

Research Article

Design of Multi-particulate Regioselective Drug Delivery System of Moxifloxacin using Curdlan Gum.

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Received 06 March 2019; received in revised form 08 April 2019; accepted 10 April 2019

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ABSTRACT

A multi-particulate buoyant alginate beads with extended gastroretentive time were designed in the present investigation. The floating alginate beads were prepared by ionic cross-linking technique, using sodium bicarbonate as a gas former. More than 95% of the beads remained buoyant after 10 hr. The controlled release floating drug delivery system of moxifloxacin hydrochloride was prepared using 3² factorial design method using a blend of curdlan gum and sodium alginate. The scanning electron microscopy confirmed the grossly spherical structure and the size of the beads was in the range of 789.49–1004 μm. The drug entrapment efficiency was found to be in the range of 54.76–64.43%. The in-vitro percent drug release for prepared formulations was found to be in the range of 74.92–97.33% in 12 hr. Therefore, the present investigation reveals the leading application of floating alginate beads for the delivery of moxifloxacin hydrochloride in stomach.

KEYWORDS

Curdlan gum, Entrapment efficiency, Factorial design, Moxifloxacin hydrochloride, Multi-particulate, Sodium alginate.

1. INTRODUCTION

A key restriction in oral controlled drug delivery is that not all drugs are uniformly absorbed from all the parts of the alimentary canal. Few drugs are absorbed only from a definite segment of alimentary canal or are absorbed at variable rate from different region of alimentary canal called as absorption window. This region co-exists due to physiological, physicochemical or biochemical features. Recent scientific and patent information indicates the increased curiosity in novel drug delivery system that can be buoyant in proximal part of alimentary canal for an extended and predetermined time. The novel therapeutic options can be provided by applying most feasible approaches to manage the gastric residence time using gastroretentive dosage forms (GRDDS). The GRDDS can improve controlled delivery of drugs by continuously releasing the drug for an extended period of time before it reaches its absorption site which ensures maximum bioavailability. [1]

The rationale behind designing a floating multi-particulate drug delivery is to develop a reliable formulation of moxifloxacin hydrochloride that has all the merits of a floating single unit dosage form but is devoid of disadvantages of single unit dosage forms, especially sticking to or being obstructed in the alimentary canal. In spite of all classical formulations, the retention time of the single unit floating drug delivery system (FDDS) depends on many physiological factors and it is a well known fact that early gastric emptying of a matrix device causes rapid lack of therapeutic efficacy, especially with drugs having an absorption window only in the stomach. [2]

Moxifloxacin hydrochloride, a quinolone or fluoroquinolone antibiotic, is absorbed in the anterior part of the gastrointestinal tract (GIT); it has a narrow therapeutic absorption window in the GIT, meeting the primary criterion for selection of moxifloxacin as the drug candidate to be formulated as a floating multiple unit dosage form. [3] The release behavior of the beads capable of floating in gastric fluid was investigated with the aim to achieve a gastroretentive, multiple unit and controlled release formulation of moxifloxacin.

2. MATERIALS AND METHODS

2.1. Materials

Moxifloxacin hydrochloride was a gift sample obtained from Panacea Biotech Ltd., (Navi Mumbai, India). Curdlan gum was purchased from Nanjing Joyful Imp. / Exp. Co. Ltd., (Jiangsu, China). Sodium alginate, sodium bicarbonate and calcium chloride were purchased from Nikhil Scientific Suppliers, (Karad, India). All other chemicals used were of analytical and laboratory grade.

2.2 Methods

2.2.1. Preparation of moxifloxacin hydrochloride beads

The moxifloxacin beads were prepared using 3^2 factorial design. Aqueous solutions of sodium alginate were prepared in deionised water. The specified amounts of curdlan gum were added in sodium alginate solutions (Table 1). The required amount of drug and the gas forming agent, sodium bicarbonate were added in above solutions. The mixtures were stirred at 100 rpm for 30 min. on magnetic stirrer. The calcium chloride (3% w/v) solution was prepared. Drug solution was extruded with 20 gauge needle with gentle stirring for 20 min. into 100 ml of calcium

chloride solution. The formed beads were separated by filtration and washed with distilled water. The beads were dried at room temperature for 24 hr. [4]

Table 1. Formulation of floating beads of moxifloxacin hydrochloride.

