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Expert Opinion Article

Design And Development Of Clarithromycin-Loaded Microspheres For The Treatment Of H Pylori Infection

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ABSTRACT
A promising strategy for improving the bioavailability and therapeutic effectiveness of drugs with absorption windows in the upper gastrointestinal tract is the use of gastro-retentive drug delivery systems (GRDDS). A macrolide antibiotic clarithromycin is frequently used to treat Helicobacter pylori-induced peptic ulcers and upper respiratory tract infections. However, the creation of a controlled-release formulation is required due to its short biological half-life and variable bioavailability. The aim of this study was to design and optimize a gastro-retentive formulation of clarithromycin-loaded microspheres using a spray drying technique. he formulation that was optimized demonstrated prolonged drug release characteristics, appropriate physicochemical features, and good entrapment efficiency. Better bioavailability and patient compliance were indicated by the in vitro drug release profile, which showed a regulated release of clarithromycin over a 6-hour period. A promising method for boosting clarithromycin's therapeutic efficacy is the new gastro-retentive microsphere formulation, which could be a useful treatment alternative for individuals suffering from respiratory tract infections.

Keywords: Gastro-retentive drug delivery system, Clarithromycin, Microspheres, Spray drying, Sustained release.

INTRODUCTION

A technique for retaining a drug candidate in a particular area of the gastrointestinal tract and extending its release is the gastroretentive drug delivery system. They therefore make it possible for the medication to reach the upper part of the GI tract for a longer duration, guaranteeing optimal bioavailability. Among the benefits of gastric retention are enhanced solubility of drugs that are less soluble in high pH environments, improved drug efficiency, higher bioavailability for drugs with an absorption window in the upper gastric region, and suitability for local drug delivery to the stomach and proximal small intestine [1,2]. Due to the absorption site and transit duration of the dosage form, many once-daily oral drug administration systems have restricted absorption. Consequently, a system designed for prolonged stomach retention extends the time that medications can be effectively absorbed and provide pharmacological action for a suitable amount of time. A macrolide antibiotic called clarithromycin is frequently used to treat upper respiratory tract infections and peptic ulcers caused by Helicobacter pylori [3,4]. Adults who have peptic ulcers caused by Helicobacter pylori should take 500 mg of clarithromycin twice day. Because a continuous-release dosage version of clarithromycin is more successful at reducing plasma swings. The drug's brief biological half-life of three to five hours makes sustained release versions beneficial.[5-7]
According to the previously stated criteria, the creation of a dosage form for clarithromycin in the stomach is essential for enhancing drug efficiency and guaranteeing continuous action. Creating gastro-retentive clarithromycin dosage formulations was the main goal of the current study. The majority of the drug content in a traditional oral CR formulation is released in the colon, necessitating the drug's absorption from the colon. The goal of the current study is to create a novel gastroretentive (GR) drug delivery system that offers a controlled release medication profile in addition to releasing the drug during the absorption window, which may lead to patient compliance and therapeutic success. By creating gastro retentive bioadhesive microspheres, the current study aimed to increase the duration of the dosage form's residency in the stomach, which would enhance drug absorption throughout the upper gastrointestinal system and, ultimately, bioavailability.

MATERIALS AND METHODS

Materials

Clarithromycin, a macrolide antibiotic used to treat upper respiratory tract infections and peptic ulcers caused by Helicobacter pylori. Hydroxypropyl methylcellulose (HPMC) was taken as a polymer used as a carrier material for the gastro-retentive microspheres and Eudragit RSPO was taken as a polymer used to prepare the gastro-retentive microspheres.

Preparation of clarithromycin-loaded microspheres for controlled release

Spray drying was used to create microspheres laden with clarithromycin. Hot water was used to dissolve HPMC K4M, and it was continuously stirred. Ethanol-dissolved clarithromycin Eudragit RSPO. An ethanol solution containing the medication and Eudragit RSPO was added while the HPMC solution was being shaken [8-10]. A magnetic stirrer was then used to agitate the finished solution for an additional ten minutes. After using a spray drier to spray the solution, the product was gathered. Below are descriptions of the criteria for spray drying. [11,12]

Table 1: Factors selected for optimization batches

Variable	Unit	Type	Low Actual (-1)	Middle Actual	High Actual
Clarithromycin	mg	Numeric	250	350	500
Eudragit RSPO	mg	Numeric	200	300	500
HPMC K4M	mg	Numeric	500	700	1000

Selection of response variables

The variables were chosen based on the desired features of microspheres. Response variables were particle size, entrapment efficiency, and drug release percentage. The response variables are presented in table 2.

Table 2: Response variables selected for optimization in Box-Behnken design

Response variables	Unit
Particle size	Micron
Entrapment efficiency	%
Drug release in 15 min	%
Drug release in 360 min	%

The microspheres in the trial batches were made using a similar procedure. Over the course of formulation optimization, the volume of the solvents (ethanol and water) stayed unchanged.

