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DEVELOPMENT AND EVALUATION OF FLASH RELEASE ORAL WAFER CONTAINING ANTIBIOTIC

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ABSTRACT: In the 21st century, human lifestyle has been faster than previous. People of this generation require faster results of each and everything which leads to change in lifestyle. Due to this immediatism invention of rapid release dosage forms are immerging in pharmaceutical market, from which Oral wafer is one of the dosage forms which provides rapid release of the drug. These oral wafers can be administered by oro-mucosal route which can be on the tongue, sublingually or buccal route. It disintegrates in saliva within 14 seconds and dissolution of 99% of drug in saliva has obtained within 60 seconds. There was total three challenges in this research. The antibiotic used in this research was BCS class II drug which leads to poor water solubility which may hamper the rapid action. Extremely bitter taste of drug was the second challenge and Incorporation of high dose in oral wafer was the third challenge. These all challenges have been conquered in this research.

INTRODUCTION: Everything is changing with the change in generation or time interval. We live in the 21st century. We are part of the lifestyle of faster results, fast growth, and of immediatism. Change in generation results in a change in lifestyle. Nowadays, no one has time to look upon themselves. Many new diseases have been introduced for variations in lifestyle and measures of illness have increased. People of this faster generation required everything faster, which leads to the development of a rapidly releasing drug delivery system. It is an alternative to conventional dosage forms for pediatric and geriatric patients who experience a problem in swallowing traditional dosage forms.

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Now a day's pharmaceutical companies mostly focus on patient compliance and had started developing novel drug delivery systems to execute the delivery of drugs efficiently to patients. Solids dosage forms preferred mainly by patients due to their accuracy of dose, easy for administration, self-medication, painless, and most importantly, patient compliance. Oral wafers are referred to as oral thin films, oral strips. The conventional pharmaceutical dosage forms are not capable of controlling the rate of drug delivery. Oral wafers are polymeric ultra-thin paper-like films which drug release can be controlled as per requirement. It can be fast disintegrating as well as sustained release

The Objective of Formulating Wafers:

- Improve patient compliance and get the rapid onset of action
- To reduce the extent of hepatic first pass metabolism.

- Reduce side effects emerge with the API due to their high dose.

Types of Oral Wafers: There are three types of oral wafers as shown in **Fig. 1.** This type of dosage form used for rapid action within a few seconds [1].

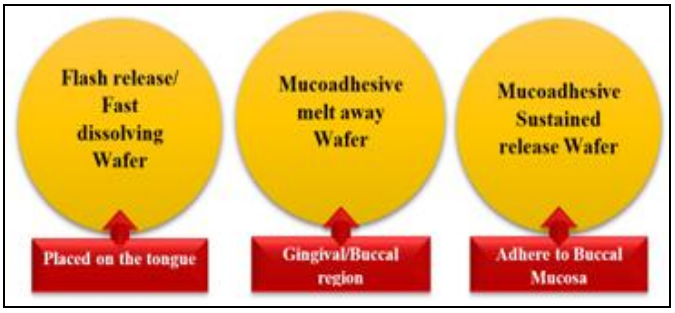


FIG. 1: CLASSIFICATION OF ORAL WAFER

MATERIALS AND METHOD:

Material: Clarithromycin is an active pharmaceutical ingredient obtained as gift sample from Emcure Pharma Ltd. Pullulan is a natural polymer and Aspartame is artificial sweetener obtained as gift ample from Cipla, R & D Centre Vikhroli, Polyethylene Glycol-400 was obtained from lobachempharma Ltd.

Method:

Preformulation Study of Clarithromycin:

Morphological Characteristics: The drug sample Clarithromycin was observed for physical appearance, colour, odour and taste.

Melting Point: Melting point was determined using melting point apparatus. Liquid paraffin has been taken in Thiel's tube. A capillary tube which is sealed at one end was filled with drug sample and tied it with thermometer by using thread, and it is suspended in thiel's tube. The arm of the thiel's tube has been heated by using burner and the point at which drug sample get melted that temperature has been noted down [2].

Solubility Determination of Clarithromycin: Saturated solubility of Clarithromycin was determined in distilled water, in organic solvent such as ethanol or methanol, and in aqueous buffers. An excess amount of drug sample has been added in conical flask containing 20 ml of solvent. This conical flask was kept on rotary shaker for 24 hrs. After 24 hrs, the mixture was filtered using Whattman filter paper and analyze UV Spectrophotometrically at 205nm [3].

Calibration Curve of Clarithromycin: Estimation of standard calibration curve has been obtained by preparing various dilutions such as 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml, 60µg/ml, 70µg/ml, 80µg/ml, 90µg/ml, and 100 µg/ml and absorbance have taken of these dilutions and plotted a graph of absorbance vs.

Concentration and find out the linearity at 205nm. Calibration curve has estimated in distilled water, Phosphate buffer pH 6.8, 0.1N HCl [4].

Characterization of Clarithromycin by FT-IR Study: The drug Clarithromycin was subjected to FT-IR studies using KBr pellet technique. Drug was thoroughly mixed with 300mg of potassium bromide, compressed to a 2mm semi-transparent disk and placed in the light path for 2 min [5] the pellets were prepared on KBr press under hydraulic pressure of 150kg/cm^2. The spectrums were scanned over the wave number range 3600-400cm^{-1} at ambient temperature with resolution of 4 cm^{-1}.

Characterization of Clarithromycin by P-XRD Study: P-XRD pattern was obtained by weighing approximately 5-10mg of pure compound or the test formulation into a sample holder KBr disc. The measurement condition was as follows: Cu anode; Voltage 40 kv; Slit 0.2 mm; Scanning speed 0.002/2.4s, room temperature (25 ^{o}C).

To check for the presence/absence of crystalline drug, subsequently, the P-XRD traces of each pure drug, the solid dispersion and the binary and ternary inclusion complexes were compared with regard to peak position and the position and the presence and or absorbance of peaks [6].

Bitterness Value of Clarithromycin: Bitterness value determination is essential to obtain threshold concentration of bitterness of the active pharmaceutical Ingredient, which is Clarithromycin. In WHO guidelines, Quinine Hydrochloride was used as a standard [7].