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Moxifloxacin hydrochloride ^a | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| Sodium alginate ^b | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 |
| Curdlan gum ^a | 30 | 40 | 50 | 30 | 40 | 50 | 30 | 40 | 50 |
| Calcium chloride ^b | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Sodium bicarbonate ^a | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Where ^a and ^b indicates values in mg and percent respectively.

2.3. Characterization of beads

2.3.1. Morphology

The shape and surface morphological study of dried beads was characterized by using scanning electron microscopy (SEM). The samples of bead were stick to the double adhesive tape, which was stuck to the aluminum stub. The stub was then coated with gold to the thickness of 300 Å using sputter coater. Then these samples were scanned using scanning electron microscopy at 500X and 100X magnification (Joel 6100, Japan). [5]

2.3.2. Percentage yield

The percentage yield of the prepared beads was determined using the following Eq. (1) [6]

$$\text{Percentage yield} = \frac{\text{Weight of beads}}{\text{Weight of bead} + \text{Weight of polymer}} \times 100 \quad (1)$$

2.3.3 Drug content

Accurately weighed 10 mg of beads were crushed and dissolved in 50 ml of 0.1N hydrochloric acid (HCL). The solution was sonicated (Imeco Sonifier, Imeco Ultrasonics, India) at 125 W for 10 min and finally the volume was made up to 100 ml using 0.1N HCL. The solution was filtered using 0.45 µm membrane filter and the filtrate was analyzed with Ultraviolet (UV)-visible spectrophotometer (Schimadzu 1700, Japan) at 294 nm.[7] The drug content and entrapment efficiency were determined using Eq. (2).

$$\text{Drug content} = \frac{\text{Weight of drug in beads}}{\text{Total weight of beads}} \times 100 \quad (2)$$

2.3.4. Entrapment efficiency (EE)

Beads (100 mg) were dissolved in 50 ml of 0.1 N hydrochloric acid (HCL) by shaking in a flask, if necessary sonicated. The solution was filtered and after sufficient dilution with 0.1N HCL, the solution was analyzed UV-visible spectrophotometrically at 294 nm. [8] The entrapment efficiency was calculated using Eq. (3).

$$\text{Entrapment efficiency} = \frac{\text{Actual amount of drug}}{\text{Theoretical amount of drug}} \times 100 \quad (3)$$

2.3.5. Swelling study

Swelling ability of beads was determined by allowing the beads to swell in 0.1N HCL. Accurately weighed 50 mg of beads were taken and immersed in 100 ml of 0.1N HCL. The beads were removed at regular intervals, washed with deionised water, blotted with filter paper

to remove excess of surface liquid and dried. [9] The swelling index was determined by using Eq. (4).

$$\text{Percentage swelling} = \frac{\text{Weight of swell beads} - \text{Initial weight of beads}}{\text{Initial weight of beads}} \times 100 \quad (4)$$

2.3.6. *In-vitro buoyancy study*

In the buoyancy study of beads, two parameters, floating lag time (FLT) and total floating time (TFT) were determined. In this study, measured quantity of beads was placed in 900 ml 0.1N HCL in United State Pharmacopoeia (USP) type II apparatus (TDT 08L, Electrolab, India) using paddle at a rotational speed of 75 rpm. The temperature of medium was maintained at $37 \pm 0.5^\circ\text{C}$. Floating lag time is the initial time taken by the beads to start float on the surface of the medium was noted. The total time of floating of beads was also observed for 12 hr. [10]

2.3.7. *In-vitro drug release studies*

The release of moxifloxacin hydrochloride sustained release floating beads was determined by using USP dissolution apparatus II. The dissolution medium used 900 ml of 0.1N HCL, and temperature was maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. A sample 5 ml solution was withdrawn from the dissolution apparatus at specified time intervals (1 hr) up to 12 hr, and replaced with equal volume of fresh dissolution medium. The samples were filtered through $0.22 \mu\text{m}$ and analyzed using UV-visible spectrophotometrically at 294 nm. Cumulative percentage drug release was calculated and plotted against time in hr. [11]

2.3.8. *Kinetic data analysis*

The matrix systems were reported to follow the zero-order release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted in to zero order, first order, Higuchi matrix, Korsmeyer-Peppas and Hixson-Crowell model. In this by comparing the regression coefficient values obtained, the best fit model was selected. [12]

