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FORMULATION AND EVALUATION OF DENTAL CONES FOR THE TREATMENT OF PERIODONTITIS

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Abstract: - Dental problems are a serious public health concern in every country, affecting people of all ages, races, and genders. In recent years, the prevalence of oral illnesses has risen dramatically. Dental disorders affect over 70% of the population. The majority of oral disorders, such as periodontal infections, tooth caries, and dry socket, afflict the general population. Periodontal disease is one of the most common dental disorders, and it is caused by a gram-negative pathogenic bacterium of the periodontal pocket, which is characterized by inflammation of the subgingival plaque and degeneration. Periodontal are made up of alveolar bones, teeth, dental cementum, and periodontal ligaments. All these surrounding tissues are destroyed in severe cases and requires tooth extraction. The aim of this study is that if a soft moldable gummy material containing antibacterial drug are formulated in the form of dental cones which are used in treatment of periodontitis. Azithromycin dihydrate is used for formulation of dental cones. Different physicochemical evaluation studies such as surface pH, swelling index, and in vitro drug release study and antibacterial study were carried out. Further, FTIR and DSC studies revealed stability and compatibility between drug and polymers .In F9 formulation highest Percentage swelling was found 21.87±0.25%. Cumulative Drug release of F9 formulation was found to be 95.17%. Antibacterial study was carried out by disc diffusion method on *E.Coli* shows good antibacterial activity. The stability studies of optimum formulation F9 revealed that there is no significant change in drug content and surface pH was observed over period of 1 month.

Keywords:- azithromycin dihydrate, dental cones, swelling index, in vitro drug release. Antibacterial study.

INTRODUCTION: - Periodontitis is derived from two terms: "**peri**" means around, "odont" means tooth, and "**itis**" means inflammation [1]. Periodontal diseases are infections of the gums, periodontal ligament, and alveolar bone, which surround the teeth [2]. Chronic periodontitis, aggressive periodontitis, systemic disorders linked periodontitis, and necrotizing periodontitis are all types of periodontal diseases [3]. These chronic oral inflammatory conditions can spread throughout the body and impact diabetes, cardiovascular disease, and infective endocarditis, among other things [4.]. In periodontal disease there is a formation of gap between gums and teeth which called as '**pockets.** This pocket provides an ideal habitat for anaerobic pathogenic bacteria to develop and multiply. Clinically, the periodontal pocket, which is slightly deeper than the sulcus of a healthy tooth, deepens as the condition advances, resulting in additional damage of the tooth's supporting tissues and, in many cases, tooth loss. The colonization of the subgingival area by bacteria is the main etiological factor in the development of inflammation and tissue damage [5]. mechanical cleaning like as scaling and root planning (SRP) and systemic or local administration of antimicrobial drugs, are current periodontal therapy which aims to heal inflammatory tissue, eliminate the depth of diseased pockets, lower the quantity of pathogenic bacteria, and stop bone resorption[6] . Although systemic antibiotic therapy is useful, high oral doses are needed to acquire effective concentrations in the gingival crevicular fluid (GCF), and long-term dosing may lead to resistance. While mouth washes, gels, and toothpastes require a lower dose, they only control dental plaques and mucosal infections.

Furthermore, in order to ensure effectiveness, such local delivery methods necessitate a high initial concentration and numerous administrations [7]

