Design and Characterization of Multi-particulate Gastroretentive Drug Delivery System of Moxifloxacin Hydrochloride

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ABSTRACT
The objective of present investigation is to design and characterize the multi-particulate gastroretentive drug delivery system of moxifloxacin hydrochloride by gelation technique. The drug beads prepared using sodium alginate & curdlan gum as polymers and calcium chloride as cross-linking agent. The prepared beads were characterized for surface morphology, drug content, entrapment efficiency, swelling index, floating ability and drug release study. The formulation, F5 was selected as optimized formulation based on drug release profile, floating ability and other physicochemical characterastics. The drug release, entrapment efficiency, swelling index and size of the beads is depend upon the amount of polymer used in the formulation. The formulation F5 was found to be stable as per ICH guidelines. The drug release from beads is mostly fits either in zero order or Higuchi model. The study concluded that moxifloxacin hydrochloride multi-particulate gastroretentive drug delivery system was designed successfully.

KEYWORDS: Beads, Moxifloxacin, Sodium alginate, Floating ability, Drug release
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INTRODUCTION

The oral route is most preferred route for medication administration.[1] The lower oral bioavailability of many drugs due to gastrointestinal degradation, presystemic metabolism, regioselective absorption, p-glycoprotein efflux mechanism, drug-gastrointestinal component interactions, low solubility or dissolution rate of drugs, pH dependent absorption, limited resident time.[2] For the drugs absorbed from stomach or upper part of small intestine, the gastro retentive drug delivery systems were developed.[3] Gastro retentive drug delivery systems (GRDDS) have grown enormous admiration and developments in the field of solid oral drug delivery.[4] They have magnificently resolved convinced complications related with conventional oral delivery systems, with multiple dosing and gastrointestinal tract (GIT) associated features, and also the residence time and drug availability because of their therapeutic rewards, patient acceptance, non-invasiveness, simplicity, adaptability, and acceptability. [5] The composition of the drug delivery matrix influences its properties such as stiffness, pH-responsiveness, swelling behavior, and processability.[6] Various innovative approaches have been employed to develop floating systems that can retain the dosage forms in the stomach. [7,8] Several other floating systems were produced, such as low-density systems, melt foaming systems, Raft forming systems, expansion of dosage forms by swelling or unfolding of the excipients, and modified shape systems. [9-12]

Floating DDS (FDDS) is also referred as hydrodynamically balanced system with density less than gastric juice (1.004 g/cc). They have bulk density lower than gastric fluids and thus remain buoyant in gastric environment for prolonged period of time, without affecting the gastric emptying rate. These drug delivery systems remain buoyance in the stomach for prolong period and release the drug in controlled rate. It will increase gastric retention time and avoid fluctuations of plasma drug concentrations. It helps in maintenance of steady state plasma level for prolong period of time and minimizing the risk of drug resistance, this is very useful in case of delivery of anti-infective agents. [13-15] The multiple unit GRDDS like, minitablets, pellets, granules, microspheres, etc., are effective in controlling the rate of release of a drug in the stomach for an extended period and are preferred over single unit GRDDS due to better release profile, causing low potential for systemic side effects. GRDDS exhibit reproducible outcomes due to less inter/intra subject variability in response. The small size floating pellets are speculated to be better in achieving extended residence time in stomach than any other monolithic GRDDS. Pellets present excellent flow properties, low friability, and narrow size distribution (500 µm - 1500 µm) that results in effective surface area for uniform coating, and encapsulation for oral administration.[16]

Moxifloxacin HCl (hydrochloride), synthetic broad-spectrum fourth-generation fluoroquinolone analogs acts as antibacterial agent. It is primarily absorbed

from the proximal region of gut (stomach, duodenum and jejunum). The retention time of drug delivery system plays vital role in therapeutic effectiveness of moxifloxacin.[17] It is an ideal candidate for a gastroretentive drug delivery system that will prolong the gastric transit time of formulation, results enhanced bioavailability.[18] Fluroquinolones are soluble at acidic pH and can precipitate at slightly basic or neutral pH of the intestine which may influence the absorption and bioavailability of these drugs. To overcome such problems associated with acidic soluble drugs, we selected moxifloxacin as a model drug for the development of gastroretentive sustained release drug delivery system using sodium alginate-curdlan gum as polymer with calcium chloride with a main focus to release the active ingredient in the acidic environment (upper part of the GIT, i.e., stomach) for a maximum period of time. Furthermore, our focus was also on the evaluation of floating and swelling properties of the formulations and effect of the concentrations of excipients on drug release from the formulations.