Preparation of Stock Solution of Quinine Hydrochloride (SQ): 100mg of Quinine Hydrochloride (QH) dissolved in 100ml safe drinking water. Further diluted 1ml stock solution in 100ml safe drinking water as shown in **Table 1.**

TABLE 1: SERIAL DILUTION FOR INITIAL TEST

	1	2	3	4	5	6	7	8	9
SQ (ml)	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	5.8
Safe drinking water (ml)	5.8	5.6	5.4	5.2	5.0	4.8	4.6	4.4	4.2
QH in 10 ml of solution	0.042	0.044	0.046	0.048	0.050	0.052	0.054	0.056	0.058

Preparation of Stock Solution of Clarithromycin (SC): 100mg of Clarithromycin dissolved in 100ml safe drinking water.

Further, diluted 1ml stock solution in 100ml safe drinking water as shown in **Table 2.**

TABLE 2: SERIAL DILUTION FOR SECOND TEST

	1	2	3	4	5	6	7	8	9	10
SC (ml)	1	2	3	4	5	6	7	8	9	10
Safe drinking water (ml)	9	8	7	6	5	4	3	2	1	---

Mouth was washed with safe drinking water. Taste most diluted solution of stock solution of Quinine Hydrochloride for 30 sec. If the bitter taste no longer felt after 30 sec, then spit out the solution and waited for 1 min. The threshold bitter concentration may define as the lowest concentration at which the solution gives bitter sensation after 30 sec. After determining the lowest bitter concentration of initial test waited for 10 min. Now above same procedure has been followed for second test and determine the most inferior bitter sensation after 30 sec [8]. Calculated bitterness value of Clarithromycin in units per gram using following formula:

$$2000 \times C / a \times b$$

Where, a = the concentration of stock solution of quinine hydrochloride (SQ) in mg/ml. b = The volume of SC in tube with threshold bitter concentration. c = The quantity of quinine hydrochloride in mg in tube with threshold concentration.

Solubility Enhancement of Clarithromycin: Clarithromycin is water insoluble drug obviously it was insoluble in simulated saliva. For oromucosal route of administration, drug needs to dissolve in water or simulated saliva. So, there is need to enhance solubility of clarithromycin [9]. Enhancement of solubility of Clarithromycin has been carried out by Beta cyclodextrin as a inclusion complex by kneading method. This method could not enhance sufficient solubility then Drug and Beta cyclodextrin complex was lyophilized to improve more solubility.

Taste Masking of Clarithromycin: Clarithromycin is extremely bitter in taste, for oral administration; there is most important requirement to mask the bitter taste of Clarithromycin for patient compliance. In this research, the bitter taste of Clarithromycin has been masked by using an artificial sweetener named Aspartame, which is 200 times sweeter than sucrose and totally Diabetes Friendly [10].

Drug -Excipient Compatibility Study: Drug excipient compatibility has been studied by DSC, FT-IR and XRD studies.

Formulation of Clarithromycin Loaded Oral Wafers: Clarithromycin loaded Oral wafer was made by solvent casting method. All excipients were weighed accurately.

FIG. 2: FORMULATION PROCESS OF ORAL WAFER

In a beaker add water to polymer and dissolved it properly after it dissolved ultimately then add plasticizer and stir it vigorously add other ingredients and at the last add weighed quantity of drug in this solution. Then, keep it under probe sonicator for 15-20 min. Then resultant mixture was casted in square shaped moulds and dry it. Formulation steps are clearly explained in **Fig. 2** [11].

Evaluation of Clarithromycin Loaded Oral Wafers:

Organoleptic Test of Oral Wafers: Oral wafers are visually inspected and observed.

Thickness: Thickness of the oral wafer was measured by using Vernier calliper. This is helpful in determination of uniformity in thickness of the oral wafer. To obtain accurate thickness standard deviation of readings have taken [12].

Weight Variation: All wafers were weighed on electronic balance separately and weight each of 1.5cm × 2.5 cm wafer was noted down.

Tensile Strength: Maximum stress applied to a point at which the wafer specimen was broken which is calculated by load applied till failure it broke divided by cross section area of wafer as given in the following equation [13].

Tensile Strength = Load at Failure × 100 / Thickness of wafer × Width of the wafer

Folding Endurance: The folding endurance value of the wafer was determined by repeatedly folding wafer at the same place till it breaks or visible crack observed. The number of times the wafer was folded without breaking was calculated as folding endurance value and to get accurate value all readings determined by applying standard deviation [14].

Disintegration Time: 5 ml of simulated salivary solution was taken in petri plate and place oral wafer on the simulate salivary solution and noted the time required to disintegrate wafer totally. This taste was performed in triplicates, and standard deviation value has taken [15].

Surface pH: Oral wafer was placed on the petri plate and moisten the surface of wafer with water and note down the pH of the surface of wafer. Measurement of pH has been carried out by using digital pH meter [16].

% Drug Content: Total 9 wafers were taken from each batch, each wafer added in 10ml od Simulated salivary solution and kept in Rotary Shaker for 1hr. After 1 hr, each wafer containing solutions were evaluated by UV spectrophotometrically at 205 nm wavelength. Resultant absorbance was calculated and estimate drug content in percentage [17].

Taste Evaluation:

Spectrophotometric Method: A known amount of taste masked sample was mixed with 10 ml of distilled water in 10 ml syringe by revolving the syringe end to end, 5 times in 30 seconds then filtered through a membrane filter and determine concentration of drug in sample by UV Spectroscopically. If this concentration is below the threshold concentration, it may be results that the bitter taste would be masked.[18]

Panel Testing: In this method, a group of 5-10 human volunteers were trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness from 0-5Subsequently. Test solution is tasted and rated on the same scale to assess its bitterness. Report has been prepared by evaluating this results [19].

Dissolution Study of oral Wafer: The dissolution study was performed in USP type II (paddle type) apparatus. Dissolution was performed in jar of 900 ml of simulated salivary solution maintained at 37°C and 50 rpm. Withdrawn 5ml of sample at various time interval and replace same amount of fresh solvent simultaneously. Then all samples were evaluated spectrophotometrically at 205nm. Obtained results were expressed as mean of three determinations [20].

Antibacterial Test:

Preparation of fresh *S. aureus* Culture: In a beaker, sufficient amount of agar was taken and added required amount of distilled water, then boil it to obtain homogeneous mixture and kept in autoclave for sterilization. Poured this sterile agar mixture in hard glass test tube an kept it in slanting position till agar get cooled and hard. Then previously inoculated culture was taken and strikes with loop on agar slant in sterile condition. Kept these agar slant in incubator at 37°C for 24 hrs and got freshly growth of *S. aureus* culture [21].

