrophotometer at the wavelength of maximum absorbance 294 nm.

Swelling index: [20, 21]

Swelling behavior is carried out by using the dissolution apparatus type-II. The microspheres were placed in the apparatus containing phosphate buffer of pH 6.8 at temperature of 37 ± 1^0 C under 50 rpm. The microspheres were removed after a certain time by filtration and blotted carefully to remove excess amount of surface water. Then the swollen microspheres were weighed, and swelling index was calculated by this formula.

$$\text{Swelling index} = \frac{\text{Weight of microspheres after swelling} - \text{Dry weight of microspheres}}{\text{Dry weight of microspheres}} \times 100 \quad \ldots(1)$$

Microscopic analysis: [18, 21, 23]

Microscopic analysis is the study to determine the particle size of microspheres with the help of an optical microscope. The diameters of microspheres were measured by spreading a thin layer of micro particles on a glass slide and an ocular micrometer was previously attached and the particles were placed on a slide and their size was measured. Each sample was observed at three times and an average value was taken as mean diameter. After collection of data, the data was divided in size ranges, and the frequency was calculated by this formula.

$$\text{Frequency (\%)} = \frac{\text{Number of particles in each size range}}{\text{Totall number of particles}} \times 100 \quad \ldots(2)$$

Drug entrapment efficiency: [21, 22]

Drug entrapment efficiency is the amount of drug physically entrapped by the polymer in the microsphere. 100 mg of microspheres were accurately weighed and triturated with the help of mortar and pestle, and dissolve in 10 ml of distilled water. The solution was filtered and diluted, then checked for absorbance in UV spectrophotometer at the wavelength of maximum absorbance 294 nm. The drug entrapment is calculated by this formula.

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content in microsphere}}{\text{Theoretical drug content in microsphere}} \times 100 \quad \ldots(3)$$

Determination of percentage yield: [17, 22, 24]

The amount of polymers and the drug incorporated was accurately weighed. This was taken as the theoretical weight. The total amount of microspheres obtained from each formulation was taken as the practical weight. Percent yield was calculated by taking the ratio of theoretical and practical weight and is given by the following formula.

$$\text{Percent yield} = \frac{\text{Weight of microspheres recovered finally}}{\text{Total weight of drug and polymers taken initialy}} \times 100 \quad \ldots(4)$$

3. RESULTS AND DISCUSSION

***In-vitro* release study:**

The results of *in-vitro* release studies are shown in the figure-1. *In vitro* release studies were carried out for the formulations of microspheres containing ofloxacin as drug and gellan gum and sodium alginate as polymer, cross-linked with counter ion solutions of calcium chloride, aluminium chloride and maleic anhydride in various ratios in phosphate buffer 6.8 for 3 hours. Drug released immediately from few formulations while a few formulations showed a lag phase in the release pattern. Formulations F2, F3, F4 and F7 showed significant lag phase up to 45 minutes while the remaining formulations were release immediately. The probable cause of immediate release at the beginning might

be due to surface drug that was deposited during drying of the microspheres. The lag phase indicates that the better cross-linking and drug entrapment, resulting in sustained release activity.

Microspheres prepared with 1% calcium chloride [F1] was found to 49.01% of drug release for a period of 3 hours, while drug release of the formulations were found to be moderate for formulations having cross-linked with only 1% maleic anhydride and combination of 1% maleic anhydride and 1% calcium chloride [F3 and F5]. Better cross-linking was observed in the formulations cross-linked with 1% aluminium chloride, combination of 1% aluminium chloride and 1% calcium chloride and combination of 1% calcium chloride and 1% maleic anhydride and 1% aluminium chloride [F2, F3 and F7].

Calcium chloride alone was insufficient as a cross-linking agent having sustained action for a short period [F1], but combining of calcium chloride with aluminium chloride and maleic anhydride improved the results. 24.98% of drug was released by the formulation cross-linked by aluminium chloride [F2] over a period of 3 hours. While formulations cross-linked by combinations was found to release approximately 30% over a period of 3 hours [F3 and F7] and approximately 50% of the drug was released by the formulation cross-linked by the calcium chloride and combination of calcium chloride and maleic anhydride and combination of aluminium chloride and maleic anhydride [F1, F5 and F6].

