Design and Development of Clarithromycin Floating Pellets Using Sodium Alginate and HPMC

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(Received: November 23, 2021; Accepted: June 1, 2022; Published (Web): June 22, 2022)

ABSTRACT: The purpose of our study was to achieve the gastro-retentive delivery of Clarithromycin by producing floating pellets to get a better therapeutic effect against gastrointestinal ulcers mostly caused by *Hedyotis pylori*. Thereby Clarithromycin floating pellets were prepared by utilizing the blending of polymers such as Sodium (Na) Alginate and Hydroxy Propyl Methyl Cellulose (HPMCK4M & HPMC K100LV). The HPMC-alginate blend containing Clarithromycin produced a hydrogel bead that was able to show buoyancy in the simulated gastric fluid. The pellets showed more than 8 hours of buoyancy depending on their polymeric ratio. In addition to the buoyancy test, several other tests like floating time (upto 12 hrs with increasing Na-Alginate), contraction ratio, particle size analysis, were performed that showed the development of acceptable floating pellets. Furthermore, SEM was performed on the prepared Clarithromycin pellet to assess their morphological characteristics. Clarithromycin floating pellets with 1.5% Na-alginate & HPMC K4M: HPMC K100LV (1:2) give the better formulation and produce pharmaceutically acceptable parameters.

Key words: Pellet, Clarithromycin, Buoyancy, Floating, Contraction Ratio.

INTRODUCTION

The property of any dosage form is to deliver an optimum amount of the active drug to the site of action in order to produce the desired pharmacological response. This property of a dosage form is sometimes called bioavailability. To have this effect drug can be subjected directly to the specific organ or the organ can be targeted from a dosage form. A sustained release drug delivery system may serve as a representative to satisfy this issue.[1] Pellet is defined as an agglomeration of fine powders or granules of active drugs and excipients. The pellets usually have a size range from about 0.5 mm to 1.5 mm. They are small, spherical, or semi-spherical solids and are used for oral administration.[2] Besides, small implants having a cylindrical shape are also called pellets in pharmacy.[3] The efficacy of an orally administered drug can be modified by changing its gastrointestinal retention properties and the drug release kinetics. As it was mentioned that *Helicobacter pylori* causing gastric or peptic ulcers can be eradicated by prolonging the gastro-retention properties of the drug and sustaining the drug release.[4] However, many factors can affect the gastro-retention time of a drug, as well as the gastric emptying time. Sometimes the size of the drug can interfere with its properties. Therefore, a huge number of investigations had been carried out to find out the techniques for making gastro-retentive drugs.[5] One of the promising approaches was found to produce a floating system of a drug, because by floating the drug, the gastro-retention time may be increased which may prolong the activity of the drug without modifying the size of the orally administered drug.

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Dhaka Univ. J. Pharm. Sci. **21**(1): 25-31, 2022 (June)
DOI: https://doi.org/10.3329/dujps.v21i1.60393

Clarithromycin (CLA) is a macrolide antibiotic. It is more stable than erythromycin as it contains a methoxy group attached to the C6 position of erythromycin.[6] It is clinically used in the treatment of lower and upper respiratory tract infections. Although the drug can be absorbed very well, the overall systemic bioavailability is reduced to about 55% due to its first-pass metabolism.[7,8] The drug is metabolized through oxidative N-demethylation and 14-hydroxylation process, resulting in nonlinear kinetics due to saturation. However, the drug is eliminated from the body in a dose-dependent manner. The elimination half-life of clarithromycin ranges from 2.3 to 6.0 h in both single and multiple-dose studies.[9]

Hydroxy Propyl Methyl Cellulose (HPMC) is a methylcellulose that is modified with a small amount of propylene glycol ether groups. Aqueous solutions of HPMC are surface active and will form films upon drying. It can be transformed from solution to gel reversibly by applying heat and cold. Two different forms of HPMC such as HPMC K4M & HPMC K100LV were used in our study. On the other hand, alginic acid, a natural polysaccharide, is widely used as a food additive. The solution of alginic acid will turn into a gel when it comes in contact with sodium ions as sodium alginate. This Na-alginate gel may act as a vehicle for many drugs. The drugs may be incorporated in the gel and prolong the release of the drug for oral administration. This type of gel has been used to produce gel matrix or beads which are used in the floating system to prolong gastro-retention.[10-12] The objective of our study is to develop clarithromycin floating pellets. In our study, clarithromycin floating pellets were prepared by utilizing a different blends of Na-alginate and HPMC K4M & HPMC K100LV that would show the gastro-retention of the pellets with their sustained action.

