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Preformulation Studies for an Intra-Gastric Floating Drug Delivery System of Clarithromycin to Sustain Its Release

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ABSTRACT

The development of an intragastric floating drug delivery system (FDDS) for clarithromycin aims to enhance its bioavailability and sustain its release within the stomach. Clarithromycin, a macrolide antibiotic, is widely used to treat Helicobacter pylori and respiratory tract infections but suffers from poor solubility in gastric fluids and limited bioavailability. This study focused on preformulation studies, including organoleptic evaluation, solubility analysis, drug-excipient compatibility studies using FT-IR and DSC analysis, and in vitro drug release profiling. The floating system was designed using sodium alginate and hydroxypropyl methylcellulose (HPMC) to achieve buoyancy and controlled drug release. The results demonstrated that the formulation remained buoyant for an extended period, ensuring sustained drug release and improved therapeutic efficacy. These findings support the potential of FDDS to enhance the clinical benefits of clarithromycin.

Keywords: *Intra-gastric floating drug delivery system, Clarithromycin, bioavailability, sustained release, hydroxypropyl methylcellulose, sodium alginate, in vitro drug release*

1. INTRODUCTION

Oral Drug delivery is the most favored route of administration owing to its suitability and patient conformity. However, many drugs, including clarithromycin, exhibit challenges such as poor solubility, low bioavailability, and rapid elimination. FDDS offers a promising solution by prolonging gastric retention and improving drug dissolution rates. This study explored the physicochemical characteristics and compatibility of clarithromycin with excipients to develop a stable and effective floating drug delivery system. Achieving sustainable and controlled drug release is critical for developing effective pharmaceutical formulations. Clarithromycin is a macrolide antibiotic. However, its short half-life and potential side effects necessitate the development of a delivery system that can prolong its release and enhance its bioavailability. Oral administration of medicine is often considered to be the most patient-friendly form of drug administration and is therefore preferred. Consequently, a significant amount of effort has been put into the search for orally active candidates that are capable of delivering a plasma concentration in vivo that is both constant and effective throughout the drug development process. Many compounds are either useless or partly absorbed after oral administration (bioavailability is a problem), or the required frequency of dose is too short to allow for once- or twice-daily administration (pharmacokinetic half-life is a problem). Both issues are problematic. Since the beginning of time, the most convenient and extensively used method of administering medicine has been oral intake. The oral route of administration has, in point of fact, received the greatest attention for delayed release systems. This is the case for product design and testing, as well as research on physiological and pharmacological constraints. These results are a consequence of the fact that oral methods provide more dosage form flexibility than parenteral approaches [1]. A feasible technique to increase the bioavailability and consequent blood concentration-time profiles of drugs that could otherwise have these shortcomings. This is made possible by the technologies used for modified-release formulations. Oral administration techniques that are delayed or prolonged in their release, as well as oral delivery systems that were developed specifically to change the release of drugs that are poorly soluble in water, are all examples of what is referred to as "modified release" (MR) [2]. Scientific research is conducted with the intention of developing systems that are as close to flawless as possible. Efforts have been made to provide single-dose therapy for the duration of treatment, which has resulted in a focus on controlled or sustained delivery methods. The term "sustained

delivery" refers to a technique of administering medication that allows for a delayed and/or prolonged release of the drug [3]. In this study, we aimed to design and evaluate an intragastric floating drug delivery system for clarithromycin to sustain its release. Intragastric floating drug delivery systems have shown promise in enhancing the bioavailability of drugs with poor solubility or short half-lives by prolonging their gastric residence times. Extended-release dosage formulations are now available for a wide variety of drugs. Patient compliance and, in certain instances, therapeutic response are both improved as a result of the reduced dosage frequency that is made achievable by these medicines.

We employed a preformulation movement to investigate the physicochemical properties of clarithromycin and the formulation components, as well as their interactions, to optimize the performance of the final drug delivery system. The results indicate that the formulation consisting of Clarithromycin, N-trimethyl chitosan, and alginate has the potential to furnish a continuous liberation profile, improve solubility, and enhance the bioavailability of Clarithromycin.[4-10]

Materials and Methods: A series of preformulation studies were conducted to evaluate the properties of clarithromycin. Organoleptic evaluation assessed the drug's physical characteristics, and solubility studies determined its dissolution profile in various media. FT-IR and DSC analyses were performed to assess the drug-excipient compatibility. Standard calibration curves were prepared using UV spectrophotometry to analyze the drug concentration. Floating beads were formulated using the ionotropic gelation method with sodium alginate and HPMC.

PREFORMULATION STUDIES

PREFORMULATION ANALYTIC

i) Organoleptic Evaluation

The organoleptic characteristics of the drug were ascertained and transcribed.

ii) Determination of drug sample- Infrared spectrum

A Shimadzu FT-IR-8400 S FT-IR spectrophotometer was used to perform FT-IR spectroscopy associated with clarithromycin. A few milligrams of the sample were integrated with 10 times the weight of potassium bromide (KBr) and triturated in a mortar and pestle. The mixture was prepared by combining the three substances. Following the use of the required amount of this combination in the production of the pressed disc, the spectra were gathered within the frequency range of 4000-650 cm-1. The structural groups present in the chemical artifact of clarithromycin are exactly what correlate with the peak observed in the FT-IR spectrum.