Table 3: Experimental plan for optimization of Clarithromycin-loaded mucoadhesive microspheres

Formulation Code	Eudragit RSPO	Hydroxypropyl methylcellulose K4M
CM 1	200	700
CM 2	200	500
CM 3	300	850
CM 4	500	1000
CM 5	200	1000
CM 6	300	700
CM 7	300	700
CM 8	300	700
CM 9	200	500
CM 10	500	1000
CM 11	200	850
CM 12	300	1000
CM 13	500	700

CHARACTERIZATION OF CLARITHROMYCIN-LOADED MICROSPHERES

The generated microsphere optimization batches were assessed for the following parameters: % yield, entrapment efficiency, particle size distribution, and in-vitro drug release profile. The results are presented in the table. [13-18]

Percentage yield of microspheres

Percentage yield of microspheres was calculated using the following formula:

$$\text{Percentage yield} = \frac{Actual\ \ yield}{Theoretical\ \ yield} \times 100$$

Entrapment efficiency

A precisely measured amount of microspheres was ground into a powder and mixed with 100 milliliters of purified water. For 92 hours, the mixture was kept. Next, the solution was filtered, and a UV spectrophotometer set to 288 nm was used to estimate the drug content [19]. The following formula was used to calculate the drug entrapment efficiency:

$$\%\text{Drug entrapment efficiency} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug taken}} \times 100$$

Table 4: Evaluation of percentage yield and entrapment efficiency of microspheres (Optimization Batches)

S. No.	Formulation Code	Percentage Yield (%)	Entrapment Efficiency (%)
1	CM 1	59.7	66.8
2	CM 2	56.1	50.1
3	CM 3	33.8	62.5
4	CM 4	29.2	76.2
5	CM 5	48.8	42.6
6	CM 6	66.1	75.7
7	CM 7	66.1	75.7
8	CM 8	66.1	75.7
9	CM 9	75.2	82.4
10	CM 10	45.1	41.8
11	CM 11	38.5	63.7
12	CM 12	42.6	44.9
13	CM 13	60.2	51.7

In-vitro drug release study

An in vitro dissolving test of microspheres was performed to determine the percentage of drug release from the generated formulation. As a dissolving medium, 0.01 M sodium phosphate with 0.5% SLS (pH 7.0) was used in the study. The microspheres were added to the dissolving media. Samples were removed, filtered through 0.45µ membrane filters, and the medium was reintroduced into the same volume of new dissolving media at the same temperature following each withdrawal at a predetermined interval [20,21]. A UV spectrophotometer is used to dilute and analyze the extracted materials at 288 nm.

Table 5: In-vitro drug release data for optimized batches of clarithromycin microspheres

S. No.	Formulation code	Cumulative drug release in 15 mins.	Cumulative drug release in 360 mins.
1	CM 1	11.4	84.7
2	CM 2	14.6	92.8
3	CM 3	10.2	76.4
4	CM 4	15.1	78.2
5	CM 5	19.8	56.9
6	CM 6,7,8	12.4	64.9
7	CM 9	11.2	56.2
8	CM 10	14.2	93.9
9	CM 11	11.4	74.1
10	CM 12	17.2	96.8
11	CM 13	13.5	81.2

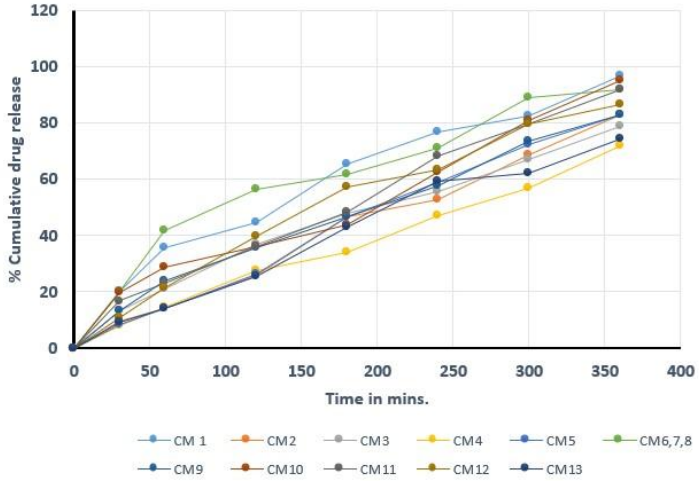


Figure 1: % Cumulative drug release of batches (CM1-CM13) at different time intervals Prediction of Optimized Mucoadhesive Microspheres of Clarithromycin

The desired criteria were established in order to acquire the optimum formulation, and the final formula for the final batch was chosen based on the optimization batches' outcomes, as indicated in table 6 below.