MATERIALS AND METHODS

Materials. The drug clarithromycin was collected from Novartis as a gift. The polymers Na-alginate and HPMC K4M & HPMC K100LV were purchased from LOBA chemicals, India, and Calcium chloride & Disodium hydrogen were purchased from Merck, India.

Method of clarithromycin pellets preparation. Sodium alginate (1%w/w) gel was prepared by overnight soaking with a sufficient quantity of distilled demineralized water and homogenized by using electronic stirring (4000rpm) for half an hour. Then the required amount of HPMC K4M & HPMC K100LV were added to form a suspension and homogenized the resultant mixture for half an hour. A requisite quantity of clarithromycin was added to the obtained mixture and further homogenized for another 45 minutes and spray the homogenized solution onto cationic ($CaCl_2$-8%) solution. 15 minutes reaction times were provided and pellets were collected, washed four times with (50 ml X 4) distilled water, and dried at room temperature for approximately 12 hours. All the parameters such as stirring time, rpm, reaction time, drying time, temperature were optimized by error and trial method. A blending ratio of different polymers was determined by using 3^2 factorial designs as shown in Table 1.

Table 1. Formulation design for Clarithromycin floating pellets.

Batch No.	Sodium Alginate (%)	HPMC K4M: HPMC K100LV
AX	1	2:1
BX	1	1:2
CX	1	1.5:1.5
AY	1.5	2:1
BY	1.5	1:2
CY	1.5	1.5:1.5
AZ	2	2:1
BZ	2	1:2
CZ	2	1.5:1.5

There are different variables involved during Clarithromycin floating pellets formulation. The formulation variables that was optimized during the preformulation study were-

Table 2. Optimized conditions for floating pellets preparation.

Parameters	Optimized value
Concentration of $CaCl_2$	0.1M
Time of Reaction	15 minutes
Drying Time	12 hrs
Drying Temperature	Room Temperature
Needle	5ml syringe needle
Rpm Stirrer	4000 rpm
Mixing Time	*30,30,45 minutes *30 minutes for mixing of Na-alginate, 30 minutes for HPMC mixing, 45 minutes for final mixing with the drug.

Buoyancy test of the pellets with their Floating time determination. Different types of test solutions (distilled water, 0.9% NaCl solution & gastric fluid) were used to perform the buoyancy test. The specific gravity of the test solutions was measured by using a standard pycnometer. Ten pellets from each sample were steeped in 50ml of each test solution. The buoyancy of the pellets was observed visually from different test solutions. The preparation was considered to have buoyancy in the test solution only when all of the granules floated in it.[11] At the same time, the floating time of pellets was also determined by observation of pellets to be floated.

Determination of particle size and contraction ratio of clarithromycin pellet. The sizes of clarithromycin pellets (n=20) from different formulations were measured with a digital slide caliper (Fisher brand). The contraction ratio of the clarithromycin bead was calculated by dividing the mean volume of dried gel (dried pellet) by that of the hydrogel (wet pellet).[11]

Characterization of morphology of pellets by Scanning Electron Microscopy (SEM). The morphology of clarithromycin pellets was examined by Scanning Electron Microscopy (SEM) at the Bangladesh Center of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh. The samples were carefully observed with SEM (Hitachi, S-3400N).