PREPARATION OF REAGENT

To create a solution of any molarity xM, 85 ml of hydrochloric acid was diluted with 1000 ml of distilled water. The result was 0.1N HCl, which was produced by diluting 8.5 ml of hydrochloric acid with 1000 ml of distilled water.

PREPARATION OF STANDARD PLOT OF DRUG

i) Scanning of Clarithromycin on 0.1N HCl

After dissolving ten milligrammes of the medicine that had been carefully weighed in the required quantity of 0.1N hydrochloric acid, the volume was then raised to 100 mL using the same solvent. This stock solution was further diluted to obtain a solution with a concentration of 10 mcg/ml. Subsequently, a UV spectrophotometer (UV-1800, Shimadzu) covering the wavelength range of 200 to 400 nm was used to scan this solution. A characteristic peak was observed at a wavelength of 271.2 nm, and it was observed at λ max.

ii) Standard plot of Clarithromycin in 0.1N HCl

To generate a stock solution with a concentration of 100 µg/ml, ten milligrammes of clarithromycin was dissolved in 100 mL of 0.1N hydrochloric acid. Aliquots of 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 ml were collected from this and added to the volume up to 10 ml to make different dilutions of 2.0, 4.0, 6.0, 8.0, 10.0, and 12.0 µg/ml. These dilutions varied in concentration from 2.0–12.0 µg/ml. An ultraviolet spectrophotometer (UV-2450, Shimadzu) was used to analyze this dilution at a wavelength of 271.2 nm. The blank for the experiment was 0.1N hydrochloric acid.

SOLUBILITY STUDY OF DRUG

The solubility of clarithromycin was examined in 0.1N hydrochloric acid at 37 ± 0.5 °C. Clarithromycin was administered in excess in 0.1N hydrochloric acid (one millilitre in volume. A Vortex mixer was used to shake the solution for a period of four hours, and then it was sonicated for approximately one hour. Following the application of the required dilutions, the solution was passed through a Whatman filter paper (No. 1), and the amount of medicine that was dissolved was determined using spectrophotometric analysis (UV – 1800, Shimadzu).

DRUG – EXCIPIENTS COMPATIBILITY STUDIES

A. FT-IR ANALYSIS

We collected the infrared absorption spectra of the pure drug and the drug with different excipients at a 1:1 ratio using the KBr disc method (Shimadzu FT IR 8400). These spectra were obtained in the region of 4000-400 cm¬1, and we sought unique drug peaks.

B. DSC ANALYSIS

DSC thermograms of clarithromycin and a physical combination of clarithromycin with all the excipients were obtained using a Shimadzu instrument with model number DSC-60. Each sample (4–7 mg) was carefully weighed into a 40-milliliter aluminium pan, which was hermetically sealed. The temperatures of these samples were raised from 30 to 300 °C at a rate of 100 °C per minute while they were being heated in a nitrogen atmosphere. The thermogram of each sample was analyzed to identify any possible interactions between the drug and the excipient.

2. RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Before the development of dosage forms, the following studies were conducted to determine the physicochemical properties of the potential drug molecules, as well as other traced belongings of the drug powder. These properties include the physicochemical characterization of the solid and solution belongings of compounds, which are helpful in explicating the drug into a delivery arrangement that is suitable for drug administration.

ANALYTICAL PREFORMULATION

i) Evaluation of the Organoleptic System

It was noticed and pointed out that the medication had organoleptic qualities. Clarithromycin is a crystalline, odorless powder available in white or off-white forms.

2. The melting point is 219 °C.

iii) Regarding solubility, it is almost completely insoluble in water and only slightly soluble in methanol, ethanol, and acetonitrile.

IV) Identification of drug samples by the use of the infrared spectrum

The infrared spectra of clarithromycin were recorded using FT-IR spectroscopy (Shimadzu FT-IR 8400 S). The KBr disc method was used to produce the infrared (IR) absorption spectra of the pure drug. The spectra were obtained in the 4000-500 cm1 range, and a unique peak of the drug was observed.

