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Formulation Of Polymeric Agglomerates Of Clarithromycin By Crystallo-Co-Agglomeration Technique To Improve Its Processability

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Abstract: This study set out to directly compress sphere aggregates of BCS class-II drug in order to create a tablet with increased processability. Clarithromycin By applying the crystallo-Coagglomeration approach and the PVP K-30 composed of polymers solution, spherical agglomerates were created. Acetone worked well as a solvent, water served as an antisolvent for the clarithromycin, and dichloromethane served as a binding liquid for the agglomeration process. Based on the findings of in-vitro drug release experiments on particle size and solubility, an optimized formulation was chosen. Compared to pure medication, formulation batches show improved dissolving behaviour. Due to size expansion and spherical shape, it was possible to notice a considerable improvement in micromeritics properties, which indicated a change in crystal habit. The spherical agglomeration is prepared in large part by determining the processing conditions Using clarithromycin and an appropriate solution to change the material's characteristics to allow for direct compression.

Keywords: Clarithromycin, Spherical agglomerates; crystallo-Coagglomeration technique, PVP K-30, Factorial Design.

I. INTRODUCTION

One of the main issues preventing the invention of highly effective pharmaceutics is the drug's poor solubility. For medications in category II of the Biopharmaceutical Categorization System (BCS), inadequate oral bioavailability and unpredictable absorption are caused by pharmaceuticals with limited solubility. Clarithromycin, a BCS Class II medication, has a low solubility but a high permeability[1,4]. Therefore, increasing the solubility of pharmaceuticals is one of those most difficult problems in medication development in order to increase their bioavailability. Many methods have been used to get around these restrictions. Physical and chemical changes are the methods used to increase solubility and the amount of surface area accessible for dissolution. A partially synthetic macrolide antibiotic called clarithromycin, shown in Figure

1, prevents bacteria from synthesizing proteins via attaching to the 50s ribosomal subunit of bacteria. In this study, the wet granulation process was used to formulate and assess traditional Clarithromycin pills in an effort to increase their bioavailability. [5-9]

Materials and Methods

Materials

Clarithromycin (Aarti pharma, West Mumbai), Polyvinyl Pyrrolidone (Research lab, Mumbai), Magnesium Stearate (Molychem, Mumbai), Sodium Starch Glycolate (Molychem, Mumbai) Dichloromethane (Loba chemicals), Chloroform (Lob chemical), Acetone(Loba chemicals) None of the other chemicals or reagents were further purified before use; they were all analytical reagent grade. Wherever necessary, USP-certified purified water was used.

Methods

Preformulation studies of Clarithromycin pure drug.

The melting point and solubility of clarithromycin (CLN) in various solvents were determined during preformulation investigations on the pure medication. Using 0.1N HCL and scanning between 200 and 400 nm, the lambda max (max) of CLN was calculated. A calibration curve was then created. The Jasco FT/IR-4100 spectrometer (Japan) was used to collect FT-IR spectrum of clarithromycin spanning the wavelength range of 400–4000 cm-1. To prevent the crystals from being triturated, dry KBr (50 mg) was first finely ground in a mortar, then medication (1-2 mg) was then added and gently mixed. Materials (3-5 mg) were squeezed in non-hermetic aluminum pans with lids and scanning from 50 to 300oC at a heating rate of 10oC/min under a constantly purged dry nitrogen environment (flow rate 20mL/min) for the Differential Scanning Calorimetry, or DSC, study. The Applying a voltage of 35 kV and 20 mA, the XRD (X-ray diffraction) pattern of the pure medication was recorded. By measuring bulk density, tapered density, Car's index, angle of repose, and Hauser's ratio, the micromeritics attributes of pure CLN medication were investigated. Utilizing FTIR spectrum analyses, drug-excipient compatibility was assessed.[10-14].

Preparation Of Spherical Agglomerates:

The crystallo-co agglomeration technique15'16 was used to generate the sphere agglomerates of clarithromycin. Acetone was chosen as the solvent for Clarithromycin based on the findings of the solubility investigation. Dichloromethane was employed as a bridging liquid, PVP K30 was used as a polymer, and water served as an anti-solvent. 0.1, 0.2, and 0.3 g of PVP K30 and 0.1 g of PVP-K30 were dissolved in 100 ml of distilled water while the temperature was held at 4°C. 500 grammes of clarithromycin were dissolved in 6 ml of acetone. Using a motorized stirrer (Remi, RQ122/D, India), the drug solution was continuously added to the polymer solution at a temperature of 4°C while being stirred at 400, 600, and 800 rpm. The solution of polymers had previously been saturated with medication to prevent drug loss during agglomeration formation. The agitation persisted until the foundation of agglomerates, which were later filtered and allowed to air dry for the entire next day. By using electron microscopy, FTIR, scanning electron calorimetry, and XRD, the agglomerates were assessed for percent yield, size, drug content, flow behaviour, ability to dissolve in water, in vitro extinction, and solid-state characterization.