Table 6: Composition of optimized formulation of clarithromycin-loaded microspheres

S. No.	Ingredients	Quantity
1.	Eudragit RSPO	200
2.	HPMC K4M	500

The final batch was prepared by using the above formula through the process which was used for optimization batches as described in above section via spray dryer.

EVALUATION OF THE CLARITHROMYCIN LOADED MICROSPHERES FINAL BATCH

Bulk density

10 g accurately weighed sample was filled in a 100 ml graduated cylinder and settled volume was noted. The following formula was used to determine the bulk density in g/cm3, which was then entered into the table 7.

Bulk density = M/Vo

Where,

M = Mass of powder taken Vo = Apparent volume

Tapped density

A 10 g weighed sample was placed in a 100 ml graduated cylinder and tapped 500 times, with the tapped volume documented. Tapping was repeated an additional 750 times, and the tapped volume was less than 2%, therefore Vf was taken as the tapped volume. The tapped density was computed in g/cm3 using the formula below and documented in the table 7.

Tapped density = M /Vf

Where,

M = Weight of the sample powder taken Vf = Final tapped volume **Compressibility index**

The compressibility index (CI) was determined using the formula below and recorded in the table.

CI = { (Vo – Vf) × 100 }/Vo

Hausner ratio

After measuring the bulk and taped densities, the Hausner ratio was calculated using the formula below, which is displayed in the table.

Hausner ratio = Vo / Vf

Table 7: Calculated values for micrometric properties

Parameters	Calculated values
Bulk density	0.16 g/cm3
Tapped density	0.14 g/cm3
Compressibility index	10.1%
Hausner's ratio	1.2
Angle of repose	35.1 degree

Inference
The flow property of microspheres was fair, and the percent compressibility was found to be excellent, according to table 7.

Entrapment efficiency % and loading of drug
Microspheres' desirable properties include drug molecule entrapment efficiency and loading. The final optimized clarithromycin loaded microspheres had a drug loading of 59.28% and entrapment efficiency of 81.16%.

Entrapment efficiency was calculated by the following formula:

$$\%\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Surface Morphology
The microspheres were morphologically characterized using scanning electron microscopy (SEM) at both greater and lower resolution. [23,24]

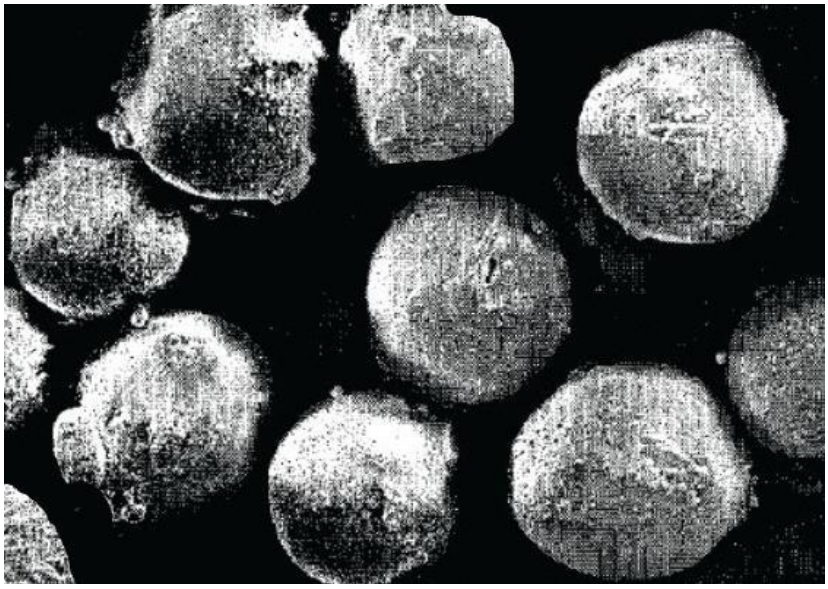


Figure 2: Scanning electron microscopic image showing surface morphology of clarithromycin-loaded microspheres

In-vitro drug release studies
An in vitro dissolution test of microspheres was used to determine the percentage of drug release from the produced formulation. The dissolving medium for the study was 0.01 M sodium phosphate with 0.5% SLS (pH 7.0). The microspheres were placed in the dissolving media. After each withdrawal interval, samples were taken out, filtered using 0.45µ membrane filters, and the medium was replenished with the same volume of fresh dissolving media while keeping the same temperature [25]. The withdrawn samples are diluted and analyzed using a UV spectrophotometer at 288 nm. The dissolution requirements are outlined in the table below.