Thus it can be safely said that the drug ofloxacin exhibited sustained activity by cross-linking and esterification with aluminium chloride [F2] while esterification was poor for formulation cross-linked by calcium chloride [F1] and moderate for maleic anhydride cross-linked formulation [F3].

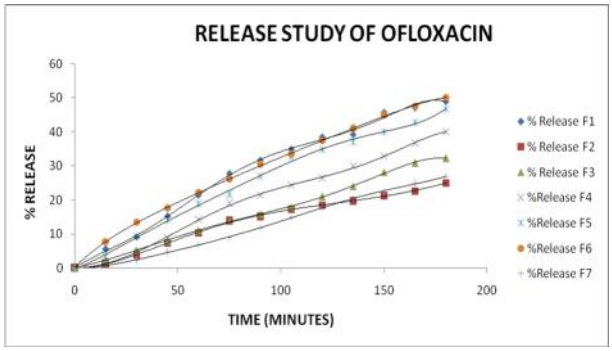

Fig 1: Release profile of ofloxacin from different formulations of microspheres.

Swelling index:

Swelling behaviour of the formulations were recorded and plotted as graph, which are shown in figure-2. The maximum swelling property is exhibited by the formulation cross-linked by the combination of maleic anhydride and aluminium chloride [F6] and least swelling is observed the formulation which is cross-linked by maleic anhydride [F3].

It is also noticeable that the percentage of swelling increased gradually with increasing the concentration of counter-ion. Swelling of formulation cross-linked by the combination of aluminium chloride and maleic anhydride [F6] is greater than individual swelling percentage of aluminium chloride and maleic anhydride. However the swelling rate was found to exhibit a decrease in the formulation cross-linked by the combination of calcium chloride, aluminium chloride and maleic anhydride. This might be due to the hard gel strength and rigid bonding of the cross-linked polymers.

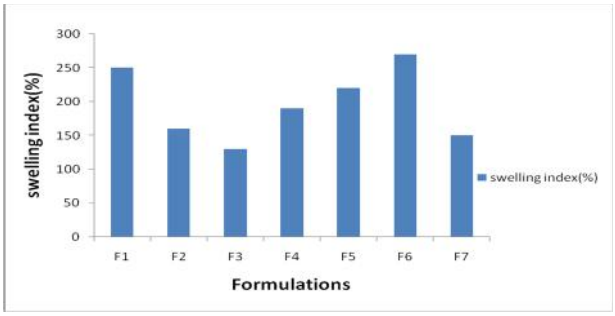

Fig 2: Swelling indices of different formulation of ofloxacin microspheres.

Microscopic analysis:

The data of microscopic analysis is plotted as a graph and the results are presented in figure-3. Microscopic analysis of ofloxacin reveals that the size range of ofloxacin microspheres lies between 30 µm to 180 µm. Microspheres which are cross-linked by 1% calcium chloride [F1] exhibited maximum frequency of size range in 120 µm to150 µm. Microspheres cross-linked by 1% w/v aluminium chloride [F2] exhibited maximum frequency of size range in 60 µm to 90 µm. Microspheres cross-linked by 1% maleic anhydride [F3] exhibited maximum frequency of size range in 120 µm to 150 µm. Microspheres cross-linked by the combination of 1% calcium chloride, aluminium chloride and maleic anhydride [F7] exhibited maximum frequency of size range in 60 µm to 90 µm. Microspheres cross-linked by the combination of 1% calcium chloride and maleic anhydride [F5] exhibited maximum frequency of size range in 90 µm to 120 µm. From this analysis, it can be inferred that frequency becomes maximum from size range 60 µm to 150 µm as the ratio of counter-ion increases.