MATERIAL AND METHOD

MATERIAL

Moxifloxacin hydrochloride was procured from Panacea Biotech Ltd., Mumbai, India. Moxifloxacin used in the current research was as per the specification of United States Pharmacopoeia (USP). Curdlan gum was purchased from Nanjing Joyful Imp. / Exp. Co. Ltd., Jiangsu, China. Sodium alginate, sodium bicarbonate and calcium chloride were purchased from S.D. Fine Chemicals, Mumbai, India. All other chemicals used were of analytical and laboratory grade. They were used as received.

METHODS

Preparation of moxifloxacin hydrochloride beads

The moxifloxacin hydrochloride floating beads were prepared using 3^2 factorial designs. Aqueous solutions of moxifloxacin hydrochloride, sodium alginate and curdlan gum in deionized water (Table 1) and stirred at 100 rpm for 30 min on magnetic stirrer. The calcium chloride (3% w/w) solution was prepared in n-Heptane and Tween 20 (3% w/v) and solution was stirred 1000 rpm for 5 min. 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.[19]

Table 1. Formulation of moxifloxacin hydrochloride beads

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Moxifloxacin hydrochloride (mg)	400	400	400	400	400	400	400	400	400
Sodium alginate (mg)	5	5	5	10	10	10	15	15	15
Curdlan gum (mg)	30	40	50	30	40	50	30	40	50
Calcium carbonate (mg)	5	5	5	5	5	5	5	5	5
Sodium bicarbonate (mg)	10	10	10	10	10	10	10	10	10

Characterization of beads

Surface morphology

The surface morphology and shape of dried beads of moxifloxacin hydrochloride were carried out using Scanning Electron Microscopy (SEM). The bead sample was stuck to the stub of aluminium with two-way adhesive tape. It was further coated with gold to the thickness of 300 A° using sputter coater. These samples were scanned using SEM at 30X and 250X magnification using Scanning Electron Microscope (Joel 6100, Japan). [20]

Practical yield

The percentage practical yield of the moxifloxacin beads was calculated as[21, 22]-

$$\%\ practical\ yield = \frac{Weight\ of\ Beads}{Weight\ of\ Drug + Weight\ of\ Polymer} \times 100$$

Drug content

Accurately weighed 10 mg of crushed moxifloxacin beads were dissolved in 80 ml of 0.1N hydrochloric acid (HCL). The solution was ultrasonicated (Imeco Sonifier, Imeco Ultrasonics, India) at 250 W for 5 min and volume was made to 100 ml using 0.1N HCL. The solution was filtered using 0.22µm membrane filter and the filtrate was analyzed using double beam ultraviolet-visible spectrophotometer (Schimadzu 1700, Japan) at 294 nm using 0.1N hydrochloric acid as blank.[23] The drug content and entrapment efficiency were determined using Eq. given below-

$$Drug\ content = \frac{Weigh\ \ of\ Drug\ in\ Bead}{Weigh\ \ of\ Bead} \times 100$$

% Entrapment efficiency (EE)

Accurately weighed 100 mg of moxifloxacin beads were dissolved in 50 ml of 0.1 N hydrochloric acid (HCL) and ultrasonicated for 5 min. The solution was filtered through 0.22 µm membrane filter and sufficiently dilution with 0.1N HCL. The resultant solution was analyzed using double beam UV-visible spectrophotometrically at 294 nm.[24]

Swelling Index

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 reweighed at regular intervals after a regular gentle wiping with tissue paper to remove excess of water. [25,26] The swelling index was determined as follows-

$$Swelling\ Index\ (\%) = \frac{Weight\ of\ Swollen\ Beads - Initia\ \ Weight\ of\ Beads}{Initial\ Weig\quad of\ Beads} \times 100$$

Floating study

In the floating study of moxifloxacin beads, the floating lag time (FLT) and total floating time (TFT) were determined. In this study, ten beads were 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± 0.5°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.[27]

Drug release study

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±0.5°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 µm and analyzed using UV-visible spectrophometrically at 294 nm. Cumulative percentage drug release was calculated and plotted against time in hr.[28]

Kinetic study

Kinetics and correlation of in-vitro release mechanism of moxifloxacin beads need to fit into an appropriate mathematical model. Dissolution data was kinetically evaluated using different important mathematical models.[29] Regression analysis was applied, and the accuracy and prediction capability of these models were evaluated by calculating the squared correlation coefficient (R^2).