Agar well Diffusion Method: In a beaker, sufficient amount of agar was taken and added required amount of distilled water, then boil it to obtain homogeneous mixture and kept in autoclave for sterilization. Cool this agar solution till 45°C. Add previously grown *S. aureus* culture in sterile saline water and stir it vigorously. Added this culture containing saline in cooled agar solution and appropriately shaken. Resultant mixture then poured in petri plated in sterile condition. Cool these plates at room temperature till agar get harden. Then a sterile hole of diameter 5mm-6mm punched and created well in these petri plates. In these well, sample solutions to test was poured and kept in incubator at 37°C for 24 hrs. After 24 hrs petri plates are observed [22].

RESULT AND DISCUSSION:

Preformulation Studies of Clarithromyci:

Organoleptic Observations: The visual inspection of CLA was done and observations were noted in **Table 3.**

TABLE 3: ORGANOLEPTIC OBSERVATIONS

Sr. no.	Parameters	Experimental Standard
1	Colour	White
2	Odour	Odourless
3	Taste	Unpleasant Bitter taste
4	Physical Appearance	Crystalline powder

All the observations declared in Table 4 comply with the standard.

Melting Point: The melting point of CLA was determined by using liquid paraffin loaded Thiel's Tube; obtained observations are reported in **Table 4.**

TABLE 4: OBSERVATIONS OF MELTING POINT

Sr. no.	Melting Point	
	Experimental	Standard
1	219 °C	216 °C - 220 °C

Melting Point of CLA was found to be 219 °C**,** which was within the range of standard melting point of 216-220 °C.

Solubilization of Clarithromycin in Water: The saturation solubility of CLA in water was found to be 0.35 mg/L is practically insoluble in water indicating that while the standard solubility was 0.33mg/L which belongs to category of poorly soluble drug of BCS class II.

Standard Calibration Curve of Clarithromycin: Standard calibration curve has taken in distilled water, PBS pH 6.8 and 0.1 N HCl and graphically represented in **Fig. 3.**

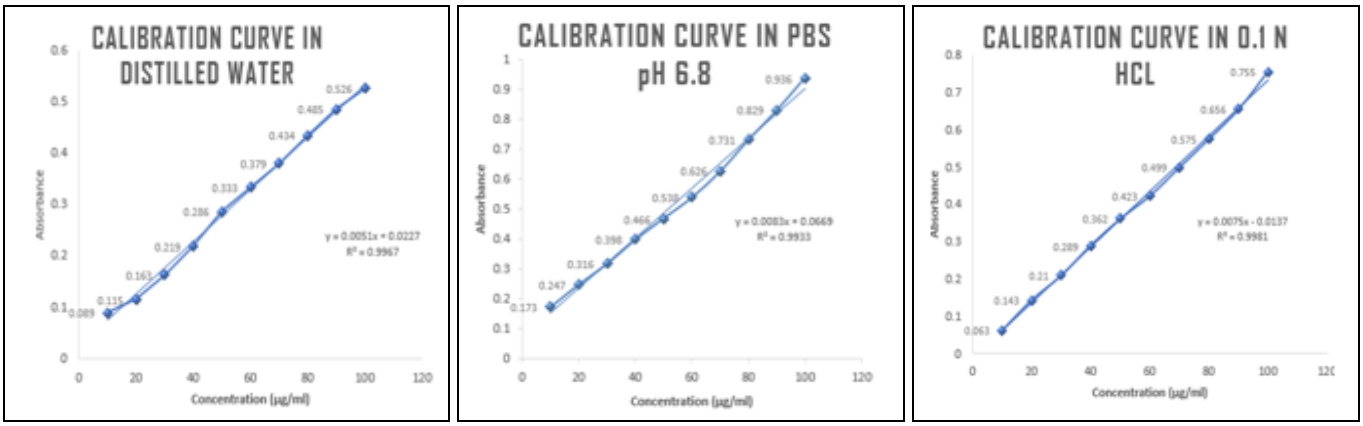
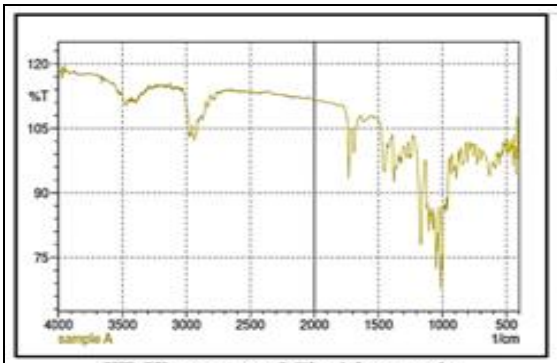


FIG. 3: STANDARD CALIBRATION CURVES IN DISTILLED WATER, PBS PH 6.8 AND 0.1 N HCL

FT-IR Spectroscopy of Clarithromycin: The frequencies are matching to the frequencies of functional groups present in composition as shown in **Fig. 4** and **5** so FTIR study is confirmatory for drug identification of purity of the compound.



Peak Frequency (cm^{-1})	Functional Group
1068.56	Sulfonic acid
1087.85	Sulfonamide
1107.14	Sulfoxide
1166.93	Sulfonyl Chloride
1377.17	Phenols
1454.33	Alkene-CH_3

FIG. 4: FT-IR SPECTRA OF CLARITHROMYCIN

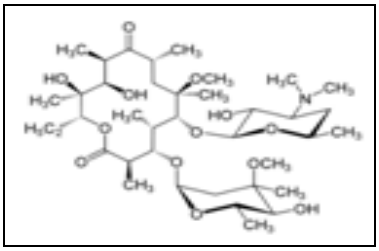


FIG. 5: CHEMICAL STRUCTURE OF CLARITHROMYCIN

Differential Scanning Calorimetry of Clarithromycin: Differential scanning calorimetric analysis was performed in order to establish melting point of drug Clarithromycin. The thermogram of pure drug Clarithromycin showed a sharp endothermic peak at 227 ^{o}C as shown in **Fig. 6.**