***In vitro* dissolution of the prepared clarithromycin floating pellets.** Dissolution tests of the prepared clarithromycin floating pellets were carried out according to the USP XXIV paddle method. Pellets equivalent to 100mg clarithromycin in 900ml of dissolution medium were maintained at 37±0.5.C with a paddle stirred at 50rpm using an automated sampling procedure. Dissolution tests were carried out under dissolution medium of PH 6.8 phosphate buffers in which 5ml sample was withdrawn at predetermined time intervals, and replaced with an equal volume of fresh medium to maintain the total volume constant samples were taken at 30 minutes, 1, 2, 3, 4, 5, 6 and 8-hour interval. Absorbance were taken at 210nm using UV spectrophotometer.[13]

RESULTS AND DISCUSSION

Formulation development of clarithromycin floating pellets by 3^2 factorial design. The clarithromycin floating pellets were prepared as per the 3^2 factorial Design mentioned in the method section. By preformulation study, different parameters were selected to make our desired pellets. After maintaining all the processes and parameters, the Clarithromycin pellets were prepared. Then the pellets were undergone different studies such as the buoyancy test, floating time test, morphology determination through SEM to evaluate that our prepared pellets maintained a satisfactory level.

Effects of different polymers on the buoyancy of pellets. After preparing the pellets, the buoyancy test was performed in physiological saline, water, or HCl solution. Some formulations showed buoyancy while others did not depend on different formulations. The clarithromycin pellets were not observed to be floated for a long time, when alginate concentration was 1% and HPMCK4M & HPMC K100LV ratio was 2%. However, the pellets were found to be floated in all test solutions for more than 8 hours, when the concentration of Na- Alginate was increased to 1.5%, 2%. The mechanism behind this long gastro-retention may be explained as initially the pellets might sink & released the clarithromycin slowly and continuously. Ultimately, the clarithromycin pellets were found to be floated. When alginate concentration was increased and

HPMC concentration was varied like the table 3 then the pellets floated in physiological saline, HCl solution, or the buffer solution (PH 4.0), all of which have a specific gravity of about 1.01.

Table 3. Buoyancy status of clarithromycin pellets.

Batch No.	Water (1.007)	0.9% NaCl (1.04)	GI Fluid (1.013)
AX	S	S	S
BX	S	S	S
CX	S	S	S
AY	F	F	F
BY	F	F	F
CY	F	F	F
AZ	F	F	F
BZ	F	F	F
CZ	F	F	F

*S=Sink, F=Float

At the same time, the floating time of the prepared pellets was calculated for each batch which is shown in table 4. The floating time was also increased with the increase in the concentration of Na-Alginate. However, as to the formulations, the Na-Alginate having a concentration of 1.5% showed a higher floating time compared to the other concentration. This may be due to the formation of gel that will release the drug and help the drug to be floated for a long time.

Table 4. Floating time of clarithromycin pellets.

Batch No.	Floating Time (hr)
AX	No Floating
BX	No Floating
CX	No Floating
AY	12
BY	10
CY	10
AZ	09
BZ	08
CZ	09

Effects of polymers on the particle size of clarithromycin pellets. Clarithromycin floating pellets were prepared at different concentrations of Sodium Alginate and HPMCK4M & HPMC K100LV. Clarithromycin pellets batches were used for diameter measurement by digital slide Calipers (Fisher Brand). The pellet size was significantly varied by differences with polymer concentrations and core polymer ratio. With an increase in polymer concentration, the mean pellet diameter was found to be increased. A similar fashion was observed for both types of polymer. Table 5 represents the size of the pellets including their standard deviation and standard error. Although the diameters of the prepared pellets varied, however, the diameters of all the pellets were found to be in acceptable size ranges.

Table 5. Diameter of pellets measured by slide calipers.

Batch no.	Mean diameter of dried pellets (n=10)	Standard deviation (S.D)	Standard error (S.E)
AX	1.18	0.058	0.018
BX	1.164	0.176	0.055
CX	1.346	0.079	0.025
AY	1.243	0.20	0.064
BY	1.198	0.059	0.018
CY	1.06	0.20	0.063
AZ	1.227	0.08	0.025
BZ	1.228	0.088	0.027
CZ	1.46	0.189	0.059

n = Number of pellets.