Evaluation of clarithromycin co-crystals powder (pre-compression Parameters)

Angle of Repose (Θ)

The funnel method was used to calculate the powder's angle of repose. The carefully measured 10 grammes of powder were placed in a funnel. The funnel's height was changed, and the granule was allowed to freely flow through the funnel and onto the surface. The powder cone's diameter was measured, and the following equation was used to get the angle of repose:

Tan = h/r, where r = the radius of the cone's base and h = the height of the cone[17].

Bulk density:

A 50 ml measuring vessel was filled with 10 g of powdered from each formulation that had been lightly shaken to break up any agglomerates. The powder's mass and bulk volume were calculated.

$$\text{Bulk density} = \frac{Weight\ of\ granules}{Valume\ of\ granules}$$

Tapped density:

For a predetermined amount of time, the measuring cylinder holding a known mass of mix was tapped. Measurements were made of the mass of the mix and the least volume contained in the cylinder.

$$\text{Tapped density} = \frac{Weight\ of\ granules}{Volume\ of\ Granules\ after\ 100\ Tapping}$$

Hausner's ratio:

According to the Hausner's ratio formula, a number of less than 1.25 implies good flow and a value of more than 1.5 indicates bad flow.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Design of Experiment:

Utilizing a full factorial design with three levels (3^2) and two factors, the compositions of sphere agglomerates were optimised according to Table 1. This experimental design18 was used to examine the main and interaction effects of the composition variables, Effect of RPM (X1) and amount of PVP K30 (X2), on percent yield (Y1) and mean particle size (Y2) of agglomerates. The surface responses and counterplots were obtained using multiple linear regression analysis, which was utilised to create mathematical relationships between factors and responses (Design - Expert).

Table 1: Information about the dependent variable for Clarithromycin spherical agglomerates

Formulation Code	Run	Independent parameters		Dependent parameters	
		X1	X2	Y1	Y2
		Agitation speed RPM	Polymer conc. (g)	particle size(nm)* Y1	Drug content (%)
F1	5	400	0.1	616.8	81.56
F2	2	600	0.2	617.9	80.85
F3	1	800	0.3	618.2	90.5
F4	3	400	0.1	629.4	83.07
F5	7	600	0.2	632.1	85.05
F6	6	800	0.3	639.4	82.4
F7	**8**	**400**	**0.1**	**661.2**	**93.03**
F8	9	600	0.2	655.1	88.12
F9	4	800	0.3	647.5	82.4

Evaluation of Spherical Agglomerates:

Yield:

Using the formula below, the yield of the prepared agglomerates was determined.

$$\%\text{yield} = \frac{Total\ weight\ of\ agglomerates}{total\ weight\ of\ drug\ and\ excipients} * 100$$

Drug Content:

Drug content was computed as a percentage and expressed as the ratio of experimentally obtained drug amounts to theoretical values. The samples were triturated in a mortar and pestle after being drawn at random from the ready batch from three distinct spots. 100 mg of powder was weighed, mixed with 100 ml of 0.1N HCl, and then sonicated for 20 minutes. The resulting mixture was then further reduced with methanol before passing through Whatman filter paper. At 271 nm, the drug concentration was measured spectrophotometrically (Shimadzu, 1900i, Japan)[19].

Micromeritic properties of agglomerates

Optical microscopy was used to measure the average size of particles and size variation for pure drug and produced agglomerates (Laurie and Mayo, India). Using BD equipment, density of the bulk (BD) and pierced densities (TD) were calculated. Then, using bulk and TD, Carr's indicator (CI) (%) and Hausner's ratio (HR) were computed. Using the fixed funnel method, the angle of relaxation (AR) for the pure drug and produced agglomerates was calculated.[20,21]

Scanning electron microscopy

Using a scanning electron microscope with field emission (FEI, Novo Nano Scanning electron microscopy 450 [SEM 450], USA), the surface morphology of agglomerates was investigated. To make the samples electrically conductive prior to estimating, an auto fine coater applied a 20-nm-thin layer of platinum. The coated samples' stubs were then put inside the field discharge scanning electron microscopy chamber. Following a random scan of the samples, microscopy images were obtained at a 15–18 kV acceleration voltage. The agglomerates were studied at various magnifications in order to assess the impact on surface morphology[22].