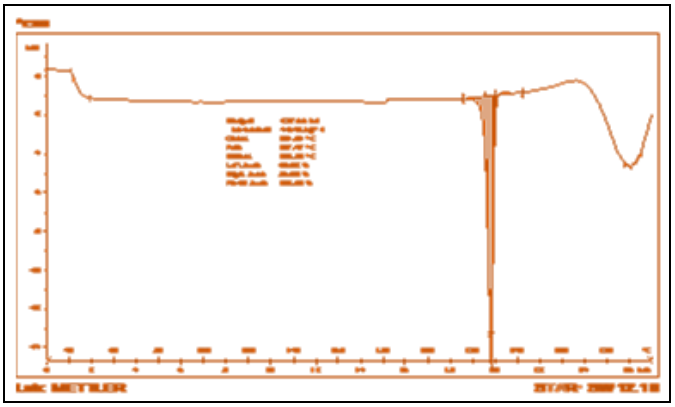


FIG. 6: DSC THERMOGRAM OF CLARITHROMYCIN

Powder X-Ray Diffraction Spectroscopy: P-XRD study is carried out of Clarithromycin. 2ɵ values were observed. It shows sharp peak which indicates the crystalline nature of the pure drug as shown in **Fig. 7.**

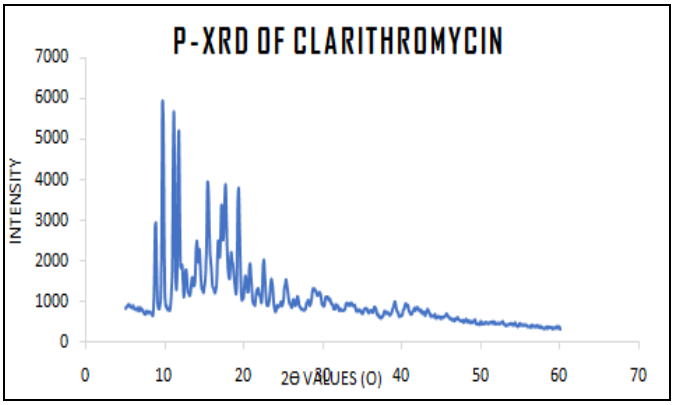


FIG. 7: P-XRD OF CLARITHROMYCIN

Threshold Bitterness Concentration of Clarithromycin: Threshold bitterness concentration of Clarithromycin has been found out 83 µg/gm. This value has been obtained by using the procedure as per WHO guidelines.

Solubility Enhancement of Clarithromycin: Solubility enhancement of CLA has been obtained by using lyophilization method with the mixture of drug and BCD complex.

TABLE 5: SOLUBILITY ENHANCEMENT OF CLARITHROMYCIN

API in artificial simulated saliva		Ratio Drug: BCD	API + BCD complex in artificial simulated saliva		API + BCD complex lyophilized in artificial simulated saliva	
Absorbance	Concentration Dissolved		Absorbance	Concentration Dissolved	Absorbance	Concentration Dissolved
0.228	19.409	1:1	0.108	11.09	0.649	72.18
		1:2	0.224	23.02	0.726	89.45
		1:3	0.435	44.34	0.916	102.30

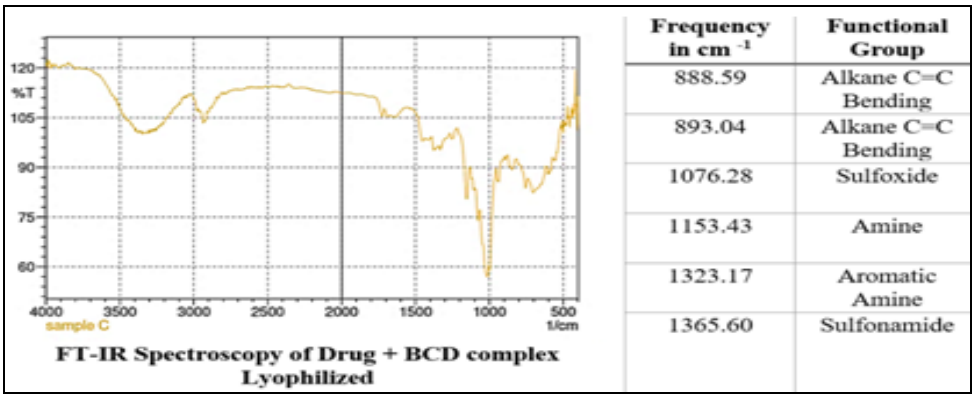
Enhancement of solubility was carried out by using lyophilization technique. There are total three batches were prepared and by observing the data of above three batches, 1:3 ratio have optimized due to the high solubility has observed in ratio 1:3. All results are noted in Table 5.

Taste Masking of Clarithromycin: CLA is extremely bitter in taste, for oral administration the most essential requirement is to mask the bitter taste of CLA for patient compliance. In this research, CLA has been complexed with BCD and further lyophilization leads to taste masking of drug in minimal amount which is not enough for oral mucosal administration of drug. Therefore, in formulation, artificial sweetener named Aspartame has been used as sweetening agent, which is 200 times sweeter than sucrose and totally Diabetes Friendly. This results in complete taste masking of bitter CLA in formulation which was evaluated using panel testing [23].

Drug -Excipient Compatibility Study:

FT-IR Spectroscopy Study: FT-IR spectra of drug, BCD, polymer and plasticizer shown same characteristics bands at same region and same range indicating that there is no interaction between drug and excipient. Graphical representation of IR spectra have presented in **Fig. 8** and **9.**

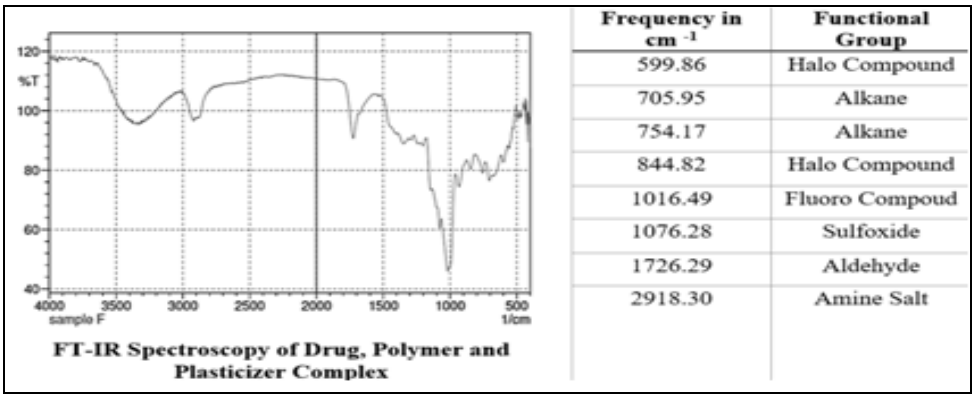
Drug + BCD Complex Lyophilized:



Frequency in cm $^{-1}$	Functional Group
888.59	Alkane C=C Bending
893.04	Alkane C=C Bending
1076.28	Sulfoxide
1153.43	Amine
1323.17	Aromatic Amine
1365.60	Sulfonamide

FIG. 8: FT-IR SPECTROSCOPY OF COMPLEX

Drug, Polymer and Plasticizer Complex:



Frequency in cm $^{-1}$	Functional Group
599.86	Halo Compound
705.95	Alkane
754.17	Alkane
844.82	Halo Compound
1016.49	Fluoro Compoud
1076.28	Sulfoxide
1726.29	Aldehyde
2918.30	Amine Salt

FIG. 9: FT-IR SPECTROSCOPY OF DRUG, POLYMER AND PLASTICIZER COMPLEX

Powder X-Ray Diffraction (P-XRD): The XRD pattern of Clarithromycin is shown in **Fig 7**. The x-ray powder diffractogram of pure drug exhibited a series peak which indicates crystalline nature of drug.

The 2 theta value for Clarithromycin was found 15, 18, 19, 20, 23, 30, 39 and 40. The x-ray powder diffractogram of Drug + BCD Complex shows amorphous in nature as shown in **Fig. 10** [24].

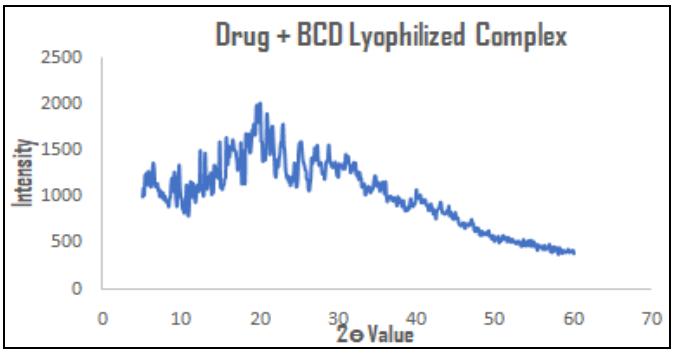


FIG. 10: X-RAY DIFFRACTION PATTERN OF DRUG + BCD LYOPHILIZED COMPLEX

Drug + BCD Lyophilized Complex:

Differential Scanning Calorimetry Study: Differential scanning Calorimetric spectra was observed to check incompatibilities. Endothermic peak at 227 °C observed in drug BCD lyophilized complex has shifted at 93.92 °C and melting point has been reduced as shown in **Fig. 11** [25].

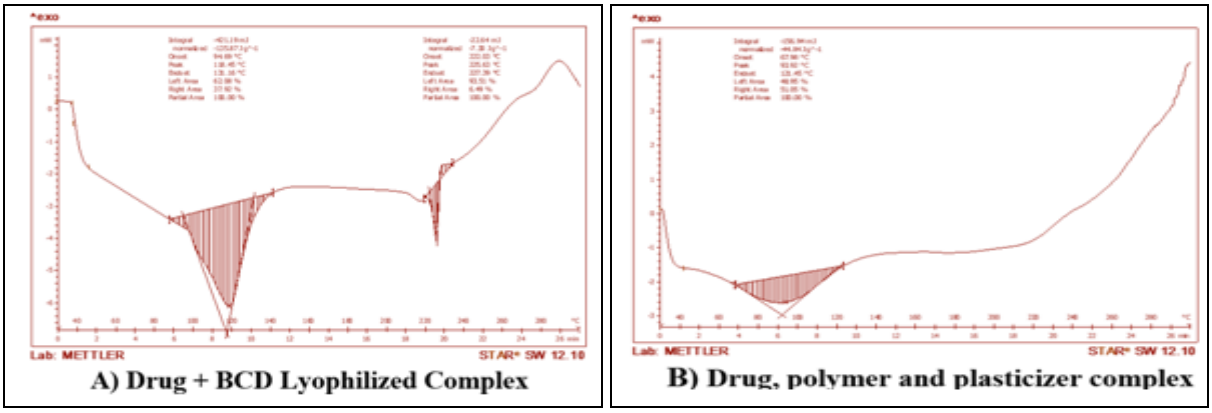


FIG. 11: DSC SPECTRA OF A) DRUG AND BCD LYOPHILIZED COMPLEX B) DRUG, POLYMER AND PLASTICIZER COMPLEX

Formulation of Clarithromycin Loaded Oral Wafers: Formulation of Clarithromycin loaded oral wafers are made by using the formula as mentioned in **Table 6** and the method of preparation has mentioned in **Fig. 2.**

TABLE 6: FORMULATION TABLE FORCLARITHROMYCIN LOADED ORAL WAFERS

Sr. no.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	CLA+BCD Lyophilized Mix	250	250	250	250	250	250	250	250	250
2.	Pullulan	200	200	200	250	250	250	300	300	300
3.	Citric acid	70	70	70	70	70	70	70	70	70
4.	Aspartame	100	25	50	100	25	50	100	25	50
5.	PEG-400	180	200	150	180	200	150	180	200	150
6.	Colour and flavour	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Evaluation of Clarithromycin Loaded Oral Wafers:

Morphology of Oral Wafers: Oral wafers are visually inspected and observed. These are thin, paper-like rectangular dosage form in various colour with unit dose. Results are enlisted in **Table 7** and resultant image of oral wafers have shown in **Fig. 12.**

TABLE 7: MORPHOLOGICAL OBSERVATIONS OF ORAL WAFER

Batches	Stickiness	Shape	Colour	Odour
F1	Non-sticky	Rectangular	Red, Yellow	Flavoured
F2	Non-sticky	Rectangular	Red, Yellow	Flavoured
F3	Non-sticky	Rectangular	Red, Yellow	Flavoured
F4	Non-sticky	Rectangular	Red, Yellow	Flavoured
F5	Non-sticky	Rectangular	Red, Yellow	Flavoured
F6	Non-sticky	Rectangular	Red, Yellow	Flavoured
F7	Non-sticky	Rectangular	Red, Yellow	Flavoured
F8	Non-sticky	Rectangular	Red, Yellow	Flavoured
F9	Non-sticky	Rectangular	Red, Yellow	Flavoured

