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Research Article

# Formulation and Characterization of Alginate Microbeads of Norfloxacin by Ionotropic Gelation Technique

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**ABSTRACT**

Norfloxacin is a synthetic antibacterial fluoroquinolone and active against a broad spectrum of gram-positive and gram-negative aerobic bacteria, its shorter biological half life (3 hrs.) necessitates that it to be administered in frequent doses of 400mg. The main objective of this study was to develop suitable micro particulate system of Norfloxacin for controlled release delivery system by varying the alginate concentrations, calcium chloride concentrations and curing time. In the present work, Norfloxacin microbeads were prepared by ionotropic gelation technique. Prepared microbeads were evaluated for granulometric studies, micrometric, scanning electron microscopy, drug entrapment efficiency, swelling studies and in-vitro dissolution studies. The prepared beads were free flowing and white in color. The drug loaded beads showed 37.26% to 91.73% drug entrapment, which was found to increase with increase in alginate concentration. In vitro drug release study of these microbeads indicated controlled release for Norfloxacin 96.19 – 97.83% release after 12 hours. Hence the observations of all results of the different batches, A3 showed controlled release action and improved drug availability. From this study it could be concluded that the free flowing microbeads of Norfloxacin could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.

**Keywords:** Microbeads, Ionotropic Gelation, Natural Polymers, Sustained Release.

## INTRODUCTION

The goal of any ideal drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve prompt response, and thus maintain the desired drug concentration. Such a conceptualized ideal drug delivery can be possible with intravenous infusion of drug at the site of action over a desired period of time. However, such a drug therapy requires hospitalization of the patient and needs to be administered by a qualified person. Therefore, among the routes preferred for the administration of dosage forms, the oral route presents a series of attractive advantages for the administration of the drug compounds, including the avoidance of pain and discomfort associated with injections and elimination of possible infections caused by the use of needles. More over, oral dosage forms are less expensive to produce, because they do not need to be manufactured under sterile conditions. In recent years, scientific and technological advancements have been made in the research and development of rate controlled oral drug delivery systems. These formulations are designed to deliver the drugs at a controlled and predetermined rate, thus maintaining their therapeutically effective concentration in systemic circulation for prolonged periods of time. A great majority of controlled release formulations have been formulated in the form of tablets. However, wide physiological and environmental variations in the gastrointestinal tract with respect to the surface area of absorption, pH, fluidity, rate of transit time, presence of food constituents and co-administered drugs may influence gastric emptying. If a controlled release product is formulated in the form of tablet which keeps its integrity throughout the gastrointestinal tract, then the location of the tablet will vary under different circumstances. This will lead to the variation in the rate of drug delivery to the systemic circulation. Compared with single unit dosage form, multiunit controlled release drug delivery systems like microcapsules and microspheres are becoming popular as they pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates[1] spread over a large area of absorbing mucosa preventing exposure to high drug concentration[2] and release drug in a more predictable manner[3].

Controlled release dosage forms cover a wide range of prolonged action formulations, which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance.

## MATERIALS AND METHODS

Norfloxacin was obtained as a gift sample from Dey's Medical Stores (mfg.) LTD., Sodium Alginate was supplied by Loba chemie pvt. Ltd., Calcium chloride (CAS 10035-04-8) was purchased from National chemicals. Solvents and water used were of HPLC grade and were procured from Spectrochem. All other Chemicals used were of Analytical Reagent grade and procured from the local suppliers.

## PREPARATION OF NORFLOXACIN LOADED MICROBEADS[4,5,6]

The microparticles were prepared by ionotropic gelation technique (R). At first, sodium alginate (1%, 2%, 3%w/v) was dispersed uniformly in warmed distilled water by stirring maintaining speed at fixed rpm so that the aqueous mucilage of sodium-alginate was obtained.[7,8] This aqueous mucilage was then kept for 5-10 minutes. To remove any air bubbles that may have been formed during stirring process. Norfloxacin was added to this mucilage very slowly and stirred for about 5 minutes, to disperse the drug uniformly. The sodium-alginate drug dispersion was added drop-wise via a needle fitted with a 10ml syringe into 100ml of 4% calcium chloride solution.[9] After incubating for a predetermined time, the gelled beads were separated by filtration and washed with distilled water. Then the microparticles were dried at the room temperature.