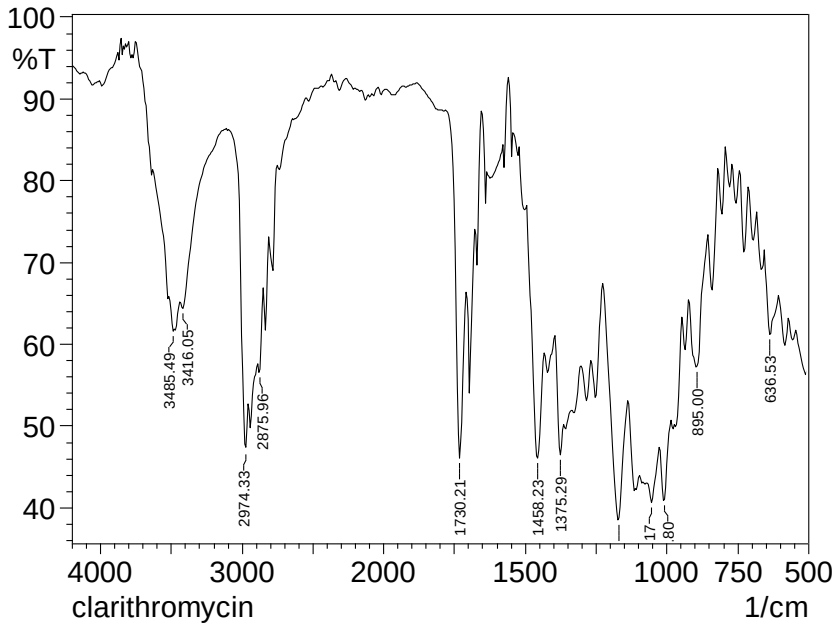


Fig. 1.1: IR SPECTRUM OF PURE CLARITHROMYCIN

Table 1.1. Different wave numbers (cm^{-1}) of pure clarithromycin

Peaks for Group	Hydrogen bonds between OH groups	Alkane stretching peaks	Lactone carbonyl	Ketone carbonyl	CH_2 groups	(N- CH_3)	-C-O-C- stretch
Wave Number (cm^{-1})	3450	2779.52 – 2974.33	1728.28	1691.63	1375.29-1456.30	1420	1008.8-1170.83

1.2. PREPARATION OF STANDARD PLOT OF DRUG

i) Scanning of the drug

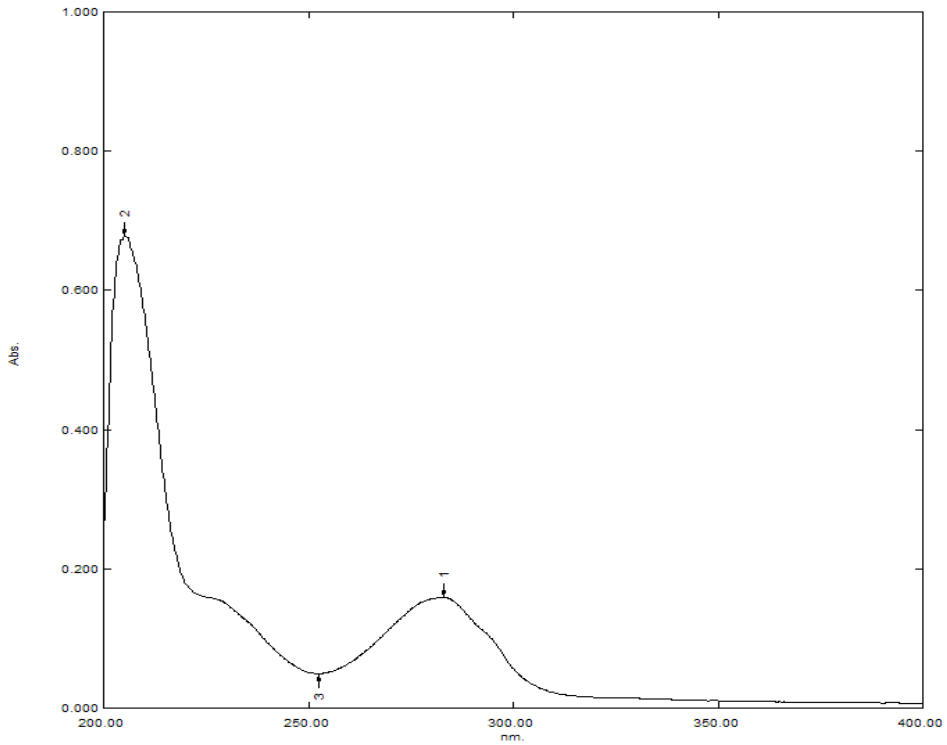


Fig: 1.2 Scanning of the drug in 0.1N *HCl*

WAVELENGTH	ABSORBANCE
271.2	0.676

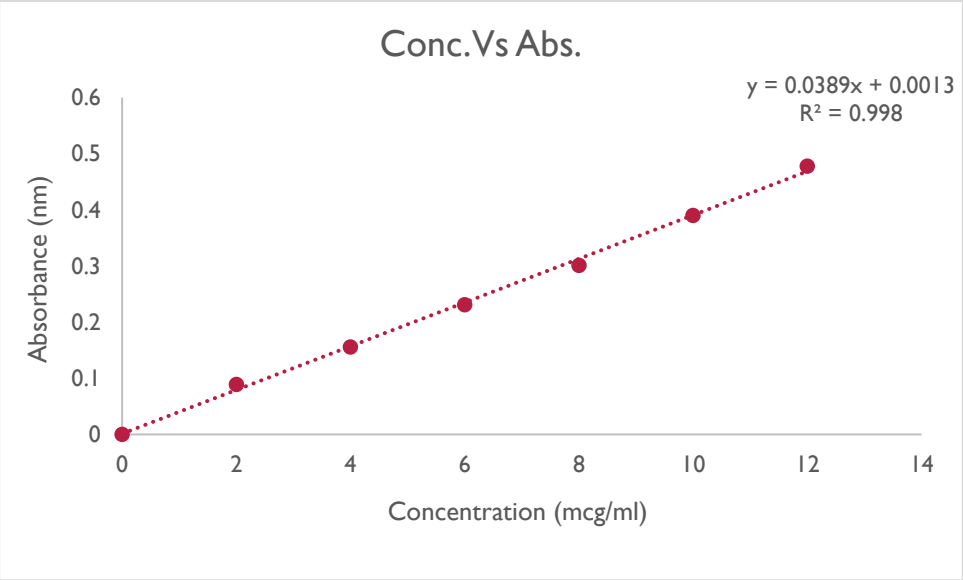
ii) Preparation of Standard Plot of the drug