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.[30]

RESULTS AND DISCUSSION

The calcium alginate beads of moxifloxacin hydrochloride were successfully prepared by gelation technique rapidly and simply. The beads were prepared using sodium alginate as gelling agent and calcium alginate as complexing agent. The curdlan gum was used as release controlling polymer.

Surface morphology

The alginate beads prepared were white, translucent, rough and rigid with spherical to slightly oval. The size of the beads was range from the range of 789.49– 1004 µm (Fig.1).

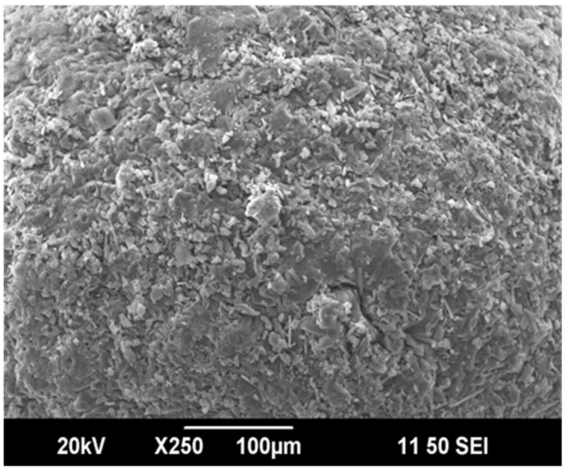

Figure 1. SEM of moxifloxacin hydrochloride beads.

Percent yield

The percentage yield of beads among the prepared batches was found between 76.32±1.97 to 90.18±1.66%. The percent yield of the beads was increased with increase in the concentration of the sodium alginate and curdlan gum in the formulation (Table 2).

Drug content

The drug content in various formulations the alginate beads was shown in Table 2. The higher drug loading was observed with increased amount of sodium alginate and curdlan gum in the formulations. It may be due to more availability of alginate to bind with calcium ion. More the notch of cross-linking was observed as the quantity of sodium alginate increases (Table 2).

% Entrapment efficiency

The effects of level of sodium alginate and curdlan gum on the entrapment efficiency of beads was shown in (Table 2). The entrapment efficiency was increased significantly with increasing amount of both polymers in formulation. Increase in the curdlan gum and sodium alginate amount led to formation of larger beads that can entraps more drug. This may be due to increased crosslinked network of sodium alginate in the beads.

Swelling Index

The swelling index of the alginate beads was found to be increased with increase in the concentration of the polymers. As both the polymers are coming from the same category i.e., swellable type of polymers. The swelling capacity was restricted to specific extent by the addition of calcium chloride which was

acting as cross linking agent. The swelling index of the prepared floating beads was recorded in Table 2.

In-vitro buoyancy study

The floating lag time and floating time of the formulations was recorded in table 2. 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. It 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.

Table 2 Physicochemical characterization of alginate beads

Form. Code	Percent yield † (%)	Entrapment efficiency † (%)	Swelling index† (%)	Drug content† (%)	Floating lag time‡ (sec)	Floating time ‡ (hr)
F1	74.53±0.38	53.89 ±2.16	39.78±1.28	83.06±0.61	302.33 ±4.73	11.44 ±0.17
F2	78.43±1.68	57.32 ±1.53	39.98±1.48	84.77±1.00	357.00 ±4.58	12.32 ±0.36
F3	80.13±2.14	58.14 ±0.57	42.32±1.57	86.97±0.82	365.00 ±3.00	13.18 ±0.26
F4	83.63±1.83	59.73 ±2.24	44.49±1.76	84.91±1.20	310.67 ±3.51	13.54 ±0.76
F5	85.28±2.09	61.63 ±0.28	46.45±0.28	87.28±1.14	369.00 ±3.61	14.21 ±0.28
F6	86.89±3.11	62.14 ±2.36	48.98±2.31	88.76±0.90	376.31 ±4.04	14.44 ±0.32
F7	88.32±2.68	63.25 ±1.88	51.63±2.13	86.50±1.29	338.33 ±3.06	14.50 ±0.50
F8	89.58±1.57	65.78 ±0.76	58.73±1.99	88.30±1.27	377.33 ±3.51	15.46 ±0.37
F9	91.42±0.92	66.49 ±0.51	63.28±1.56	89.35±1.89	413.01 ±2.65	16.23 ±0.54