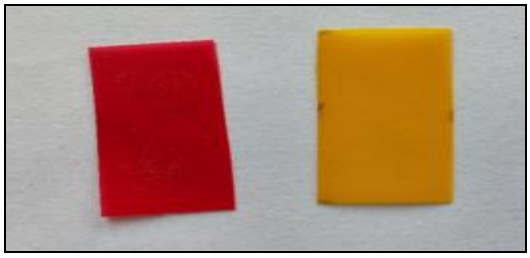


FIG. 12: IMAGE OF RESULTANT ORAL WAFER

TABLE 8: RESULTS FOR QUALITY OF ORAL WAFERS

Batches	Thickness (mm)	Weight Variation (mg)	Tensile Strength (gm/cm^2)	Folding Endurance in no of times	Dis-integration time (sec)	Surface pH	% Drug content	Taste
F1	0.06±0.02	37.12±0.85	89.46±1.02	7±01	14.05±0.58	6.87±0.03	99.89±0.16	Sweet
F2	0.11±0.01	42.67±0.19	90.66±0.15	8±01	16.10±0.34	6.64±0.05	97.08±0.89	Moderately Bitter
F3	0.07±0.02	39.04±0.95	90.18±0.25	6±01	14.22±0.59	6.91±0.10	99.19±0.58	Slightly Bitter
F4	0.13±0.01	46.16±1.28	91.86±0.50	5±01	17.19±0.00	6.44±0.00	96.78±0.14	Sweet
F5	0.12±0.01	45.74±1.39	91.41±0.25	4±01	19.05±0.58	6.68±0.71	97.11±0.15	Moderately Bitter
F6	0.10±0.02	40.06±1.57	90.64±0.50	5±01	16.57±0.10	6.87±0.07	97.46±0.07	Slightly Bitter
F7	0.14±0.01	49.73±2.01	92.66±0.25	2±01	19.30±0.00	7.34±0.0.97	98.01±0.71	Sweet
F8	0.13±0.02	47.19±1.64	92.08±0.10	3±01	20.45±0.30	6.59±0.04	96.77±0.34	Moderately Bitter
F9	0.15±0.01	51.57±0.11	94.02±0.10	2±01	18.15±0.00	6.30±0.10	98.58±0.13	Slightly Bitter

Thickness: Thickness of the oral wafer was measured by using Vernier calliper. This is helpful in determination of uniformity in thickness of the oral wafer. To obtain accurate thickness, values are noted using standard deviation. Thickness of oral wafer increases with increasing amount of polymer. The low values for standard deviation indicate physical uniformity of the wafer. Thickness values are noted in **Table 8.**

Weight Variation: Weight of all wafers is taken by using electronic digital balance. Weight of wafer gets increased with increasing polymer concentration. Results of weight variation are noted in **Table 8.**

Tensile Strength: As concentration of polymer increases viscosity also get increased. Increase in viscosity affects thickness and brittleness of the oral wafer. As the concentration of polymer and plasticizer increases, the tensile strength of the wafer increases. Results of tensile strength are shown in **Table 8.**

Folding Endurance: The folding endurance of the wafer was determined by repeatedly folding wafer at the same place till it breaks. The folding endurance was found to increase with the increase in polymer concentration. Folding endurance of wafer indicates the good physical and mechanical properties. Results of folding endurance are noted in the **Table 8.**

Disintegration Time: Disintegration time of oral wafer was found to be in the range of 14 second to 20 seconds which is shown in table. When disintegration time get decreases dissolution time also get faster as mentioned in **Table 8.**

Surface pH: Surface pH of oral wafers which have no significant difference was found in surface pH of all wafers and all were within the range of salivary pH.

The measured surface pH was found to be close to neutral in all the formulations which means have less potential to irritate the buccal mucosa. Results of surface pH are shown in **Table 8.**

% Drug Content: The % drug content were determined by using UV spectrophotometry. Maximum % drug content was found in batch F1 and F3 which is 99%. All results are shown in **Table 8.**

Dissolution Study of Oral Wafer: *In-vitro* drug release study has been carried out for all batches from F1 to F9 to observe the drug release pattern of the oral wafer. It was observed that drug release has been decreased with the increase in polymer concentration. The maximum drug release has been found 99.01 % in F1 batch. % cumulative drug release has been shown in the **Table 9** and graphically represented in **Fig. 13.**

TABLE 9: % CUMULATIVE DRUG RELEASE

Time (Sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	20.03	17.02	21.982	12.02	14.98	13.82	10.45	11.98	10.15
30	53.10	51.94	50.13	51.02	50.45	48.05	49.13	46.99	48.15
45	89.15	83.48	88.97	73.01	78.26	75.82	75.61	70.65	72.98
60	99.01	94.37	98.78	89.45	86.75	87.15	81.25	82.01	81.84
75	99.98	96.01	98.47	93.18	88.02	92.15	92.76	90.52	89.73

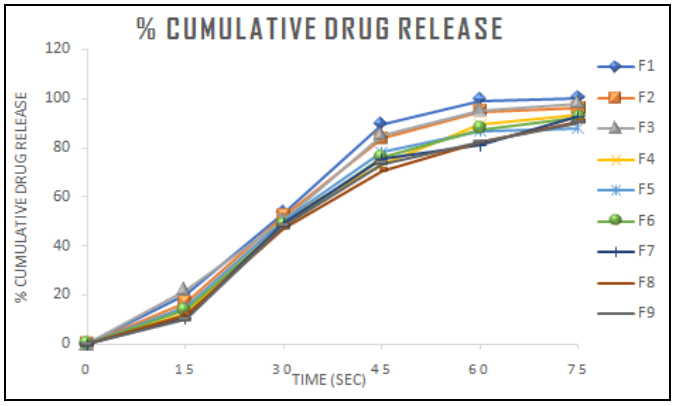


FIG. 13: GRAPHICAL REPRESENTATION OF % CUMULATIVE DRUG RELEASE

Dissolution study of all batches from F1 to F9 was carried out and from obtained results, it was concluded that drug from oral wafer was utterly dissolve within 60 sec.