For the purpose of generating a stock solution with a concentration of 100 µg/ml, ten milligrammes of clarithromycin were dissolved in one hundred millilitres of 0.1N hydrochloric acid. Aliquots of 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 ml were collected from this and added to the volume up to 10 ml in order to make different dilutions of 2.0, 4.0, 6.0, 8.0, 10.0, and 12.0 µg/ml. These dilutions varied in concentration from 2.0 to 12.0 µg/ml. An ultraviolet spectrophotometer (UV-2450, Shimadzu) was used to analyse this dilution at a wavelength of 271.2 nm. The blank for the experiment was 0.1N hydrochloric acid. The absorbance measured at various concentrations is tabulated in Table 1.2, and figure depicts the results. 1.2.

Table 1.2 : Data for Absorbance of Clarithromycin in 0.1N HCl

S. No.	Conc. (mcg/ml)	Absorbance 1 (nm)	Absorbance 2 (nm)	Absorbance 3 (nm)	Avg Abs. (nm)	Std. deviation
0	0	0	0	0	0	0
1	2	0.088	0.089	0.089	0.089	0.000471
2	4	0.156	0.154	0.156	0.156	0
3	6	0.23	0.231	0.231	0.231	0.000471
4	8	0.302	0.301	0.302	0.301	0
5	10	0.309	0.308	0.309	0.39	0.000471
6	12	0.478	0.475	0.478	0.478	0.002357

Fig.1.3. Standard plot of clarithromycin in 0.1N HCl at 271.2 nm



1.3. Solubility Study of Drug

Because drug is insoluble in water, the solubility study was performed in dissolution media i.e, 0.1N HCl and result are as follows:

Table 1.3. Solubility of Clarithromycin in 0.1N HCl medium

Media	amount of drug taken(mg)	Dil. Fac.	Absorbance	Solubility (mcg/ml)
0.1N HCl	60	100	0.034	0.426

At (maximum wavelength) = 271.2 nm

1.4. DRUG – EXCIPIENTS COMPATIBILITY STUDIES

Before optimizing the polymer ratio and their concentration for the formulation of drug ladened alginate beads, the compatibility of the polymer and drug were studied.

i) FT-IR ANALYSIS

The infrared (IR) absorption spectra of the pure drug and the drug with different excipients were acquired in the range of 4000-500 cm¬1 using the KBr disc technique (Shimadzu ft-IR 8400S). These spectra were then analysed to look for unique drug peaks.