Impact on contraction ratio for different formulations of pellets. The contraction ratio of the pellet was determined by dividing the mean volume of dried gel (dried pellet) by that of the hydrogel (wet pellet). The results were shown in table 6. It was found from the result of the contraction ratio that the contraction of the particle was increased with the increase of the polymer (Figure 1). The increased contraction ratio might affect the release of clarithromycin from pellets.[11]

Study of the morphology of clarithromycin pellets by using scanning electron microscopy. Clarithromycin floating pellets were prepared at different concentrations of sodium alginate and HPMCK4M & HPMC K100LV. Different batches of clarithromycin pellet were used for taking Scanning Electron Micrographs "SEM" *(HITACHI, Model: S-3400N)*. Micrographs were taken using different magnifications. The magnifications were used for

taking micrographs at 10-3500 (SE-Secondary Electron). Morphology and surface properties of the pellets were found to be affected by the extent of core loading and polymer type.

Table 6. The contraction ratio of clarithromycin pellets.

Batch no.	Diameter of hydrogel pellets (mm)	Diameter of dried pellets (mm)	Contraction ratio (CR)
AX	2.41	1.11	0.46
BX	2.44	1.14	0.47
CX	2.72	1.21	0.44
AY	2.81	1.25	0.44
BY	2.73	1.24	0.45
CY	2.81	1.43	0.51
AZ	2.85	1.38	0.48
BZ	2.88	1.46	0.51
CZ	2.93	1.54	0.52

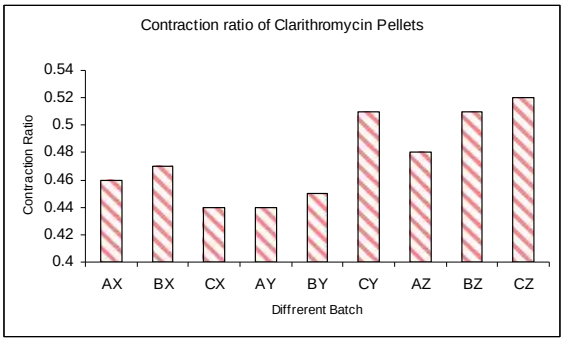

Figure 1. Contraction ratio of clarithromycin pellets.

It is evident from the figures that magnifications of the figure can show the morphology of the pellet. It was also clear from figure 2 where a single pellet with its diameter was shown (Figure 2) and it was also observed that the pellet was roughly spherical (Figure 3). The idea of pellet surface was also conceptualized and visualized by the magnifications. The pellet surface was found to be relatively smooth. The drug distribution pattern was also visualized in figure 4. It was found that the drug particles were present on the surface but they were scattered and amalgamated (Figure 4). However, the idea of gel networks, entrapment of drugs in the networks between Na alginate & the polymer for the palletization, were shown in the figure (Figure 5). This networks type of rearrangement might be responsible for the stability and strength of pellets.

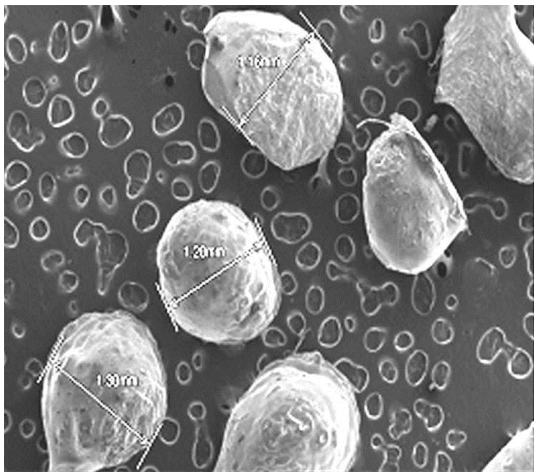

Figure 2. SEM photograph showing the diameter of prepared clarithromycin pellets.

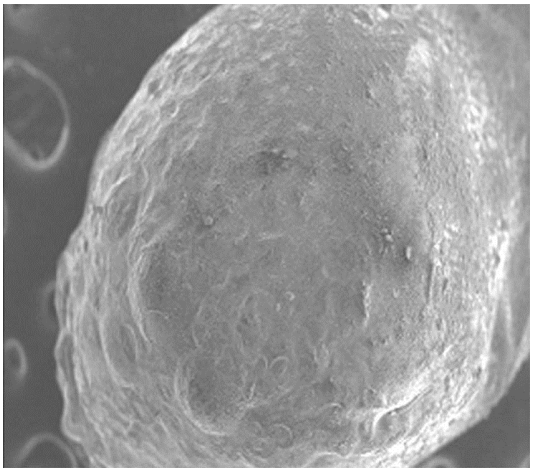

Figure 3. SEM photograph showing the shape of prepared clarithromycin pellets.