2.3.9. *Stability studies*

The accelerated stability studies were conducted for selected formulation as per the International Council of Harmonization (ICH) guidelines. The selected formulations were analyzed for the drug's physical appearance, entrapment efficiency, floating ability, and in-vitro release study. [13] **Long-term testing:** $25 \pm 0.5^\circ\text{C} = 60\% \pm 5\%$ Relative Humidity (RH) for 3 months:

Accelerated testing: $40 \pm 0.5^\circ\text{C} = 75\% \pm 5\%$ RH for 3 months:

3. RESULTS AND DISCUSSION

3.1. *Morphology*

The beads prepared were white, translucent, rigid and rough with spherical to slightly oval in shape. The size of the beads was range from the range of $789.49\text{--}1004 \mu\text{m}$ (Figure 1).

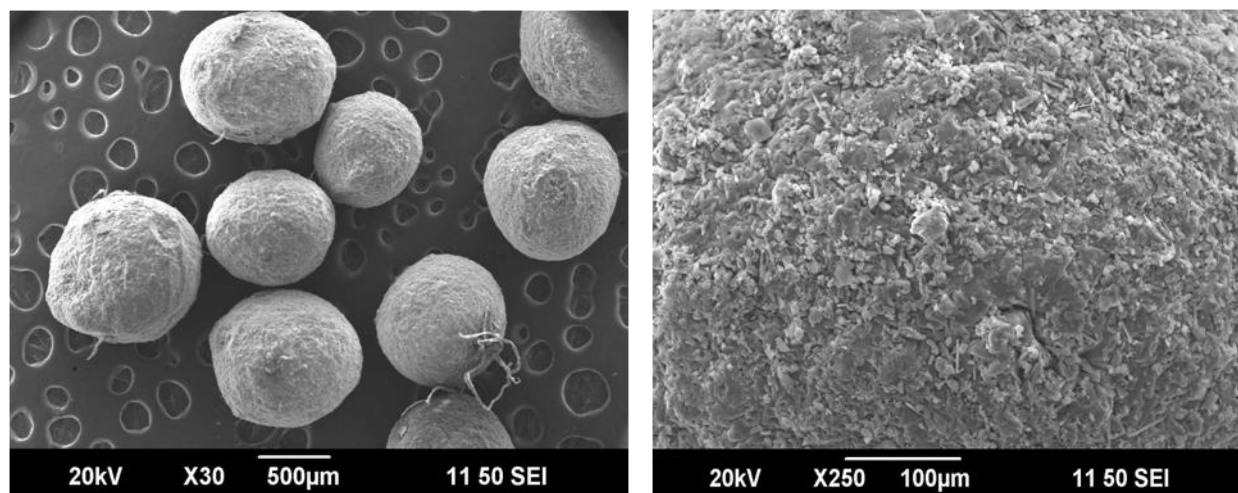


Figure 1. SEM of moxifloxacin hydrochloride beads

3.2. Percent yield

The percentage yield of floating beads was ranged from 76.32 ± 1.97 to $90.18 \pm 1.66\%$ for F1 and F9 respectively. The results showed that the percent yield of beads increased by increasing polymer concentration (Table 2).

3.3. Drug content

The drug content in the floating beads was ranged from 83.06 ± 0.61 to $89.35 \pm 1.89\%$ for F1 and F9 respectively. Higher drug loading was obtained due to increase in alginate and curdlan gum concentration. This may be attributed due to greater availability of Ca^{2+} for binding to alginate. The greater degree of cross-linking was observed as the quantity of sodium alginate increases (Table 2).

3.4. Entrapment efficiency

The effects of various formulation parameters on the entrapment efficiency of prepared floating beads are shown in (Table 2). The entrapment efficiency of the prepared floating beads was varied from 54.76 ± 1.59 to $64.43 \pm 0.86\%$. The entrapment efficiency increased significantly with increasing polymer concentration. This is because of increase in the curdlan gum concentration resulted in the formation of larger beads which entrapping more drug. The entrapment efficiency was also found to be proportionally increased with increasing sodium alginate concentration. This is due to increase in complex network of sodium alginate in the beads which may encapsulate the larger amount of drug.