To avoid the limitations of both systemic and localized drug delivery, controlled release devices for intrapocket administration have been proposed [8]. These devices can directly target the bacteria that are multiplying in the pockets. However, all these therapies are beneficial at initial stages of disease to treat and prevent further infection. in other cases, such as severe periodontitis, previous attachment loss may make it difficult to reach such therapeutic goals, and periodontal treatment may not be enough to restore tooth health and function. Teeth with periodontal disease should be removed in these cases [9]. After extraction of infected teeth, a bioresorable substance is required to heal the surrounding tissues and prevent bacterial infection. Here attempt as to made to formulate a biodegradable polymer containing dental cones which can be placed in an empty socket. The purpose of dental cones is to heal the infected area, to inhibit the bacterial in surrounding area of teeth. These cones can also useful in dry socket condition. For formulation of dental cones Azithromycin dihydrate were selected. Azithromycin is a first and most important member of new class of antibiotics known as azalides, used for aerobes and anaerobes found in periodontal pocket. Azithromycin is commonly used for a wide variety of mild-to-moderate bacterial infections caused by susceptible strains of the designated microorganisms in the specific conditions: *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*[10]. It exhibits bacteriostatic activity by blocking synthesis of bacterial proteins. Tissue concentrations of azithromycin may reach 100 to 1000 times that of blood and persist long after blood levels have declined because of their significant post-antibiotic effects. The tissue concentration of azithromycin may exceed the microorganism's MIC for 2 to 10 days and the elimination ½ life in abscesses is 4 days. It shows high concentration in periodontal tissues, GCF and in saliva. It can be used for treatment of advanced, chronic or aggressive periodontitis[11]. Gelatin, a natural protein derived from the hydrolysis of collagen, is highly biocompatible and biodegradable in a physiological environment. In dental formulation gelatin is used as is a topical hemostatic that helps to speed up and stabilise the production of clots in wounds and bleeding locations. Because of its porosity, flexibility, and biocompatibility, it can be utilised as a scaffold or a carrier for medicinal substance that can be administered within wounds with osseous defects to promote bone repair and speed wound healing[12].

2. MATERIAL AND METHODS: -

2.1 A gift sample of Azithromycin Dihydrate was obtained from Century Pharmaceuticals sayijigunj, Vadodara. Gelatin and sodium alginate, dihydrogen potassium phosphate, and sodium hydroxide from Research-Lab Fine Chem Industries, Mumbai, and PEG400 from Loba Chemie.

2.2 Method: - Natural biodegradable polymers were used for the preparation of dental cones, in which weighed quantity of gelatin was dispersed in sufficient amount of distilled water and kept aside for 30 minutes to hydrate. After hydration it is subjected to continuous stirring at a water bath at 60^0C was maintained until gelatin was dissolved. The above solution was then introduced with co-polymer, sodium alginate and PEG 400 as solubility enhancer, and stabilizer with continuous stirring. Drug was dissolved separately in small quantity of ethanol and added to the polymeric solution for homogenous mixing. After complete mixing for about 15 minutes, the solution was slowly poured into the mould. The solution is then allowed to stand for 5 minutes without any further disturbances. Then the Mould were placed on ice bath for 30 minutes to set. The formulated dental cones were stored at 4^0C in refrigerator until further use. Each cone contains 25 mg of azithromycin dihydrate.

Formulation Batches of Dental Cones

Ingredients (w/w)	Batches code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Azithromycin dihydrate (g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Gelatin (g)	0.65	0.7	0.75	0.65	0.7	0.75	0.65	0.7	0.75
Sodium alginate(g)	0.05	0.05	0.05	0.1	0.1	0.1	0.15	0.15	0.15
Polyethylene Glycol 400(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium benzoate(g)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Distilled water q.s.(ml)	10	10	10	10	10	10	10	10	10

2.3 DRUG EXCIPIENT COMPATIBILITY STUDY.

2.3.1 FT IR spectroscopy: FT IR spectra for pure drug and polymer at room temperature using FT-IR spectrophotometer (FTIR-8400S, Shimadzu, Japan) in transmittance mode. The samples were ground in a mortar, mixed with Nujol and placed between two plates of KBr and compressed to form a thin film. The sandwiched plates were placed in the infrared spectrometer and the spectra were obtained. Scanning was performed between wave numbers 4000-400 cm-1.

2.3.2 DSC:- The compatibility between drug and polymers were determined by differential scanning calorimetric (DSC). The thermal behavior of pure drug and polymer was studied at heating rate of 10°C min^{-1} from 25°C to 400°C in a hermetically sealed pan with a pinhole in the lid under a nitrogen purge of 20 ml min^{-1}.The differential scanning calorimetry analysis gives an idea about the interaction of various materials at different temperature.