Nine formulations of microparticles (A1,A2, A3, A4, A5, A6, A7, A8 & A9 ) were prepared in identical manner by changing the amount of sodium alginate, amount of Calcium chloride and variation of curing time as presented in Table 1. These nine formulations were subsequently subjected to evaluation tests.

**Table 1: Composition of Norfloxacin Microparticles**

| Formulation | Sodium Alginate Concentration (w/v) | Calcium chloride Concentration (w/v) | Curing time (min.) |
|---|---|---|---|
| A1 | 1% | 2% | 10 |
| A2 | 2% | 2% | 10 |
| A3 | 3% | 2% | 10 |
| A4 | 2% | 1% | 10 |
| A5 | 2% | 3% | 10 |
| A6 | 2% | 4% | 10 |
| A7 | 2% | 4% | 5 |
| A8 | 2% | 4% | 15 |
| A9 | 2% | 4% | 30 |

## EVALUATION STUDIES

### DRUG ENTRAPMENT EFFICIENCY:[10.11]

Accurately weighed amount of norfloxacin loaded A1, A2, A3 beads were kept in 100ml of USP phosphate buffer solution of pH 6.8 and kept for 24 hours. The solution was filtered and an aliquot following suitable dilution was assayed spectrophotometrically using UV-VIS Spectrophotometer (Thermo Spectronic UV-1) at 270 nm. The drug entrapment efficiency was determined using the following relationship:

**Drug Entrapment Efficiency (DEE) =**
**Experimental drug content / theoretical drug content x 100**

**Table 2: Drug Entrapment Efficiency of prepared formulations**

| Formulation Code | % Drug Entrapment Efficiency |
|---|---|
| A1 | 83.56 |
| A2 | 85.78 |
| A3 | 91.73 |
| A4 | 87.56 |
| A5 | 67.45 |
| A6 | 59.37 |
| A7 | 67.38 |
| A8 | 48.58 |
| A9 | 37.26 |

**SCANNING ELECTRON MICROSCOPY (SEM):** The shape and surface morphology of microparticles was analyzed by scanning electron microscopy (HITACHI E-1010). The sample was deposited on brass hold and sputtered with gold by using (model no.) fine coat ion sputter device. The SEM photographs were taken with the scanning electron microscope at required magnification at room temperature. The working distance of 39 mm was maintained and acceleration voltage used was 15 kv.

**PARTICLE SIZE DETERMINATION:** Particle size of the alginate beads was determined using an optical microscope using a compound microscope (OLYMPUS 01C) and presented in Table 3. A standard stage micrometer was used to calibrate the optical micrometer.

**Table 3: Particle Size**

| Formulation code | Diameter (µm) |
|---|---|
| A1 | 523.85 (± 46.742) |
| A2 | 525.3833 (± 46.929) |
| A3 | 542.6 (± 47.125) |
| A4 | 513.71 (± 43.048) |
| A5 | 528.54 (± 41.896) |
| A6 | 542.13 (± 45.025) |
| A7 | 518.06 (± 40.903) |
| A8 | 531.05 (± 47.625) |
| A9 | 536.83 (± 48.051) |

## SWELLING STUDY

The swelling characteristics of blank ALG and drug loaded ALG beads were determined by immersing about a definite weight of dried test samples in 50 ml of a solution at pH 1.2 and pH 6.8. At specific time intervals, samples were removed from the swelling medium and were blotted with a piece of tissue paper to absorb excess water on surface. The swelling ratios (Q) of test samples were calculated from the following expression:

$$Q = (W_s - W_d) / W_d$$

Where $W_s$ is the weight of the swollen test sample and $W_d$ is the weight of the dried test sample.