Fourier transform infrared spectroscopy

Spectroscopy By using the KBr pellet technique (Shimadzu, 8400S, Japan), the FTIR spectrum of Clarithromycin, its physical mixing with excipients, and optimised spherical agglomerate formulation were recorded in order to analyse the changes that occurred during the agglomeration process. FTIR spectra were captured between 400 and 4000 cm123. Calorimetry that uses differential scanning Using differential scanning calorimetry (Hitachi, DCS7020, Japan), the possibility of any interactions among Clarithromycin and the remaining excipients during the spherical agglomeration process was evaluated. Clarithromycin was used as the physical mixture of the polymer drug and the agglomerate. The specimen was heated at a rate of 10°C/min from 40°C to 240°C. Throughout the experiment, gas was purged at a rate of 40 ml/min to maintain the inert environment. The sample (1-4 mg) was meticulously moved, heated in a pan of crimped aluminum for precise results. The resulting temperatures were used to determine whether Clarithromycin and polymer[24] interacted at all.

X-ray diffraction

An X-ray diffractometer (Brucker, D8Advanced, USA) was used to conduct the XRD investigation utilizing Cu K -rays at a 40 kV and 40 mA voltage and current. Samples were scanned at a 15°/min scanning speed for 2 from 10° to 80°. Clarithromycin, a physical combination, and an agglomerate's diffraction patterns were obtained[26,27].

Solubility analysis

The level of saturation solubility of a particular agglomerate in a water formulation was assessed in order to observe the change in medication solubility during crystallo-co-agglomeration. The sample was weighed, and then 2 ml of 0.3% sodium chloride sulphate solution and distilled water were added incrementally until saturation. The saturated solution spent 48 hours at 25°C + 0.5°C in a rotating shaker (Remi, CIS 24 BL, India). After 48 hours, samples were centrifuged at 1000 rpm for 30 minutes in a research centrifuge (Remi, R-8C, India). The resulting solution was then filtered, diluted as needed, and its drug content was assessed by ultraviolet (UV) spectrophotometry at 271.0 nm[28]

In vitro dissolution study

Utilizing a USP type II equipment (Lab India), a drug releasing study of pure drug and manufactured, optimised batch of aggregates was conducted[28,29]. According to the USP monograph, dissolution investigations were conducted utilizing 900 ml of 0.1N HCl as the dissolving medium at 37°C and 50 rpm stirring speed. After every 10 minutes, 5 ml aliquots were removed and replaced with the equal amount of

fresh dissolving medium. Aliquots were properly diluted before being subjected to UV spectrophotometer analysis at 271nm[30].

RESULTS AND DISCUSSION

Preformulation Study:

Physical appearance: The physical properties of the API was found to given in table No.2.

Table No.2: Physical properties of the API

Sr. No	Parameters	Results
1	Physical state	Solid
2	Colour	White
3.	Odour	Odourless
4.	Taste	Bitter

Melting point:

Melting point of Clarithromycin was determined by capillary method and result was found to be 218°C hence compiles with USP standards (217-220°C), thus indicating the purity of the drug sample.

Table No.3: Melting point

Drug	Standard Melting Point	Observed Melting Point
Clarithromycin	217-220	218-220

Solubility Analysis

The solubility studies of Clarithromycin were done by using various solvents like distilled water DMSO, methanol and ethanol. Data for solubility studies in different solvents are shown in table 8.the result showed maximum solubility in methanol and ethanol, was soluble in methanol, hence these solvents were selected for determination of calibration curve[24].

Table.No.4 The solubility studies of Clarithromycin

Sr. No	Solvents	Solubility (mg/ml)
1	Water	Practically insoluble
2	Methanol	1.00±003
3	Ethanol	1.00±020
4	DMSO	0.50±010
5	Acetone	2.00±021

Solubility of pure API(n=3)

Clarithromycin's solubility in several solvents was evaluated in order to choose a suitable solvent. Clarithromycin's solubility in DCM, methanol, ethanol, DMSO, water, and acetone is shown in Figure

4.Compatibility study using FTIR:

The FTIR spectrum was measured in the solid state. The FTIR spectrum of clarithromycin is shown in Figure No.9.1. Observed peaks are shown in Table No.9.4. These peaks are similar to that of reported peaks of clarithromycin (USP N/F 2006).