2.4 Standard Calibration Curve of Azithromycin dihydrate in Phosphate Buffer pH 6.8

Weigh accurately 10mg of pure drug and transfer it in to 100ml volumetricflask and make up volume upto 100ml labeled the flask with 6.8 Phosphate buffer. labelled it as stock solution-I.(100mcg/ml). Then pipette out 2 ml, 4 ml, 6 ml, 8ml and 10ml from stock solution- I and make up volume upto 10ml. to make the resultant concentration in the range of 2, 4, 6, 8 & 10mcg/ml respectively. All dilutions are made with pH 6.8 Phosphate buffer. Take the absorbance of all dilution at 208 nm by using UV-Visible spectrophotometer.[13]

2.5 EVALUATIONS: -

2.5.1 Surface pH: The cones were first allowed to swell in contact with 5 ml of distilled water (pH 6.5 ± 0.05) for few minutes. The surface pH was noted by bringing a combined glass electrode near the surface of cones and allowing it to equilibrate for one minute. The surface pH of the dental cones was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the mucosa, hence attempt was made to keep the surface pH close to the neutral pH [14].

2.5.2 Swelling Index: - Dental cone were weighed (W1) and allowed to swell on a petridish in phosphate buffer, pH 6.8 at 37± 0.5°C 10 ml for 30 mins. Then cone was taken out and excess fluid was removed with filter paper. Then the weight (wet weight) of the formulation was taken and recorded. When the weight became constant. (W2), the weight taken was used for calculating the swelling index (S.I) [15].

Swelling index was calculated from following equation.

Swelling index = (W2- W1 / W1) ×100

Where

SI (%) is percent swelling.

W2 is the final swollen cone weight.

W1 is the initial weight of the cone.

2.5.3 Drug Content Estimation: - Drug content uniformity was determined by dissolving the dental cone in 10 ml of phosphate buffer (pH 6.8) for 1h under occasional shaking. The 1 ml solution was withdrawn and diluted with phosphate buffer pH 6.8 up to 10 ml, and the resultant solution was filtered through a whatman filter paper. The drug content was then determined after appropriate dilution at 208 nm using a UV spectrophotometer (Shimadzu, 1800, Japan) [16].

2.5.4 In vitro Drug Release: The pH of gingival fluid varies from 6.5 – 6.8, so 6.8 phosphate buffer is used as simulated gingival fluid. In addition, because the dental cones should be immobile in the periodontal pocket, and in oral cavity there is a continuous flow of saliva is occurred. So, to maintain the flow a peristaltic dissolution model is adopted for in vitro drug releases studies. This method is closely related to flow through method USP 4 apparatus operated in open-loop mode is capable of maintaining a continuous flow of fresh dissolution medium Ph 6.8, thus, maintaining infinite sink conditions. By peristaltic pump the dissolution fluid is flow at 4ml/mins, $37^0.5^0$C directly on dental cone which are placed on glass slide in beaker. Samples were taken at predetermined intervals, filtered, and analyzed by UV [17].

2.5.5 Antibacterial Study: -

Disc diffusion method: - Antimicrobial activity of formulation was performed by using disc diffusion method on *E.coli*. Firstly, nutrient agar media was prepared for the growth of bacteria. After that, autoclave for a 15 mins at a specific temperature to sterilize the nutrient media. Then transfer the needed quantity of nutrient media into the petri dish. After solidification of media inoculation of bacteria was done in an aseptic condition and the test micro-organism were inoculated by the spread plate method.

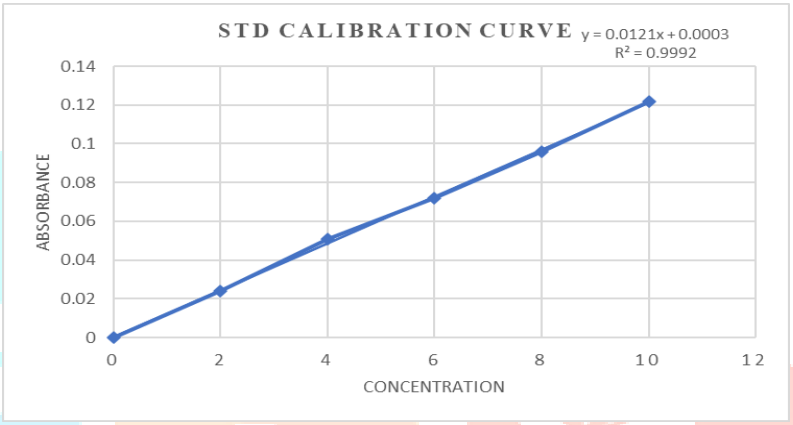
Then standard and test sample was prepared with different concentration. Std sample contains pure drug and test sample were prepared by dissolve the dental cones and then different dilution of 1,2,5 10 ug/ml were prepared. The sterile disc is soaked in different concentrations of test and std sample and then placed in the prepared agar plates. Each disc was placed down and uniformly dispersed to achieve appropriate contact with the surface of the agar. After that, the agar plates were incubated for 24 hours at 37°C. Each plate was evaluated after 24 hours of incubation. The outcome was a consistently circular zone of inhibition with a confluent lawn of growth.