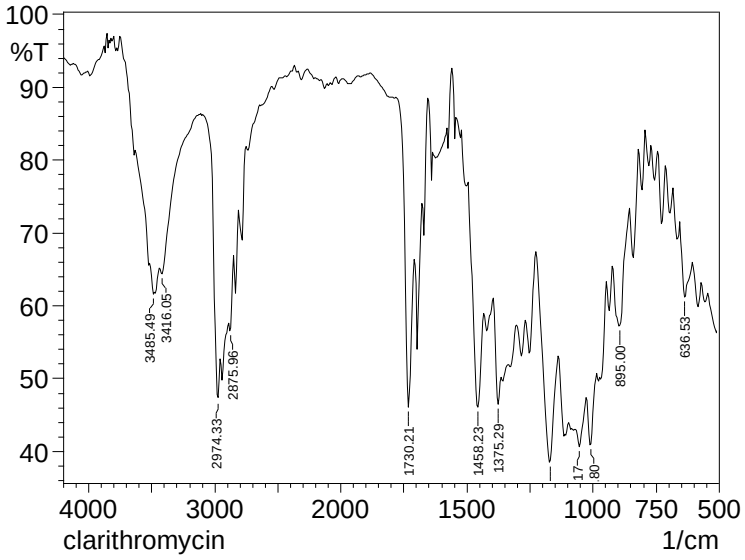


Fig:1.4: IR Spectrum of pure drug Clarithromycin

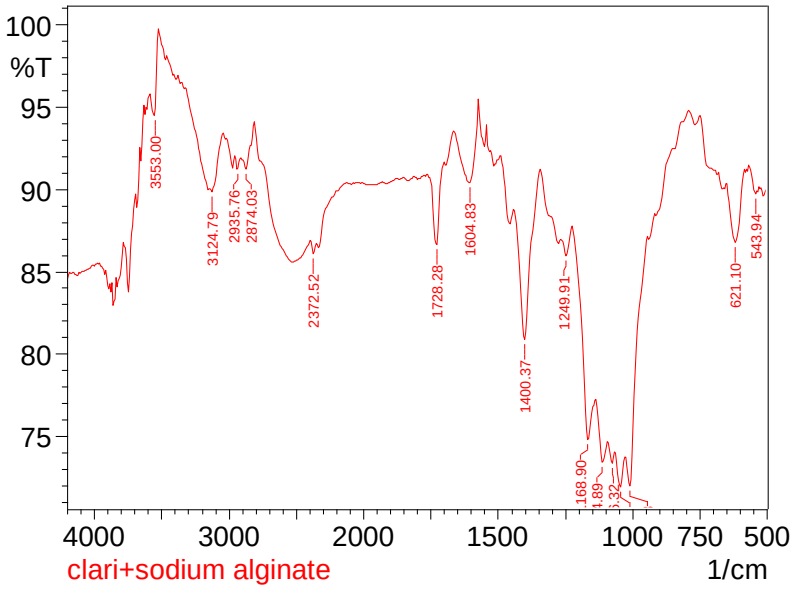


Fig. 1.5. IR Spectrum of 1:1 physical mixture of Clarithromycin and Sodium Alginate

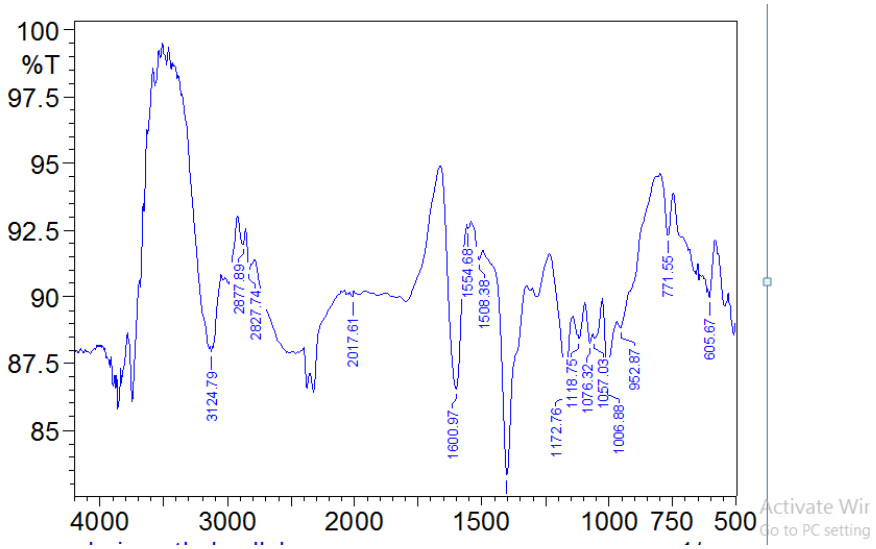


Fig: 1.6. IR Spectrum of 1:1 physical mixture of Clarithromycin and HPMC

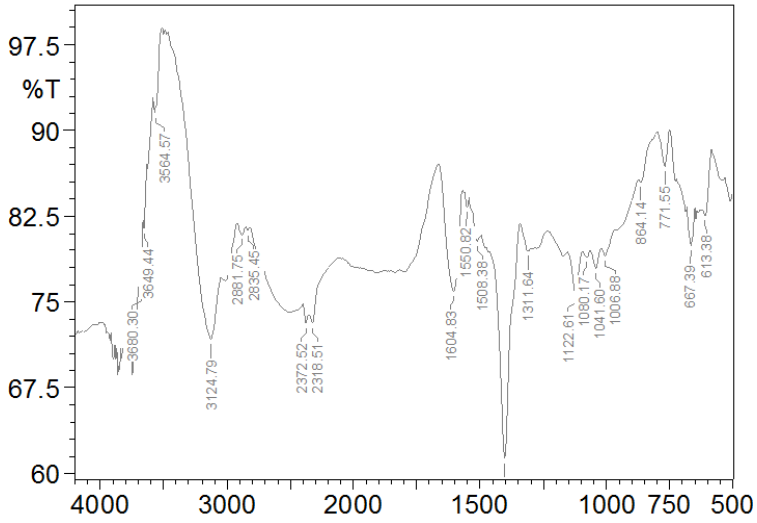


Fig. 1.7 : IR Spectrum of 1:1 physical mixture of Clarithromycin and methyl cellulose

Table 1.4: Wave Numbers of different functional groups present in Clarithromycin and physical mixtures.