Effect of different concentrations of Sodium Alginate, Calcium Chloride and difference in curing time showed clear effect on the swelling study of the formulations, which are represented in the following figures.

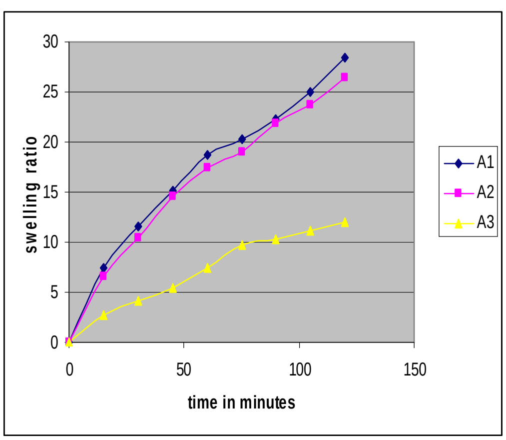


**Fig 1: Effect of alginate concentrations on swelling study**

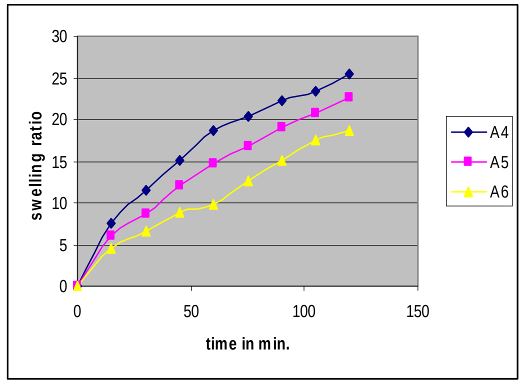


**Fig. 2: Effect of Calcium chloride concentration on swelling study**

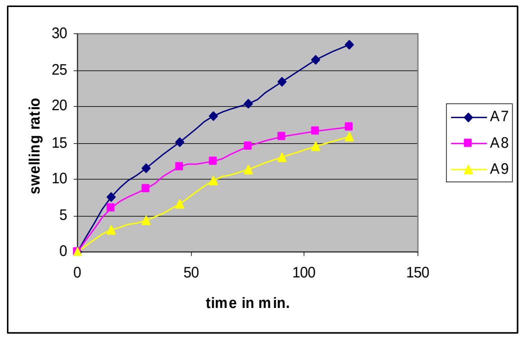


**Fig. 3: Effect of Curing time on Swelling study**

## IN-VITRO DRUG RELEASE STUDY[12,13]

The in vitro dissolution study was carried out using six station dissolution rate apparatus USP at 50 rpm AT 37± 0.5 ◦ C for 5 hrs. using simulated intestinal fluid as the dissolution medium. 5ml of the fluid containing the microbeads in the apparatus were removed every 30 minutes and an equivalent amount of fresh dissolution medium was replaced. The content of Norfloxacin was determined after filtration and analyzed at 278 spectrophotometrically. The plot of percentage cumulative drug release against time (hrs.) are plotted all the formulation and presented in the fig 4,5 & 6.