***In vitro* release of clarithromycin pellets.** Drug release kinetics from clarithromycin pellets was studied using an Automate tablet dissolution tester (USP XXIV paddle method). Dissolution tests were carried out under a dissolution medium of PH 6.8 phosphate buffers. The release of drug content was measured by UV spectrophotometrically at absorption maxima of 210 nm. From the different batches of pellets, the following release profile was observed (Table 7). When the release was plotted against the time, it was found from the correlation

coefficient values of different batches pellets that most of the prepared pellets would follow the first-order release kinetics (r^2>0.94) in comparison with the other models.

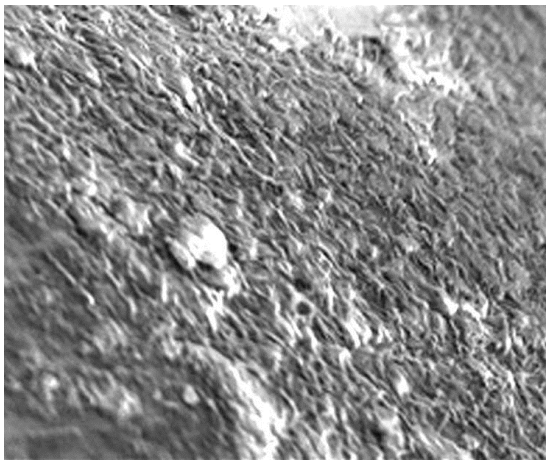

Figure 4. SEM photograph showing the drug distribution in the polymer network

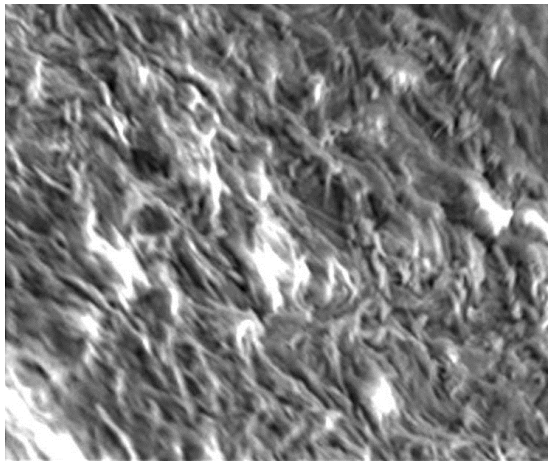

Figure 5. SEM photograph showing polymer network in the pellet surface.

From the dissolution study, it was found that most of the pellets showed release profiles within the range of 46% to 55% indicating that it can show the floating properties due to its polymeric network and sustain the release. Although the initial release was high as there was some drugs present on the surface of the pellets. However, a high amount of polymer around the drug particles slower the drug release from pellets.

Table 7. Release rate and correlation coefficient value of clarithromycin pellets.

Batch No.	Release rate (%mg/hr)	r2 value from Higuchi Plot	r2 value from First order Plot	r2 value from Zero order Plot
AX	8.12	0.86	0.93	0.85
BX	8.25	0.88	0.94	0.87
CX	8.29	0.87	0.99	0.81
AY	9.98	0.95	0.99	0.91
BY	10.11	0.97	0.96	0.93
CY	11.94	0.92	0.91	0.95
AZ	8.428	0.82	0.97	0.92
BZ	8.220	0.87	0.94	0.79
CZ	8.32	0.90	0.97	0.85

CONCLUSION

The approach of the present study was to develop floating pellets with HPMC K4M & HPMC K100LV & Sodium alginate polymer to retain the drug in the site of action for the better eradication of *H. pylori* the bacteria responsible for gastric ulcer. Considering all parameters obtained from the physical characteristic as well as the release pattern that pellets were floated in significant time and bouncy of the most of the batches were satisfactory. However, further studies in context should be carried out to check the reproducibility of floating pellets by using another polymer. *In vitro- in vivo* correlation should also be performed to get information about the efficacy of the HPMC & Na-alginate-based floating pellet of Clarithromycin.

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