S.NO	Composition	H-bonds between OH groups	Alkane Stretching Peaks	Lactone Carbonyl	Ketone Carbonyl	CH_2 groups	(N-CH3)	-C-O-C- Stretch
1	Pure drug	3450	2779-2974	1728	1691	1375-1456	1420	1008-1170
2	Pure drug & Na alginate	3468	2779-2974	1728	1689	1375-1458	1419	1006-1172
3	Pure drug & HPMC	3477	2791-2972	1730	1689	1371-1460	1420	1006-1174
4	Pure drug & MC	3481	2972	1728	1689	1373-1458	1417	1006-1172

The following table, which was obtained from the analysis of the infrared spectra, shows that the primary peaks of the pure drug were preserved in the drug that had individual excipients. The spectra did not exhibit any shifting, deleting, or broadening of peaks on any occasion, indicating the absence of any chemical interaction.

ii) DSC Analysis

DSC thermograms of clarithromycin and the physical mixture of clarithromycin with all excipients were obtained using a DSC-60 Shimadzu instrument. 4-7 mg f each sample was accurately weighed into a 40µl aluminium pan under hermetically sealed conditions. These samples were heated at a rate of 10^0C/min from 30 to 300 ^{0}C in a nitrogen atmosphere. The thermograms obtained for each sample were studied for possible interactions between the drug and excipients.