The diameter of the zone of inhibition was measured.[18,19].

2.5.6 Stability study: - Formulation batch F9 has shown best results amongst all 9 batches. So, stability study was carried out on formulation batch F9. The stability of the formulation was studied against temperature change at 2-8^{0}C, 15 ^{0}C and 25^{0}C respectively for the period of one month and evaluated after one month [20].

3. RESULT AND DISCUSSION

3.1.1 Std calibration curve of azithromycin dihydrate in phosphate buffer 6.8 pH at lamda max 208



Graph No. 3.1: Standard calibration curve of azithromycin in pH 6.8 Phosphate buffer.

The standard calibration curve of drug obey's beer law in concentration range of 2, to 10 µg/ml in phosphate buffer pH 6.8 drug show good linearity with regression of coefficient R2 = 0.9992 and equation for this line obtained was found to be y = 0.0121x which is used in calculation of amount of drug and in vitro drug release study.

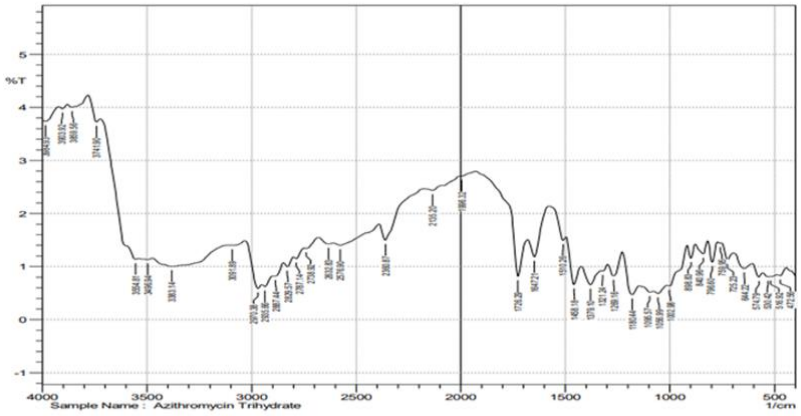
3.1.2 Fourier Transform Infrared Spectroscopic Studies: -The samples were scanned in the region of 4000–400 cm−1 for FTIR studies. Pure azithromycin dihydrate showed characteristic peaks.

Table no: - 3.1 FTIR Interpretation of Drug

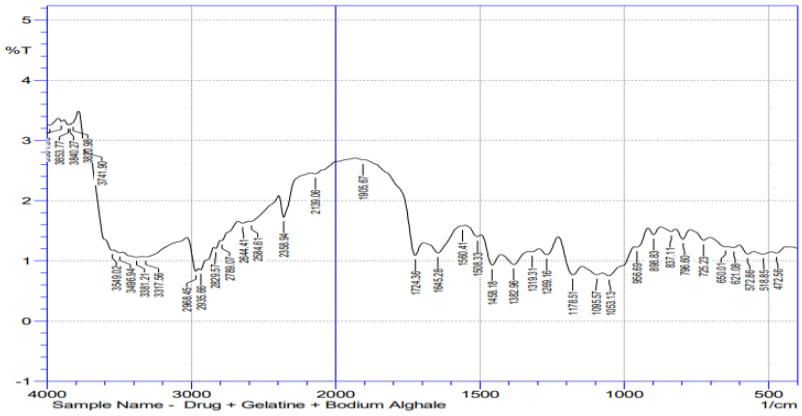
Sr. No.	Functional groups	Frequency (cm^{-1})
1	C-O	1379.10
2	C=O	1726.29
3	N-H	3984.93
4	C-H(Aromatic)	2970.38
5	O-H	1180.44

Table No. 3.2 FTIR Interpretation of Drug with polymers

Functional Groups	Frequency (cm^{-1})
N-H	3853.77, 3317.56
C-H	2968.45, 2935.66, 2829.57
C=O	1724.36, 1645.28,
O-H	1178.51, 3549.02
C-O	1382.96, 1095.57