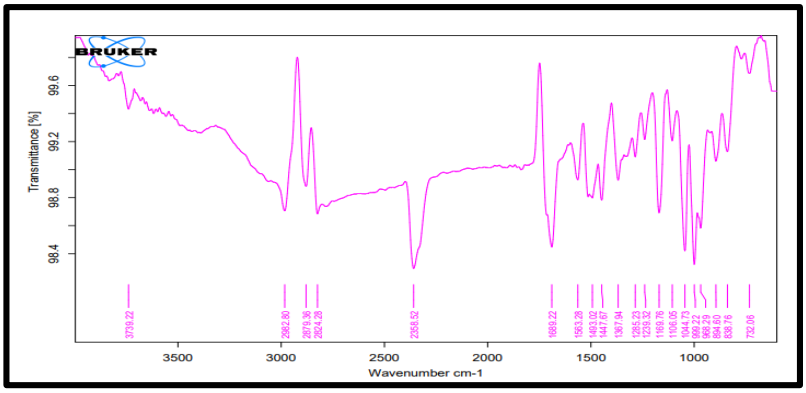


Fig No 1: FTIRs Spectra of Clarithromycin

Table No.4: Major Objective IR Peaks Of Clarithromycin

Sr. No	Functional groups nterpretation	Frequency(cm^{-1})	
		bserved (API)	Reported
1.	C-H	29205.57	3000-2850
2.	O-H	2978.17	2978.17
3.	C=O	1718.03	1740-1720
4.	C=C	1600.00	1630

Micromeritics Studies:

The results of each microsphere formulation, from F1 to F9, are displayed in the table below. Various micromeritic properties, including bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose, were studied. All of the formulations from F1 through F9 had % Compressibility indices between 11.83 and 26.20, suggesting satisfactory flow characteristics. Angles of repose for all tiny sphere's formulations were found to be between 22.56° and 32.26°, indicating outstanding to good flow characteristics for the spherical crystals that had been created.

Table No.5: Evaluation of Flow Property:

Batch number	BD(g/ml)	TD(g/ml)*	HR	CI (%)	AR(.)
F1	0.3616	0.4657	1.28	22.19	32.78
F2	0.4345	0.5263	1.21	17.26	32.24
F3	0.5512	0.4057	1.15	13.30	31.92
F4	0.5099	0.5512	1.17	15.26	29.38
F5	0.4783	0.5099	1.11	14.58	28.72
F6	0.4338	0.5330	1.14	12.25	26.45
F7	**0.3518**	**0.5289**	**1.12**	**11.83**	**22.56**
F8	0.4255	0.4783	1.22	18.18	26.12
F9	0.3908	0.5131	1.23	18.11	26.34
Pure Drug	0.365	0.4692	1.35	26.20	32.26

Partical size analysis:

Utilising a Horiba device, the mean average size of the particles of clarithromycin sphere agglomerates is determined. The outcomes are displayed in Table 9.5. Particle sizes for batches F1–F9 were found to range from 616–661.2 nm. The improved batch's particle size was F7 661.2 nm.

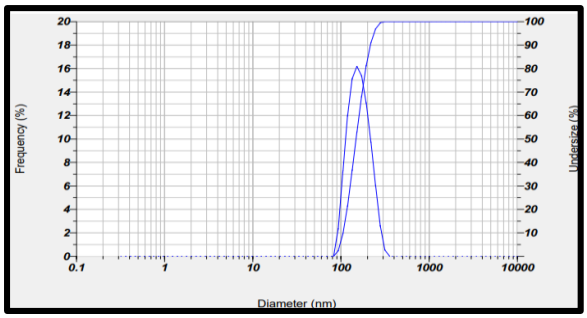


Figure No.2: Partical size of optimized batch F7

Table No.6 Partical Size

Formulation code	particle size(nm)
F1	616.8
F2	617.9
F3	618.2
F4	629.4
F5	632.1
F6	639.4
F7	**661.2**
F8	655.1
F9	647.5

Optimization by design of experiments

Spherical agglomerates were evaluated for a number of evaluation criteria, and the findings are shown in Tables 1 and 2. Spherical agglomerates' particle size was discovered to be within the permitted range (616.8-661.2). Spherical agglomerates' drug content was discovered to be between 80.85 1.022 and 92.05 0.94%. Table 1 displays the outcomes of the variables that are dependent, Particle Size (Y1) and Drug Content (Y2), from nine studies. Equations 1 and 2 express the mathematical correlations created for the investigated response variables.