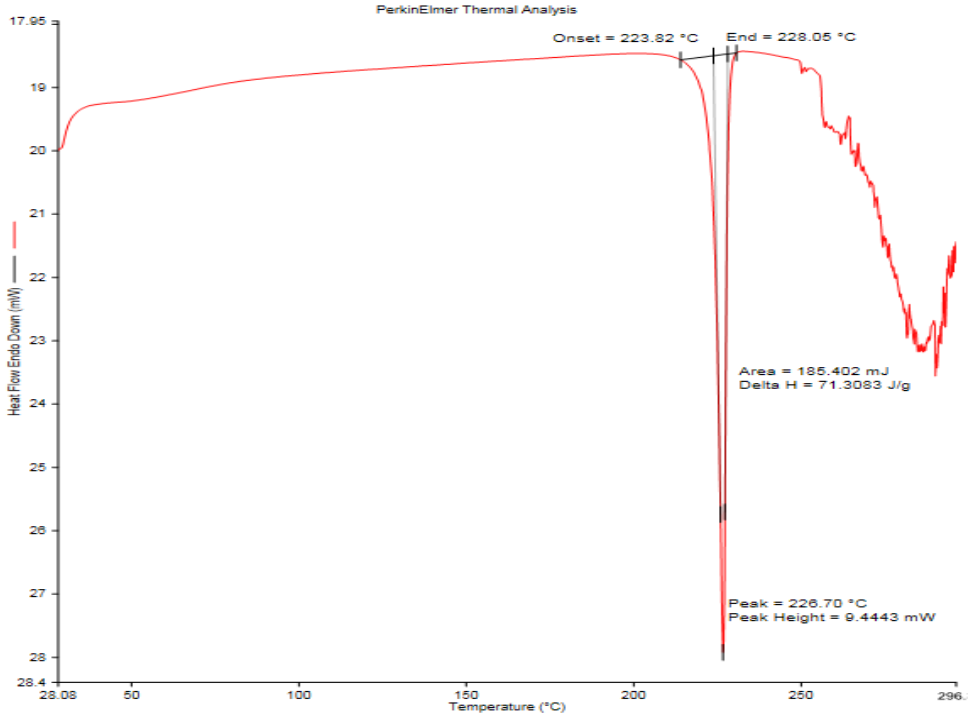


Fig:1.8 DSC thermogram of pure clarithromycin

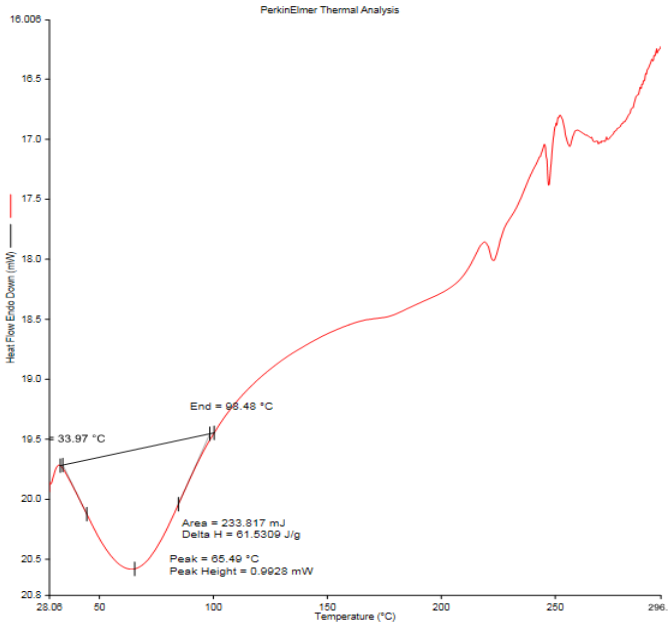


Fig:1.9 DSC thermogram of Sodium alginate

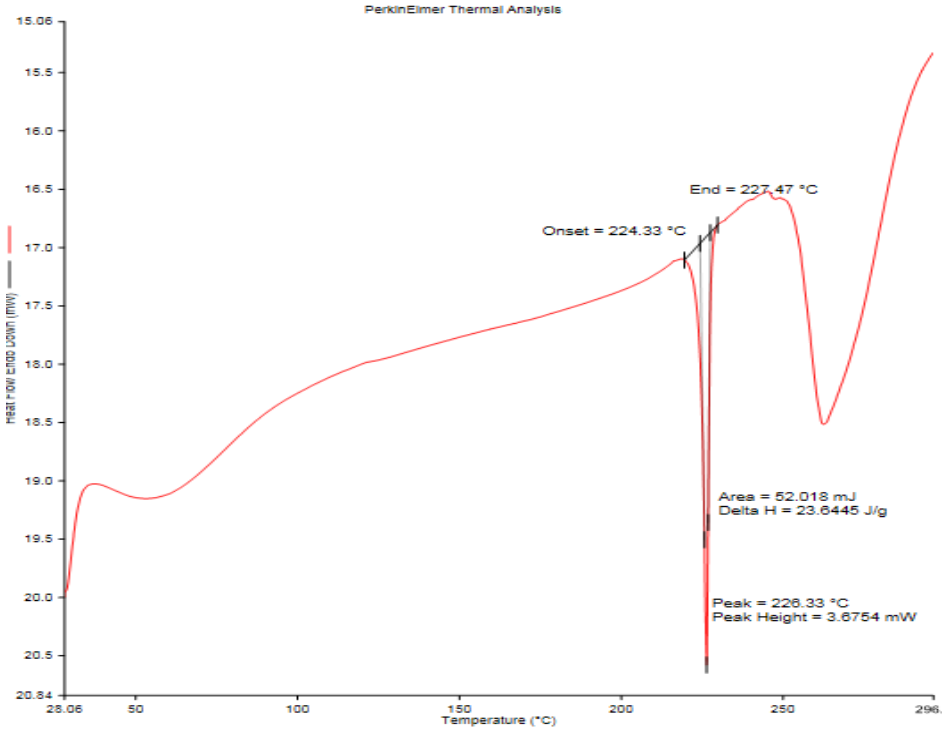


Fig:1.10 DSC thermogram of clarithromycin and sodium alginate

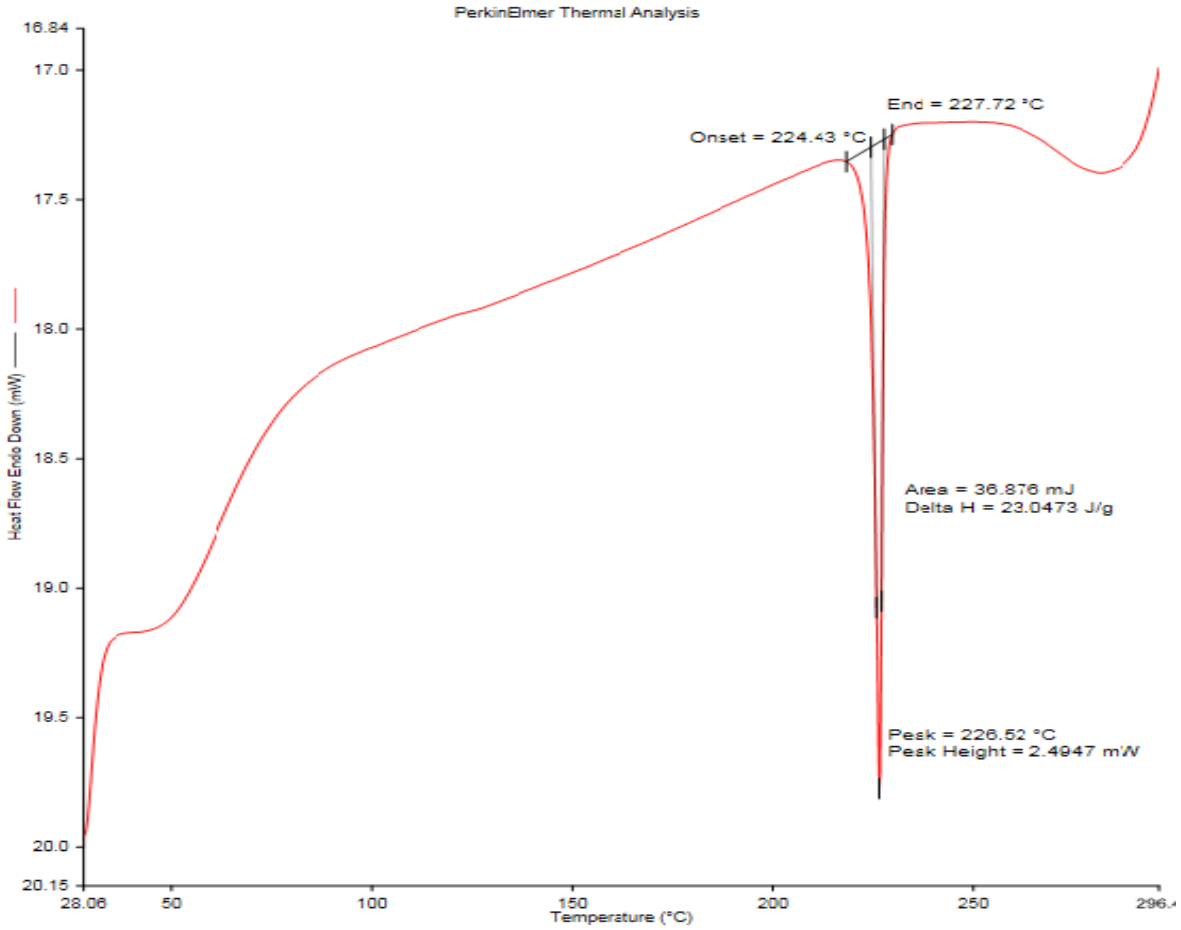


Fig:1.11 DSC thermogram of clarithromycin and HPMC

3. DISCUSSION

According to this interpretation, the DSC thermogram showed that clarithromycin had a distinct endothermic peak at 227 °C, which corresponds to the temperature at which it melts. Because the peaks are comparable, it can be deduced that the polymer used to make the microspheres and the medicine do not undergo chemical reactions with one another. To treat H, an antibiotic of the advanced generation of macrolide antibiotics known as clarithromycin is used. upper respiratory tract infections and peptic ulcers caused by Helicobacter pylori. The combination of this medication with an acid-suppressing medication and another antibiotic is common. The objective of this project is to develop an intragastric floating drug delivery system that will allow for the sustained release of clarithromycin and to optimize the manufacturing process of floating alginate beads loaded with clarithromycin molecules. The antibiotic clarithromycin is stable in stomach acid and is absorbed from the gastrointestinal tract in a short amount of time. This medication has a bioavailability of 55% when taken orally and is rapidly metabolized into its active metabolite, 14-hydroxyclarithromycin. Soon after absorption, it undergoes first-pass metabolism, resulting in the production of 14-hydroxyclarithromycin, the active metabolite of the antibiotic. Clarithromycin is considered a first-line medication as part of the combination therapy regimen for the treatment of Mycobacterium avium complex (MAC) infection in patients, clarithromycin is considered the first-line medication. Additionally, it is authorized for the treatment of leprosy, atypical pneumonia, peptic ulcers caused by Helicobacter pylori, and infections of the upper and lower respiratory tracts. Clarithromycin-loaded floating alginate beads, which float for at least 12 h and release the medication in the stomach environment where solubility and stability are at their highest, are another goal of the research. The antimicrobial drug clarithromycin suppresses protein synthesis by binding reversibly to the 50S ribosome subunit of sensitive organisms and blocking aminoacyl transfer RNA (tRNA). It produces 14-hydroxyclarithromycin, an active metabolite with increased antibacterial activity. A synergistic effect is produced when clarithromycin and its metabolites are combined. Sodium alginate is a powder with a molecular weight of 10,000–600,000 and a chemical formula of C6H7 NaO6n. Its color ranges from cream to light yellowish brown. It is used in several pharmaceutical formulations, such as aqueous solutions, tablets, and capsules. Hydroxypropyl methyl cellulose has a