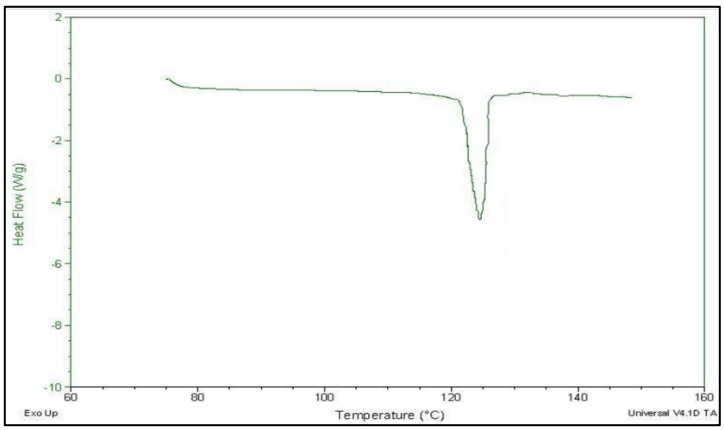
Graph No 3.2: FT-IR Spectra of azithromycin dihydrate



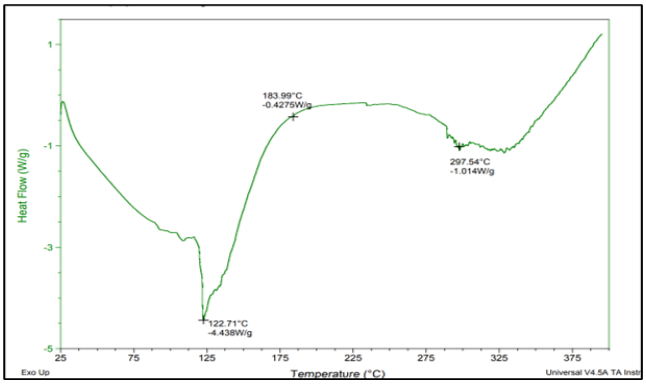
Graph No 3.3: - FT-IR Spectra of physical mixture of Drug with polymer

The FT-IR spectrum of pure drug was obtained to be similar to the reference standard FT-IR spectrum of Azithromycin given in IP Pharmacopoeia graph. Compatibility study of drug with polymers was performed. All the characteristic peaks of azithromycin dihydrate were appears in spectra which are representing that compatibility between drug and excipients. No change in the peaks of drug in the mixture of polymers. Hence there is no interaction between pure drug and polymers. It means that all the polymers are compatible with drug.

3.1.3 DSC: - The thermal analysis of drug was studied using Differential scanning calorimetry (DSC). In graph 3.4 Azithromycin dihydrate have shown melting sharp endotherm at 125^{0}C, which is in range of its melting point. DSC studies were performed to characterize the solid state of drug and polymers. The figure (graph3.5) exhibits total three endothermic peaks. Azithromycin shows sharp peak at 122.71^{0}C which is closed to its melting point. The sharp melting peaks exhibited by drugs confirm their existence as crystalline. Gelatin shows endothermic peak at 183.99^{0}C and sodium alginate shows peak at 297.54^{0}C. Physical mixture of azithromycin with polymers showed the presence of characteristic peaks of drug, indicating physical compatibility between excipients.



Graph 3.4 DSC of Pure Drug



Graph 3.5 DSC of Drug with polymers

3.1.4 Surface PH: - The surface pH of formulated batches was found to be in the range of 6.34±0.18 to 6.74±0.15 for all formulations were almost within the range of salivary pH i.e. 6.1 to 6.74 The details of values are included in the Table No: -3.3

3.1.5 Swelling Index: -The swelling index was determined in terms of percentage water uptake at 37°C.In Fig no: -3.6. swelling index of formulates batches F1-F9 are given. The results show that the highest percentage swelling of formulation F9 was found to be 21.87±0.25%. In tab no: - 3.3 swelling index of all formulated batches are given.