3.5. Swelling study

The swelling index of the beads was found to be increased with the increase in the concentration of the polymers. As both the polymers are coming from the same category i.e., the water insoluble swellable type of polymers. Though the polymers are swellable in nature their swelling capacity was restricted to particular extent by the addition of calcium chloride which was act as cross linking agent. The swelling index of the prepared floating beads varied from 38.78 ± 1.27 and $53.23 \pm 1.56\%$ (Table 2).

Table 2. Evaluation of moxifloxacin hydrochloride beads.

| Formulation | Percent yield ^c (%) | Entrapment efficiency ^c (%) | Swelling index ^c (%) | Drug content ^c (%) | Floating lag time ^c (sec) | Floating time ^c (hr) |
|-------------|--------------------------------|--|---------------------------------|-------------------------------|--------------------------------------|---------------------------------|
| F1 | 76.32±1.97 | 54.76±1.59 | 38.78±1.27 | 83.06±0.61 | 302.33±4.73 | 12.66±0.57 |
| F2 | 80.35±1.06 | 55.45±1.87 | 38.72±1.48 | 84.77±1.00 | 357.00±4.58 | 12.83±0.76 |
| F3 | 82.47±0.87 | 55.81±0.83 | 40.38±1.52 | 86.97±0.82 | 365.00±3.00 | 13.00±0.86 |
| F4 | 85.12±0.56 | 58.16±1.64 | 41.23±1.87 | 84.91±1.20 | 310.67±3.51 | 13.66±0.76 |
| F5 | 85.32±1.14 | 60.54±0.80 | 42.45±1.25 | 87.28±1.14 | 369.00±3.61 | 13.83±0.28 |
| F6 | 87.37±1.01 | 61.02±1.38 | 45.98±1.31 | 88.76±0.90 | 376.31±4.04 | 14.16±0.28 |
| F7 | 89.42±1.09 | 62.30±1.30 | 47.64±1.86 | 86.50±1.29 | 338.33±3.06 | 14.50±0.50 |
| F8 | 90.00±2.06 | 63.93±0.52 | 50.70±0.99 | 88.30±1.27 | 377.33±3.51 | 15.66±0.76 |
| F9 | 90.18±1.66 | 64.43±0.86 | 53.23±1.56 | 89.35±1.89 | 413.01±2.65 | 16.83±0.57 |

Where ^c indicates the values in mean ± SD when sample size was used in triplicate.

3.6. In-vitro buoyancy study

The floating lag time of the formulations was found to be in the range from 302.33±4.73 to 413.01±2.65 sec. This might be attributable to entry of dissolution fluid into the beads and its subsequent reaction with sodium bicarbonate resulting in the generation of carbon dioxide gas, which is entrapped in the beads and help the beads to remain buoyant on dissolution fluid. The floating time of the formulations was found to be in the range from 12.67 to 16.83 hr which ensured that the formulations, due to lesser density as compared to the gastric fluid would remain in the stomach in floating condition for more than 8 hr releasing the drug continuously over prolonged period of time (Table 2). This ensuring the sustained release of formulation with floating ability imparted to the same.

3.7. In-vitro release study

The in-vitro drug release profiles of beads prepared with curdlan gum and sodium alginate are shown in (Figure 2). The drug release rate from beads characterized with rise in polymeric matrix density and diffusion path length that the drug molecules have to travel (by formation of bigger sized beads). The drug release from these beads was characterized by an initial phase of high release due to burst effect and good solubility of drug at acidic pH. However, as gelation proceeded (cross-linking of polymer dispersion with Ca²⁺ ions from calcium carbonate), the remaining drug was released at a slower rate followed by a phase of moderate release. This biphasic pattern of release is a characteristic feature of matrix diffusion kinetics. The initial burst effect from the curdlan gum-alginate beads was considerably reduced as amount of curdlan gum in the beads increases. This was resulted in better incorporation efficiency with formation of a thick coating layer around the beads and increases the path length that drug have to travel through the curdlan gum. The internal ionotropic gelation effect of calcium carbonate prolongs the release of drug from bead. In acidic medium, the calcium carbonate dissolves and the ionized Ca²⁺ ions then promote internal gelation by cross-linking with the alginate and retarding the drug release from polymeric matrix. In addition, the increased entrapment of drug within curdlan gum-alginate bead may contribute for slow drug release. When the drug-loaded curdlan gum-

alginate beads were evaluated for drug release in 0.1N HCL, pH 1.2, the beads showed more drug release at the end of 2-3 hr. The optimized formulation, the formulation F5 of curdlan gum-alginate beads showed controlled drug > 12 hr.