molecular weight of 10,000–220,000 Da and a chemical formula of C7H14O5. It is a tasteless and odorless powder. It is used in many pharmaceutical applications, such as coating materials, thickening agents, emulsification, suspending agents, controlled release in tablets, binding in tablets and granules, and as a highly effective water-retention agent. Drug sample identification, analysis, scanning, standard curve construction, solubility study, solution stability, drug-excipient compatibility studies, FTIR analysis, DSC analysis, physicochemical assessment, and organoleptic evaluation were all performed during the formulation development process. Clarithromycin, polymers, chemicals, and equipment such as an FTIR spectrophotometer, UV-visible spectrophotometer, vortex mixer, hot air oven, magnetic stirrer, oven, sonicator, PH meter, dissolution test apparatus, and scanning electron microscope were used in the experiment. The development of dosage forms for drug molecules and their derived qualities, such as the physical and chemical characterization of compounds, are the main subjects of this research. The preparation process included organoleptic assessment, FT-IR spectroscopy drug sample identification, standard plot construction, solubility tests, and drug-excipient compatibility investigations. Organoleptic examination entails identifying the drug sample using infrared spectrum analysis and observing and documenting the drug's organic nature. To create standard plots, distilled water was used to dilute HCl until 0.1N HCl was obtained. An examination of the drug's solubility in 0.1N hydrochloric acid at a temperature of 37±0.5 °C is referred to as a solubility investigation. Formula preparation involves creating oil-entrapped beads using the emulsion gelation technique or traditional alginate beads using the ionotropic gelation method. SEM was used to measure the surface shape and particle size, while spectrophotometric analysis was used to extract the medication from the beads and assess its content and encapsulation effectiveness. The formulae % drug loading = (amount of drug in beads/amount of beads) × 100 and AQ/TQ × 1OO were used to determine the drug loading and percentage encapsulation efficiency. A spectrophotometer was used to determine the drug content. In summary, the goal of this research is to create efficient dosage forms for therapeutic compounds and the attributes that result from them.

A USP Type I dissolving apparatus was used for in vitro drug release investigations, and it was kept at 37±0.5 °C in a water bath with a thermostat. The beads of each formulation were added to the dissolving jar and spun at 50 rpm. Five milliliters of samples were taken from the dissolving flask at various intervals, and five milliliters of new medium were added. A spectrophotometer was used to examine the aliquots for drug release measurements. Drug dissolution/release properties are characterized using these models. [10-14]

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