Where † and ‡ indicates the values in mean ± SD when sample size n = 3 and n = 10 respectively.

Drug release study

The drug release profiles of beads are shown in (Figure 2). The drug release 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 in acidic pH. However, as gelation proceeded (cross-linking of polymer dispersion with Ca^{2+} ions from calcium carbonate), the remaining drug was released at a slower rate followed by a phase of moderate release. This biphasic pattern of drug 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 Ca^{2+} 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.

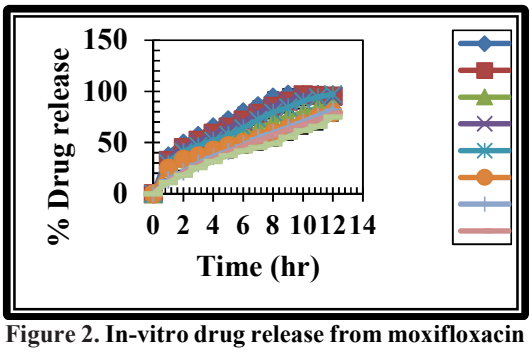

Figure 2. In-vitro drug release from moxifloxacin hydrochloride beads

Kinetic study

The results of the drug release profiles of the prepared formulations when fitted in various release models they gave an idea about the drug release mechanism from drug delivery system. The fitting of the drug release data into the kinetic models revealed that formulations such as F7, F8 and F9 follow the zero-order kinetics. All other formulations profile were fitted into the Higuchi matrix model as shown in (Table 3). The release exponent (n) value of Korsmeyer-Peppas model were > 0.5 indicates the drug release mechanism from beads was by non-Fickian diffusion.

Table 3 Kinetic study data

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 *	0.932	0.724
F2	0.894	0.453	0.921	0.992 *	0.929	0.745
F3	0.944	0.499	0.966	0.994 *	0.929	0.718
F4	0.895	0.455	0.923	0.991 *	0.955	0.682
F5	0.939	0.487	0.964	0.992 *	0.927	0.675
F6	0.933	0.486	0.979	0.986 *	0.903	0.617
F7	0.987 *	0.627	0.951	0.967	0.927	0.782
F8	0.986 *	0.639	0.939	0.970	0.936	0.797
F9	0.986 *	0.650	0.949	0.958	0.913	0.759

Where * indicates the best fitted model.

Stability studies

A stability study of F5 formulation was conducted per ICH guidelines for three months. The samples were characterized after 3 months for appearance, EE, drug release studies, swelling index and floating behavior of beads. There was no significant change observed in the physical appearance, EE, floating ability of beads and floating behavior after 3 months. The results of stability studies are given in (Table 4).

Table 4. Stability study of optimized batch

Sr. No.	Parameter	Storage condition for 3 months	
		25±2°C at 60±5% RH	40±2°C at 75±5% RH
1	Physical appearance	No change	No change
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.

CONCLUSION

A novel controlled release regioselective drug delivery system of moxifloxacin hydrochloride was prepared using sodium alginate and curdlan gum. The prepared beads were formulated by an emulsion gelation method. The prepared beads were white, translucent, rough and rigid with spherical to slightly oval with narrow size distribution. The beads were easily and rapidly prepared. The size of beads increased with increase in the amount of sodium alginate and curdlan gum in the composition. The extent of cross-linking was depend upon availability of sodium alginate in the formulation for crosslinking with Ca^{2+}. The drug release and floating ability was depend upon the amount of polymers in the beads since both the polymers are swellable polymers. The most of the formulations follow zero order or Higuchi model for drug release model. Formulation F5 was selected as optimized was found to be stable as per ICH guidelines for short term stability study. Further preclinical and clinical studies are necessary before product commercialization.

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