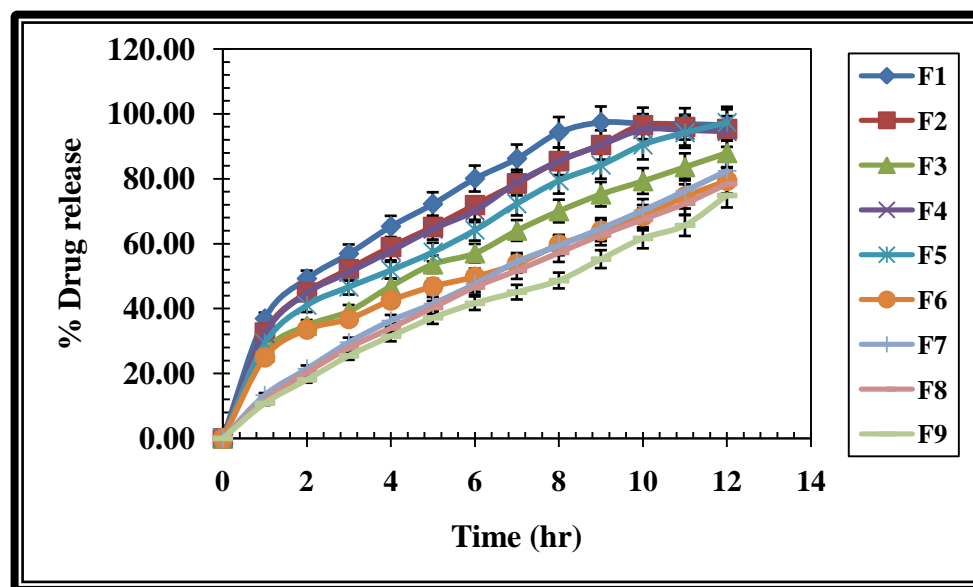


Figure 2. In-vitro drug release from moxifloxacin.HCL beads.

3.8. Kinetic data analysis

The curve-fitting results of the release rate profile of the prepared formulations gave an idea about the drug release rate profile and the mechanism of the drug release. Fitting of the release rate data to the various models revealed that formulations such as F7, F8 and F9 follow the zero order model. Remaining all the formulations release profile fits into the Higuchi matrix model as shown in (Table 3). The ‘n’ value Korsmeyer-Peppas model values were > 0.5 indicates the drug release mechanism from beads was non-Fickian diffusion.

Table 3. Kinetic data analysis.

| Formulation | Zero order | First order | Hixon- Crowell | Higuchi | Korsmeyer- Peppas | |
|-------------|--------------------|----------------|----------------|--------------------|-------------------|-------|
| | R ² | R ² | R ² | R ² | R ² | ‘n’ |
| F1 | 0.839 | 0.423 | 0.87 | 0.975 ^d | 0.932 | 0.724 |
| F2 | 0.894 | 0.453 | 0.921 | 0.992 ^d | 0.929 | 0.745 |
| F3 | 0.944 | 0.499 | 0.966 | 0.994 ^d | 0.929 | 0.718 |
| F4 | 0.895 | 0.455 | 0.923 | 0.991 ^d | 0.955 | 0.682 |
| F5 | 0.939 | 0.487 | 0.964 | 0.992 ^d | 0.927 | 0.675 |
| F6 | 0.933 | 0.486 | 0.979 | 0.986 ^d | 0.903 | 0.617 |
| F7 | 0.987 ^d | 0.627 | 0.951 | 0.967 | 0.927 | 0.782 |
| F8 | 0.986 ^d | 0.639 | 0.939 | 0.970 | 0.936 | 0.797 |
| F9 | 0.986 ^d | 0.650 | 0.949 | 0.958 | 0.913 | 0.759 |

Where ^d indicates the best fitted model.

3.9. Stability studies

A stability study was conducted for the prepared beads, of formulation F5 at 25°C and 40°C with a relative humidity (RH) of 60% and 75%, respectively, for a period of 3 months. However, the stability testing of beads at various pH values was not studied. The samples after exposing to extreme conditions were analyzed for physical appearance, EE, drug release studies, swelling index and floating behavior of the moxifloxacin beads at the end of 3 months. There was no significant change observed in the physical appearance, EE, floating ability of beads and floating behavior as conducted after 3 months. The results of stability studies are given in (Table 4).