Table 8: % Cumulative drug release of optimized formulation in different time intervals

S. No.	Time Interval (min.)	% Cumulative drug release
1	15	11.5
2	30	29.6
3	60	41.1
4	120	56.8
5	180	69.2
6	240	81.3
7	360	95.2

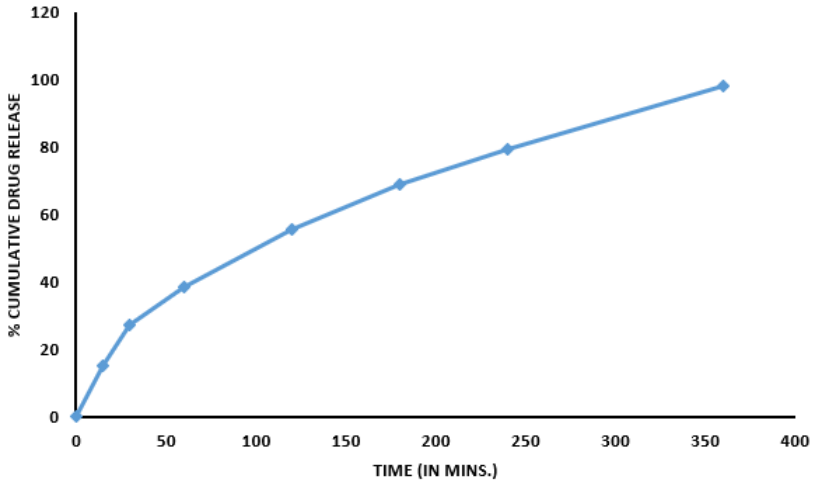


Figure 3: % Cumulative drug release graph of optimized formulation of clarithromycin- loaded microspheres

RESULTS AND DISCUSSION

Characterization of Clarithromycin: The melting point of clarithromycin was found to be 218- 220°C. The UV analysis showed the highest wavelength at 288 nm. The DSC analysis was performed to confirm the purity of the drug sample. The UV, DSC analysis, and melting point were compared to the literature of pure drug samples, and it was found that the procured drug sample was pure and was further used in the current research work. In preformulation studies a calibration curve of clarithromycin in ethanol and phosphate buffer pH 7.4 was prepared. Solubility studies were performed on different solvent media. The partition coefficient of the drug sample was performed in water and octanol, and it was found to be 2.6, indicating that the drug is highly lipophilic in nature. Drug-excipient interaction studies were performed to evaluate the compatibility of the drug with the excipients.

Physicochemical Characteristics of Clarithromycin-Loaded Microspheres

Table 7 displays the optimized formulation's physicochemical properties. The compressibility index, Hausner's ratio, tapped density, and bulk density were determined to be 0.14 g/cm^3, 10.1%, 1.2, and 0.16 g/cm^3, respectively. Bulk density, tapped density, compressibility index, and Hausner's ratio were among the appropriate physicochemical properties of the clarithromycin-loaded microspheres' improved formulation. Additionally, the improved formulation's drug loading and entrapment efficiency were determined to be sufficient.

Entrapment Efficiency and Drug Loading

The optimized formulation was found to have an entrapment efficiency of 81.16% and a drug loading of 59.28%.

Surface Morphology

Scanning electron microscopy was used to describe the optimized formulation's surface morphology (SEM). It was discovered that the microspheres had a smooth surface and were spherical in shape, indicating acceptable morphology.

In Vitro Drug Release Studies

The optimized formulation's in vitro drug release profile is displayed in Figure 13 and Table 14. The cumulative drug release at 15, 30, 60, 120, 180, 240, and 360 minutes was 11.5%, 29.6%, 41.1%, 56.8%, 69.2%, 81.3%, and 95.2%, in that order. Over the course of six hours, the improved formulation's in vitro drug release profile demonstrated a sustained release of the medication. At the conclusion of six hours, the cumulative release of drugs was 95.2%, showing good characteristics of release. A promising candidate for controlled release of clarithromycin, the optimized formulation of clarithromycin-loaded microspheres was shown to have appropriate physicochemical qualities, excellent morphology, and sustained release characteristics.

CONCLUSION

The current work used a spray drying approach to successfully design and optimize a gastro- retentive formulation of microspheres loaded with clarithromycin. High entrapment efficiency, appropriate physicochemical features, and sustained drug release were all displayed by the optimized formulation. Clarithromycin was released in a controlled way over a period of six hours, according to the in vitro drug release profile, indicating that patient compliance and bioavailability may have improved. Clarithromycin's therapeutic efficacy can be improved with the help of the new gastro-retentive microsphere formulation, which could also be a useful therapy option for patients suffering from respiratory tract

infections. Future research can concentrate on evaluating the enhanced formulation in vivo and scale up for clinical use.

SOURCE OF SUPPORT
Nil

CONFLICT OF INTEREST
I hereby declare that there is no conflict of interest, financially and otherwise. All the work done is original.

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