Mathematical equation:

Particle Size= $+635.29 + 4.18 * A + 18.48 * B + 3.07 * AB$

i) 3D Graph of Counter plot and Response surface plot of Particle size:

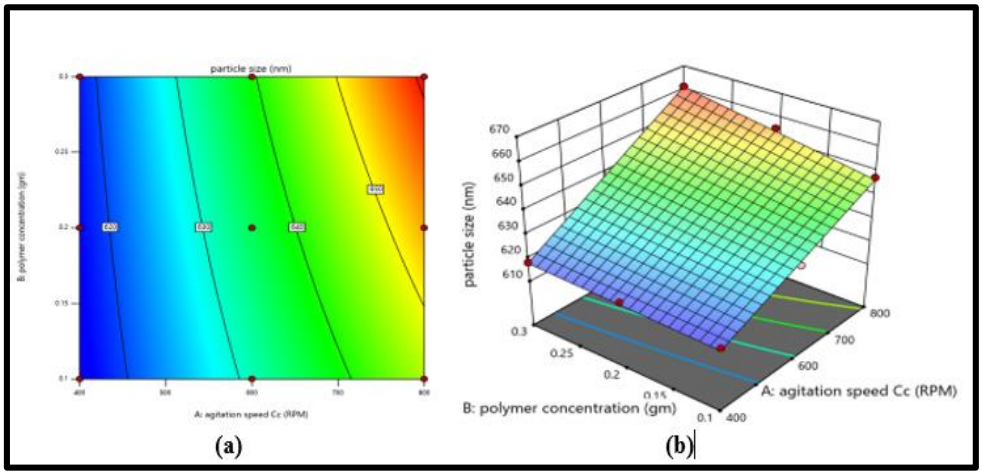


Figure No:3 (a) Contour plot b) Surface plot

ii) 3D Graph of Counter plot and Response surface plot of %Drug Content:

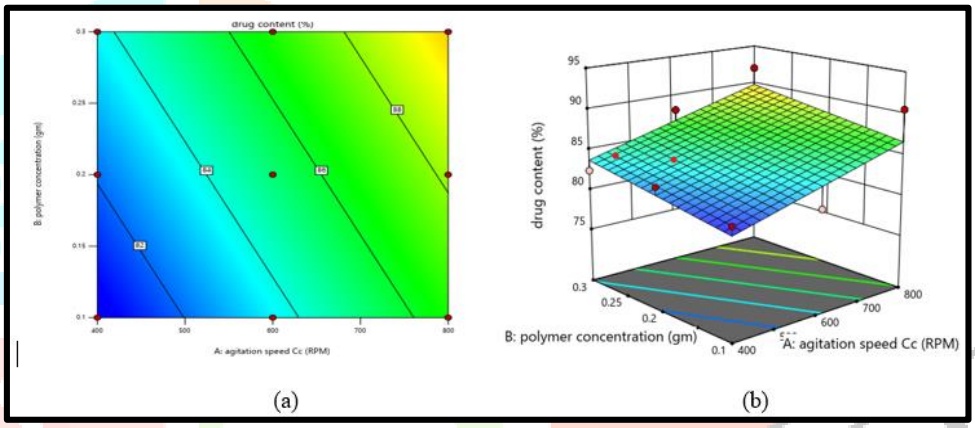


Figure No:4 (a) Contour Plotes (b) Surface Plotes

Percent yield:

The final product of the spherical agglomeration was affected by the PVP k-30 concentration. The -1 coefficient of A* in the equation showed that the percent yield decreased as Pvp-K-30 concentration increased. This could be explained by the excipients and medication being lost during the agglomeration process as a result of increased adhering to the container walls and a rise in PVP K-30 concentration. The derived equation was a linear equation. There was no interaction between A* and B* on the percentage drug content, according to the outcome lotting and counterplots in the second figure. Counterplots showed various percent yield zones with changing PVP K30 concentrations. It can be assumed that the higher yield (66% or more) was caused by the decreased PVP concentration (0.1 mg or less). lower yield value.

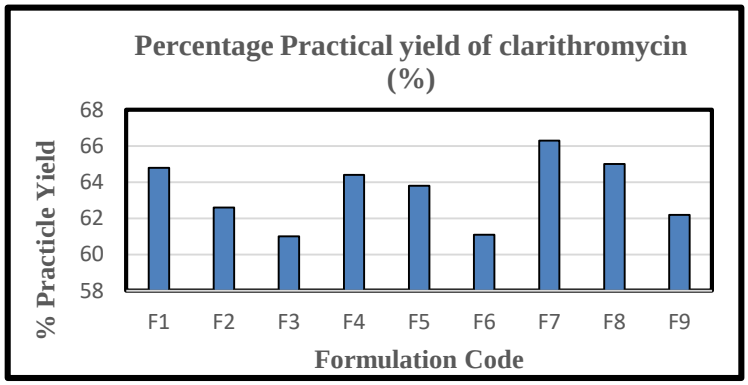


Figure No 5: Percentage Practical Yield of Prepared Formulations

Drug Content:

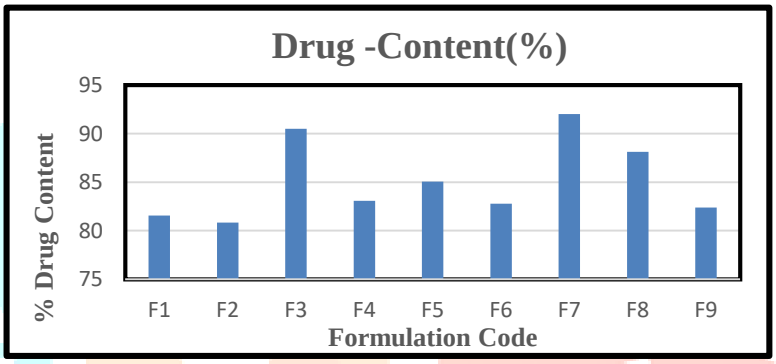
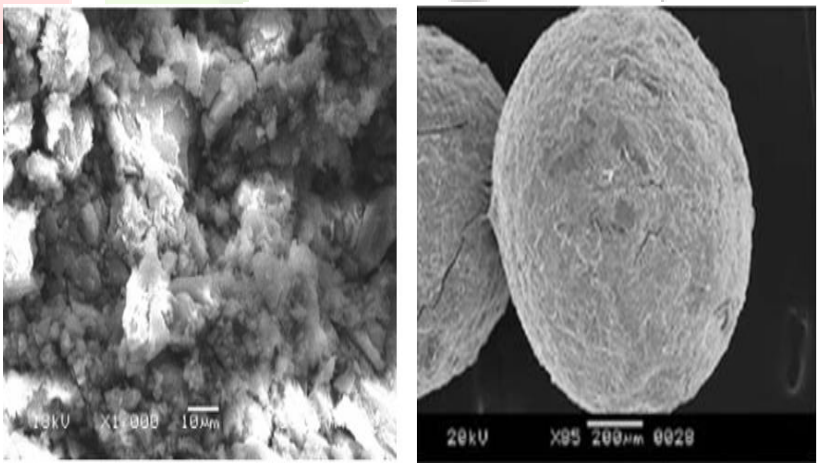


Figure No.6: Drug Content of Prepared Formulations

Scanning Electron Microscopy (SEM):

SEM imaging showed that the pure drug's needle-shaped crystals were a factor in Clarithromycin's poor flow characteristics. Agglomerates' improved flow could be attributable to their spherical shape, which is demonstrated by SEM.



(A) **(B)**

Figure No.7: Scanning Electron Microscopy of Pure API (A) Spherical agglomerates (B)

Fourier transform infrared spectroscopy:

The primary PVP K-30 characteristic peaks in the IR spectra of the physical combination and Clarithromycin agglomerates were unaffected. As a result, the formulation underwent no chemical change during the agglomeration process.

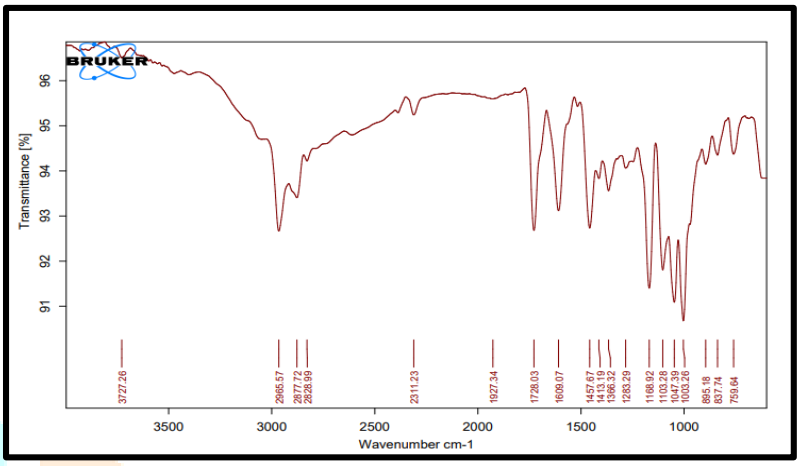
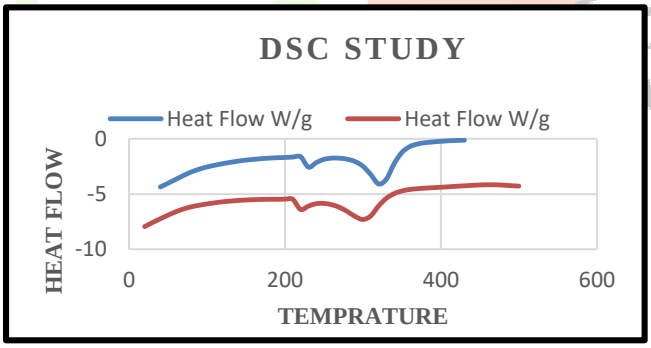