Table 4: Stability study of moxifloxacin beads.

| Sr. No. | Parameter | Storage condition for 3 months | |
|---------|--|--------------------------------|-------------------------|
| | | 25°C at 60% RH | 40°C at 75% RH |
| 1. | Physical appearance | No change in appearance | No change in appearance |
| 2. | Entrapment efficiency (%) ^e | 59.81 ± 0.82 | 59.11 ± 0.73 |
| 3. | Floating lag time (sec) ^e | 366.67 ± 3.06 | 362.17 ± 2.00 |
| 4. | Floating time (hr) ^e | 13.33 ± 0.29 | 13.17 ± 0.29 |
| 5. | Swelling index (%) ^e | 42.17 ± 0.66 | 41.84 ± 0.89 |
| 6. | Drug content (%) ^e | 87.22 ± 1.17 | 86.76 ± 0.84 |

Where ^e indicates the values in mean ± SD when samples were used in triplicate.

Also the in-vitro release characteristics of the beads stored as per ICH guidelines, shows that no significant difference (Figure 3).

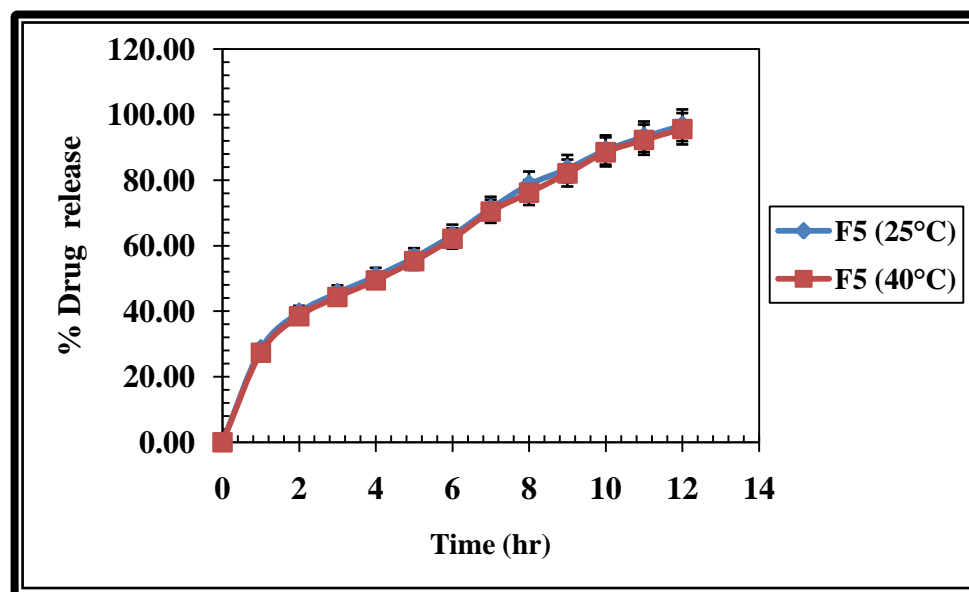


Fig. 3. In-vitro release from moxifloxacin beads stored for stability study.

4. CONCLUSION

Via cross-linking of calcium, sodium alginate and curdlan gum, the dried moxifloxacin beads, which remain buoyant more than 12 hr, were prepared. Depending upon the physicochemical

properties of the drugs, more than 90% drug release was achievable in about 10 hr, and release kinetics modulation was possible by controlling extent of cross-link formation and bead sizes. The release characteristics from the beads were independent of the hydrodynamic conditions. Therefore, this approach seems to provide opportunity and potential for development of a gastroretentive drug delivery system of moxifloxacin for selectively targeting either the stomach or proximal intestine for maximization of bioavailability and improvement of drug therapy.

5. ACKNOWLEDGEMENT

The authors would like to thank Panacea Biotech Ltd., Navi Mumbai for providing kind gift sample of Moxifloxacin hydrochloride and also thank to Government College of Pharmacy, Karad and Gourishankar Institute of Pharmaceutical Education and Research, Satara for providing the facility to perform the present research work.

6. CONFLICT OF INTEREST

None declared.

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