Model Fitting:

TABLE 10: DISSOLUTION MODEL FITTING

Model Fitting	R	k
Zero order	0.9640	68.1984
T-test	7.248	(Passes)
Matrix	0.9470	503.2431
T-test	5.894	(Passes)
Peppas	0.9702	55.0265
T-test	8.005	(Passes)
Hix.Crow.	0.6936	-0.0776

Dissolution model fitting has observed using PCP Dissolution software which shows passing zero order model which represents matrix tablets with low soluble drugs, Matrix model represents that drug dispersed uniformly in polymer matrix and Peppas model indicates that its release mechanism is not well known or more than one phenomenon could be involved Results are mentioned in **Table 10.**

Taste Evaluation:

Panel Testing: Taste evaluation has been carried out by panel tasting. Five healthy human volunteers were selected and were ask to taste the prepared dilutions of sample and denote numbers from 0-4 for their intensity of bitterness. Results are shown in the **Table 11.**

TABLE 11: PANEL TESTING FOR INTENSITY OF BITTERNESS OF FORMULATION

Batches	Number of Volunteers					Average Number Assigned by Healthy Volunteer	Taste
	1	2	3	4	5		
F1	4	3	4	4	3	4	Sweet
F2	3	2	1	2	2	2	Moderately Bitter
F3	3	3	2	3	3	3	Slightly Bitter
F4	4	2	4	4	3	4	Sweet
F5	1	2	2	2	2	2	Moderately Bitter
F6	3	3	1	2	3	3	Slightly Bitter
F7	4	4	4	3	4	4	Sweet
F8	2	1	2	1	2	2	Moderately Bitter
F9	2	3	3	2	3	3	Slightly Bitter

From above results, formulations of batch F1, F4, and F7 were found complete masking of bitter taste of drug loaded in oral wafer. Formulations from batch F2, F5 and F8 shows moderately bitter taste of oral wafer and formulations from batch F3, F6 and F9 shows Slightly bitter taste of oral wafer.

Spectrophotometric Method: This method has been used to check the intensity of bitter taste by UV spectroscopy. The concentration was found to be varying which were obtained from slope value obtained by calibration curve and are listed in **Table 12.**

TABLE 12: RESULTS OF SPECTROPHOTOMETRIC METHOD OF TASTE EVALUATION

Sample	Absorbance	Concentration (µg/mL)
Drug+BCD Lyophilized	0.294	27.361
Formulation	0.186	14.349

Spectrophotometric method shows concentration of drug + BCD lyophilized complex and optimized formulation (F1) was below threshold concentration, which is 83 µg/ml as mentioned in 9.1.8. This indicates the bitter taste has masked.

Antibacterial Test: This test has performed by well diffusion method where the plate observed antibiotic loaded oral wafer showed to be resistant towards bacteria as shown in **Fig. 4.**

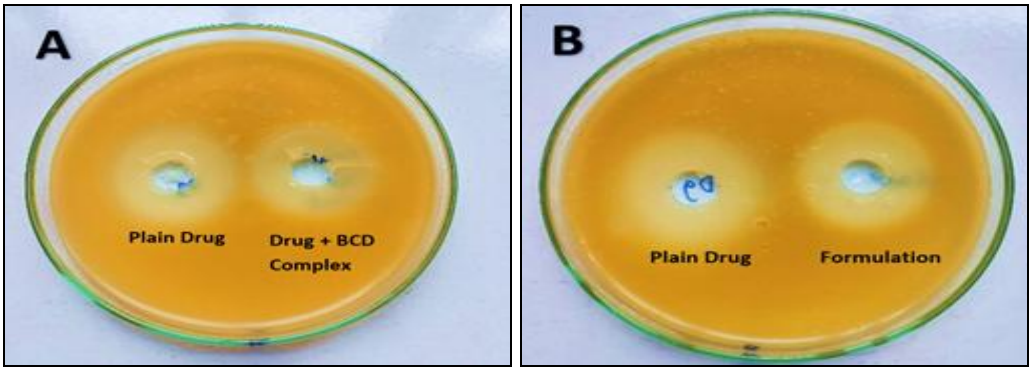


FIG. 14: ANTIBACTERIAL ACTIVITY OF A) DRUG AND BCD COMPLEX B) FORMULATION (ORAL WAFER) COMPARISON WITH PLAIN DRUG

Drug and BCD complex as well as formulation both created inhibition zone around the well which conclude the antibacterial activity of drug and BCD complex as well as oral wafer (formulation). This inhibition zone declared that drug BCD complex and formulation both have capacity to inhibit the growth of bacteria.

Field Emission Scanning Electron Microscopy (FESEM): The FESEM study has been carried out to observe surface morphology of oral wafer at 500x, 1000x, 2000x and 5000x magnifications as shown in **Fig. 15.**

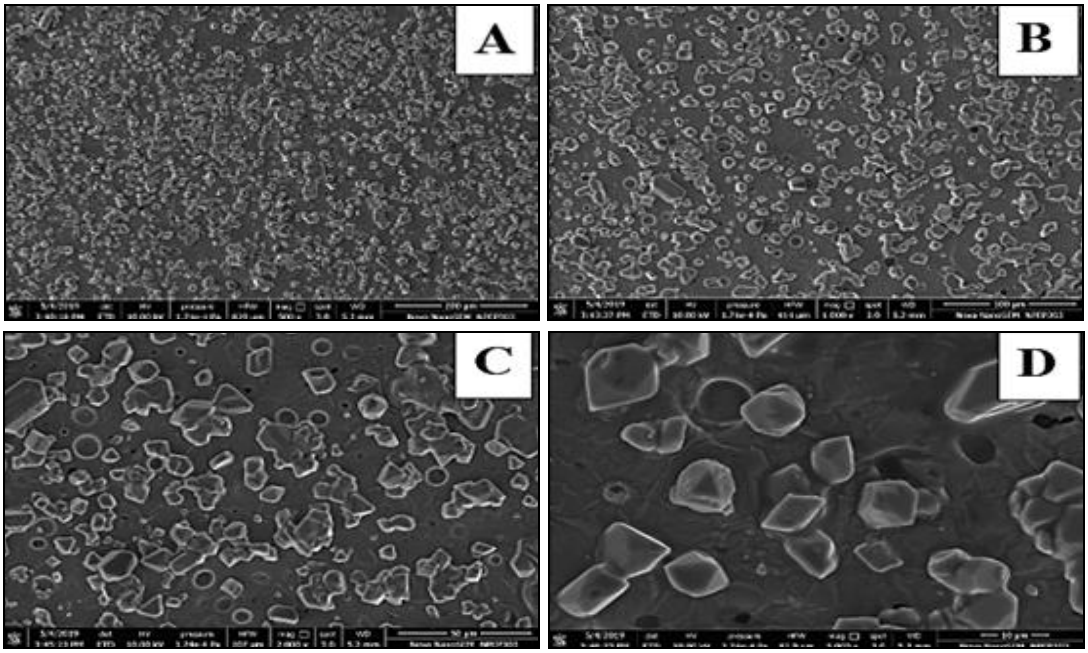


FIG. 15: SEM OF OPTIMISED BATCH AT A) 500X B) 1000X C) 2000X D) 5000X

Integrity of structure was observed under scanning electron microscopy and found to be intact and smooth surface which indicates the uniform distribution of the drug and polymer in the optimized oral wafer.