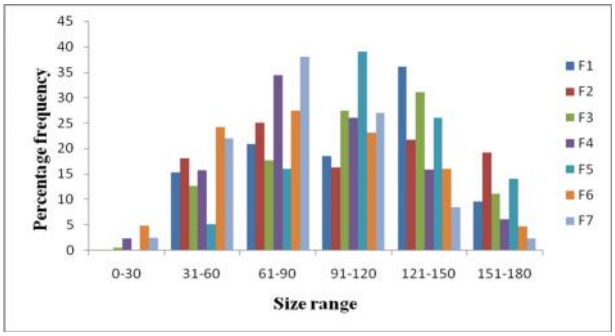

Fig 3: Microscopic analysis of different formulation of ofloxacin microspheres.

Drug entrapment efficiency:

The results of the drug entrapments are shown in table-2. Drug entrapment in the formulations was found to be fairly good, the maximum entrapment being exhibited by the formulation cross-linked by the combination of aluminium chloride and maleic anhydride [F6]. The formulation cross-linked by 1% aluminium chloride [F2] also exhibited good entrapment efficiency. The formulations cross-linked by the combination of all three cross-linking agents are also showed good entrapment efficiency. The probable reason for the high entrapment efficiency of formulation F2 might be due to cross-linking reaction of aluminium chloride and ofloxacin. Due to strong bonding of the drug and polymer and counter-ion poymers, entrapment of the drug in the polymer matrix is high.

Table 2: Drug entrapment efficiency of different formulations of ofloxacin microsphere

Code	% Entrapped
F1	81.9
F2	89.2
F3	78.9
F4	82.4
F5	96.2
F6	97.1
F7	74.6

Percentage yield:

The results of the percentage yield are shown in table-3. Percent yield was found to be the highest in formulation cross-linked with aluminium chloride [F2]. 98.5% yield was found in [F2] formulation microspheres, and 75.6% yield was found in calcium chloride cross-linked microspheres [F1] and 80.2% yield was found in maleic anhydride cross-linked microspheres [F3]. Incorporation of aluminium chloride in formulations [F1] as cross-linking agent increased the percent yield of the microspheres [F4], while yield was reduced in formulation that used the combination of aluminium chloride and maleic anhydride as cross linking agent [F6]. The incorporation of all the three cross-linking agents in formulations resulted in a fair and moderate the percent yield [F7].

Table 3: Percentage yield of different formulations of ofloxacin microsphere

Code	%Yield
F1	75.6
F2	98.5
F3	80.2
F4	91.3
F5	92.8
F6	76.4
F7	87.8

4. CONCLUSIONS

The objective of project work was to exploit the activity of ofloxacin as a model drug by attempting to prolong its release activity for a longer period of time. To achieve the design of sustained delivery of ofloxacin, microspheres were prepared by the incorporation of sodium alginate and gellan gum as the polymer and calcium chloride, aluminium chloride and or maleic anhydride served as the counter ion solutions for cross-linking of the drug and from where the rate of release was reduced. Cross linking occurs by formation of covalent bonds between two or more molecules. The cross linking agents contain two or more reactive ends to chemically attach with functional groups. This phenomenon is known as cross-linking.

After the formulation of microspheres, they were evaluated to estimate their *in-vitro* release profile, swelling behavior, particle size distribution, percentage drug entrapment efficiency and percentage yield. From this experiment, we have come to know that the formulation with aluminium chloride as a cross linker [F2] is the better formulation among the rest of the formulations. Swelling of the formulation F2 was least while the entrapment and yield percent was the maximum. A 98.5% of yield and entrapment efficiency 89.2% was recorded by the formulation F2. Release profile of the formulations revealed the sustained design of the drug, particularly formulation cross-linked with the aluminium chloride [F2] releasing 24.98 % and F7 (calcium chloride, aluminium chloride and maleic anhydride all are used as cross-linking agents) releasing 26.95 % over 3 hours respectively. It was also observed that on increasing the cross-linking agent solutions, the release rates were also improved. The particle size analysis revealed that the maximum frequency of microspheres lied in the range between 60 µm to 150 µm as counter-ion ratio increases. Therefore, the long term stability study and clinical trial is required for future development of this dosage form.

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