Figure No.8: FTIR Spectra Of Mixture Of optimized batch

Differential Scanning Colorimetry (DSC):

DSC (differential scanning calorimetry) research was done to see how Clarithromycin changed during the spherical agglomeration process. Clarithromycin is physically mixed with PVP K30 to create a spherical agglomeration, as shown in Figure 11's DSC. At 229.50 °C, which corresponds to clarithromycin's melting point, a pronounced endotherm was seen. The physical mixture's DSC showed a modest shift in endotherm to 230.80°C as well as an increase in intensity. A wide endotherm observed over this temperature range



indicates that PVP K30's melting point is between 160°C and 165°C. Endotherm was detected by the formulation's DSC at 230.80°C.

Fig No.9: Differential scanning calorimetry thermogram of agglomeration formulation, physical mixture, and pure drug.

X-ray diffraction study

The intense peaks observed in XRD of Clarithromycin indicated crystalline nature of drug. XRD of spherical agglomerate formulation indicated increase in the intensity of Clarithromycin peaks. This could be due to crystallinity of drug during agglomeration process. The increase in intensity for peaks at 3349° to 6098° indicates possibility of some crystalline change occurred in drug during the agglomeration process.

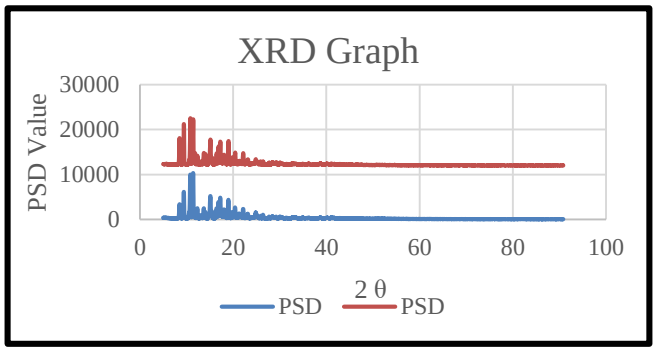


Figure No.10: Overly XRD of Pure Drug (a) spherical agglomerate (b)

In vitro dissolution study

When compared to pure medication, the drug release from spherical agglomeration formulations was significantly improved. The hydrophilic properties of PVP K 30, which was utilised in co-agglomeration, may be responsible for the increased drug release. Additionally, during the process of spherical agglomeration, Clarithromycin's crystal structure changed from Lowley to Highly, which may have increased drug release. These findings concurred with the findings of the DSC and XRD. The amount of PVP K30 present was observed to affect the release of clarithromycin.

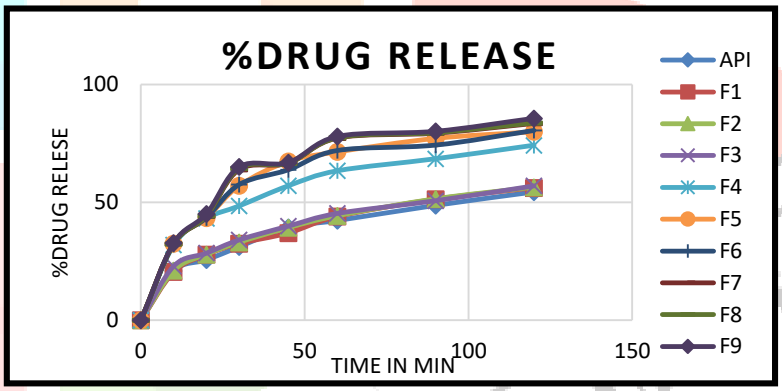


Figure No.11: Percentage Drug Release of SA of Batches F1 to F9

Evaluation of the prepared tablet:

Table no.7: Evaluation Parameters Of the Tablet from Optimized Agglomerates Batch.

Tests	Assay (%)	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	DT
Result Obtained	97%	352±10	4.4±0.2	4.3±0.3	0.23±0.11	9 min 27 sec

These studies revealed that the formulated tablets were found to be stable and meeting I.Pspecified limits for weight uniformity, hardness, friability, and time until disintegration.