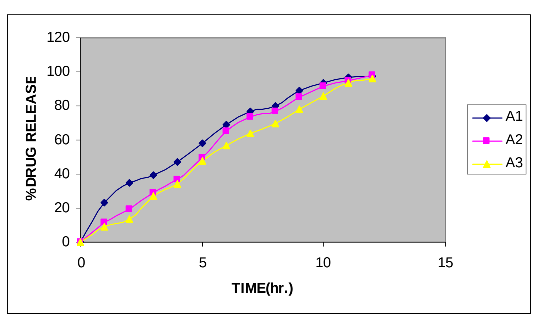


**Fig. 4: Effect of alginate concentrations on In-vitro drug release**

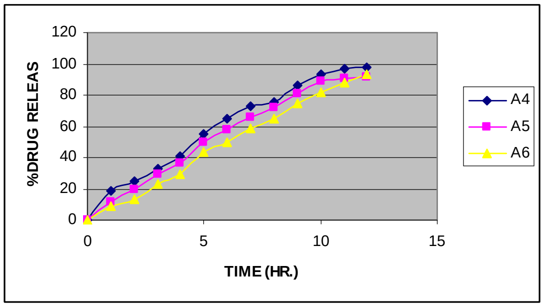


**Fig. 5: Effect of Calcium chloride conc. on In-vitro drug release**

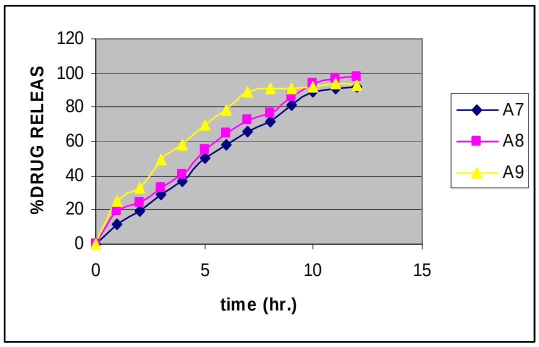


**Fig. 6: Effect of Curing time on In-vitro drug release**

## RESULT AND DISCUSSION

Microbeads of Norfloxacin were prepared by ionotropic gelation technique and different evaluation parameters were assessed, with a view to obtain oral control release of Norfloxacin. In the drug entrapment efficiency study, decrease in initial alginate concentration decreased DEE at a given curing time (10 min.) and $CaCl_2$ concentration (4%). Decrease in initial alginate concentration provides lesser number of binding sites of alginate for $Ca^{2+}$ ions resulting in the formulation of a less compact gel membrane which, in turn, increases influx of $Ca^{2+}$ ions leading to decrease in DEE. Increase in curing time during preparation of alginate beads decreased DEE considerably. Increase in curing time allows more $Ca^{2+}$ ions to diffuse into the beads. The free drug subsequently diffuses out of the beads into the aqueous medium resulting in a decrease in DEE. Keeping the alginate concentration and curing time fixed, increase in Calcium chloride concentration also decreased the DEE.The particle size of the prepared different batches of microparticles were presented in Table No. 3. The microparticles were found to be in the size range of 500-550 µm. It was observed that in these prepared Norfloxacin microbeads, with the increase in alginate percentage the distribution of particle size shifts to the higher value due to increase in the initial viscosity of the medium. In order to find the effect of cross linking on the release rates of Norfloxacin from the matrix, swelling was studied in terms of percentage of water uptake by the beads. However the swelling property of the beads was measured in terms of percentage of water uptake by the beads at a particular time interval. The results of the percent of water uptake by different beads are presented in GRAPH No.1. It was observed that from the GRAPH NO. 1,the higher the amount of sodium alginate in the beads, the lower the swelling rate. The in-vitro drug release studies of different formulations cumulative percentage drug release was observed in the range of 96.19-97.83. The in-vitro drug release profile were mentioned in the Graph No. 4,5,6. The formulations A1, A2, A3 containing 1%, 2%, 3% sodium alginate respectively showed a release of 97.83%**,** 97.34% and 96.19% after 12 hours. This shows that more sustained release was observed with the increase in percentage of sodium alginate. The best formulation was observed as A3, by the observation of all results of the nine formulations Norfloxacin microbeads.

## CONCLUSION

This study reveals that oral controlled release of Norfloxacin can be successfully achieved by ionotropic gelation technique using sodium alginate as polymer. Prepared microbeads shown higher drug entrapment efficiency and prolonged release characteristics. Norfloxacin release from microbeads was influenced by different alginate concentrations. Among the different formulations of microbeads, A3 was estimated as best formulation because this formulation drug release was observed that drug was released in controlled manner.

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