***Ex-vivo* Permeation Study:** Permeation study of drug from optimized formulation (F1) by oral mucosal route is an important parameter to study the amount of drug diffuses from oral mucosal route into the systemic circulation [25]. This study was performed by Franz diffusion cell using egg membrane as a diffusion membrane. Obtained results are shown in **Table 13** and graphically represented in **Fig. 16.**

TABLE 13: RESULTS OF *EX-VIVO* PERMEATION STUDY OF OPTIMIZED FORMULATION (F1)

Time (min)	% Drug Release
0	0
2	15.01
4	23.17
6	41.08
8	58.38
10	64.64
12	78.23
14	97.28

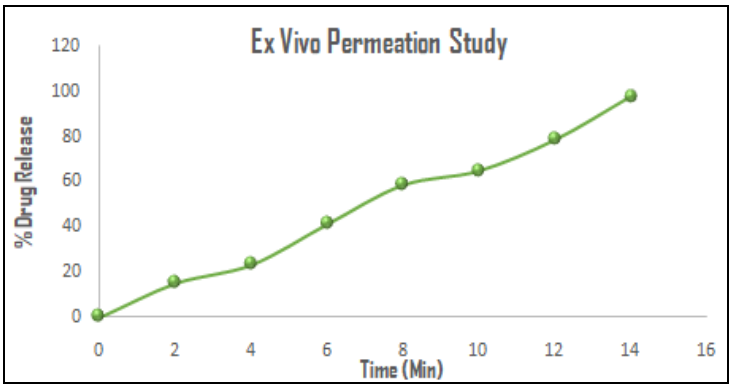


FIG. 16: GRAPHICAL REPRESENTATION OF *EX-VIVO* PERMEABILITY STUDY

According to above obtained results of *ex-vivo* permeation study, drug disintegrates in oral mucosa and takes around 15 min to diffuse in systemic circulation through oral mucosal route.

Accelerated Stability Study of Oral Wafer: Accelerated Stability study of oral wafer was performed at 40±2°C and 75±5 % RH for a month. As per above results, from 9 batches (F1-F9), F1 has been optimized for better mechanical strength, disintegration time and rapid drug release as well as better taste masking. Formulation batch F1 was kept for accelerated stability study for a month. While accelerated study and after accelerated study some test has performed to understand whether there are any changes occurred in characteristics of oral wafer. All results are mentioned in below **Table 14** and drug release profile of oral wafer was evaluated and mentioned in **Table 15** and graphically represented in **Fig. 17**. All results of accelerated stability study of oral wafer do not show significant difference than initial results obtained. This concludes the antibiotic loaded oral wafer is stable.

TABLE 14: RESULTS OF VARIOUS CHARACTERIZING PARAMETERS OF ORAL WAFER AFTER ACCELERATED STABILITY STUDY

Time	Visual Inspection	Disintegration Time (second)	Weight Variation (mg)	% Drug Content
Initial	Pink	14.05±0.58	37.12±0.85	99.89±0.16
After 15 Days	No Decolouration (Pink)	14.52±1.02	37.06±0.22	99.01±0.57
After 30 Days	No Decolouration (Pink)	14.98±0.80	36.97±1.09	98.93±1.01

TABLE 15: RESULTS OF % DRUG RELEASE AFTER ACCELERATED STABILITY STUDY OF ORAL WAFER

Time in Seconds	% Drug Release		
	Initial	After 15 Days	After 30 Days
0	0	0	0
15	20.03	16.81	15.86
30	53.1	49.21	50.4

45	89.15	86.91	85.34
60	99.01	98.9	96.08
75	99.98	99.05	98.46

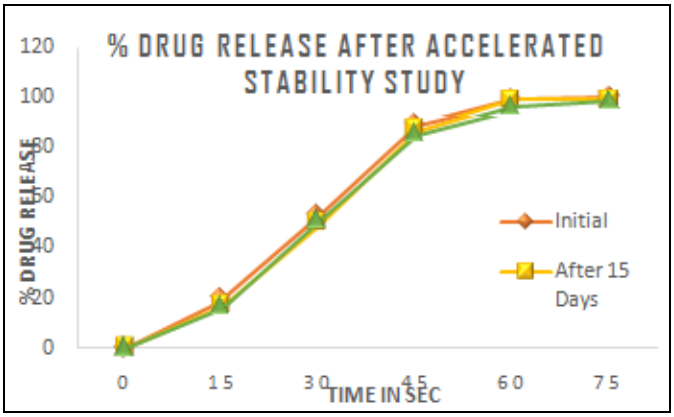


FIG. 17: GRAPHICAL REPRESENTATION OF % DRUG RELEASE AFTER ACCELERATED STABILITY STUDY OF ORAL WAFER

CONCLUSION: There were total three challenges during this research, they are as follows: Solubility of drug, Taste masking of drug and Incorporation of high dose in an oral wafer.

Solubility of Clarithromycin was improved by complex with BCD in various ratios in which 1:3 ratio shows more improved solubility in simulated saliva so 1:3 ratio complex was optimized for formulation of oral wafers.

Taste masking of Clarithromycin was another challenge for this research. Masking of bitter taste of drug in small amount was obtained by complexing drug with BCD which was carried out for enhancing solubility. After complexing drug with BCD, masking of bitter taste was not enough for oral mucosal administration. Therefore, in formulation of oral wafer aspartame was used as a sweetening agent which mask the bitter taste of drug in formulation.

Total nine batches (F1-F9) of oral wafers were formulated by solvent casting method and evaluated using various evaluation parameters for understanding quality and drug release pattern of the formulation. From which F1 batch was optimized on the basis of disintegration time of formulation, quality of wafer, dissolution of drug in simulated saliva and masking of bitter taste of drug.

Optimized batch F1, disintegrates within 14 sec. % cumulative drug release was found 99.89% within a minute and it tastes sweet due to sweetening agent. This formulation permeates through oral mucosal route and reaches to systemic circulation within about 15 min.

Hence, from the present investigation it can be concluded that antibiotic loaded flash release oral wafer can be a potential novel dosage form as an antibiotic.

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CONFLICT OF INTEREST: No Interest

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