In-*Vitro* Dissolution Study of Formulated Tablets:

The dissolution studies of formulated tablet of Clarithromycin crystals were performed byusing USP type II dissolution test apparatus in 900 ml of 0.1N HCl

Table No.8: Percentage Drug Release of Prepared Tablet

Time (min)	% Drug Release	
	Batch F7	Marked Formulation
0	0	0
10	32.89	34.90
20	44.55	48.58
30	58.54	59.57
45	65.20	67.30
60	81.39	81.40
90	90.40	91.03
120	96.9	94.60

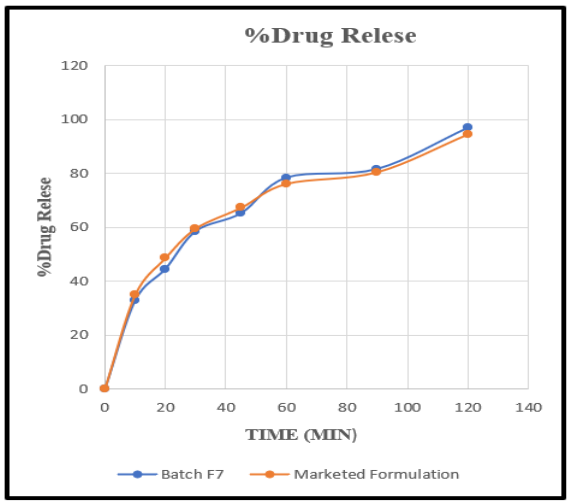


Figure No 12:Comparetive study between Batch F7 & Marketed Formulation

In-*Vitro* Antimicrobial Study:

The optimised formula F7 was fast released compared to the commercially available antibiotic, according to in vitro antibacterial testing. When compared to commercially available drugs, the drug from the round crystal was released at a faster pace, leading to higher inhibitory activities being seen.

Table No.9: In-*vitro* antimicrobial activity study

sr.no	Inhibition zones for F7	Inhibition zones Marketed drug(mm)
1	1.4	0.9
2	2.7	1.2
3	3.6	1.6
4	4.0	2.5
5	4.2	3.1

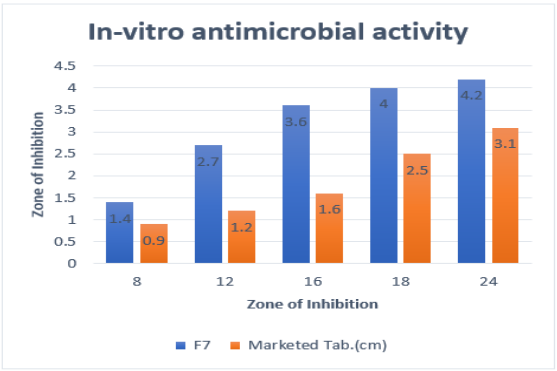
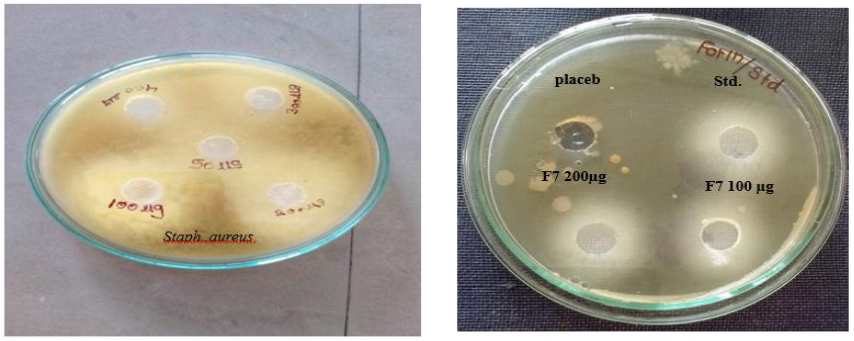


Figure No.13: In- *vitro* antimicrobial activity Comparative study between batch F7 and Marketed Formulation



(a) **(b)**

Figure.No.14: Zone of Inhibition(cm) of Batch F7 and Marked Drug

Stability Study of Optimized Formulation:

According to ICH requirements, an instability study was conducted for the optimised formulation. The F7 batch's tablets were put in a screw-capped glass container and kept in compliance with ICH storage conditions at a temperature of 400°C 20°C (75% 5%RH). The samples were further examined for physical characteristics and drug content over a period of 4 weeks.

Table No.9: Stability Study Batch F7

Conditions	Physical Appearance	Dissolution (In 120 min)	% Assay
Initial 40°C/75% RH	White	95.10	97%
15 Days 40°C/75% RH	White	93.16	96%
1 month 40°C/75% RH	white	92.56	94%

CONCLUSION

PVP K30 was used as a polymer in the effective formulation of clarithromycin agglomerates using the crystallo-co agglomeration process. The concentration of PVP K30 in the clarithromycin agglomerate formulation significantly affected the percentage yield and mean particle size. In comparison to pure Clarithromycin, the optimised formulation, F7, had better the ability to flow, pliability, solubility in water and drug release. Infrared spectroscopy (IR), DSC, and XRD were used to support the observations. The current study suggested crystallo-co-agglomeration as a possible method for improving flow characteristics and drug dissolution profiles in poorly soluble medication formulations.

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