3.1.6 Drug content: The drug content in the dental cones ranged from 88.26±0.54 to 94.54±0.52 %, indicating the favorable drug loading and uniformity with respect to drug content. The drug content detail values for all batches given in the Table No: -3.3

Table No: - 3.3

Batch codes	Surface pH (±SD)	% Swelling index(±SD)	% Drug Content(±SD)
F1	6.68±0.13	6.6±0.15	88.92±1.02
F2	6.56±0.11	9.67±0.11	90.90±0.88
F3	6.48±0. 16	13.3±0.25	89.25±0.63
F4	6.44±0.13	10.28±0.12	88.26±0.54
F5	6.74±0.15	11.42±0.15	90.57±0.64
F6	6.68±0.13	12.25±0.20	92.89±0.62
F7	6.44±0.13	15.62±0.25	91.90±0.86
F8	6.34±0.18	18.32±0.15	93.22±0.65
F9	6.68±0.13	21.87±0.25	94.54±0.52

n=3

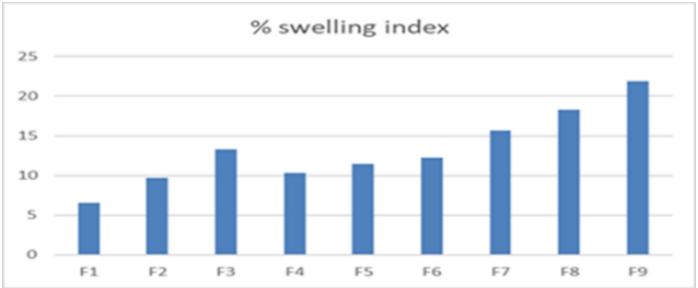


Fig no 3.6: -Bar graph of % swelling index of all batches

3.1.7 In vitro drug release: -The *in vitro* drug release of all batches was determined by using Peristaltic Pump. In F9 batch the release of drug was found in the range of 44.03 to 95.17%. The details of data are given in Table No 3.4, And graph is plotted in Graph No**:** -3.7

Table no: - 3.4 In Vitro Drug Release

	%Cumulative drug release CDR								
Time in mins	F1	F2	F3	F4	F5	F6	F7	F8	F9
00	00	00	00	00	00	00	00	00	00
10	13.22	16.00	24.25	36.45	37.12	29.94	33.47	38.75	44.03
20	34.50	41.40	39.34	45.07	48.46	50.47	53.39	54.73	60.16
30	52.89	60.61	53.93	67.76	68.64	66.66	68.35	72.60	71.63
40	75.67	78.61	72.17	79.69	81.05	75.72	79.29	81.83	83.56
50	86.23	84.22	82.77	84.83	86.10	84.34	82.94	85.42	87.11
60	90.47	90.62	88.30	90.92	90.41	91.19	89.38	93.10	95.17

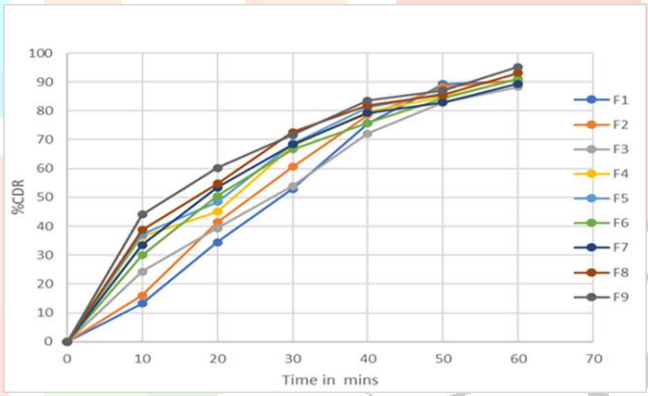


Fig no: - 3.7: -%Cumulative Drug Release

3.1.8 Antibacterial study: - The diameter of zone of inhibition was measured and the value was shown in the table no 3.5

Table no: - 3.5 Antibacterial activity (zone of inhibition)

	Standard Sample (ug/ml)				**Test Sample (ug/ml)**			
Zone of inhibition	S1	S2	S3	S4	T1	T2	T3	T4
	1	2	5	10	1	2	5	10
	3mm	4mm	8mm	11mm	5mm	7mm	10mm	14mm

After 24hrs of incubation, the diameter of zone of inhibition was measured and it was compared with the standard drug diameter. It shows better antibacterial activity over that micro-organism. The zone of inhibition of standard and test sample of different concentration was measured by agar disc diffusion method as shown in the following figures:

Fig no: -3.8 zone of inhibition of test and std sample

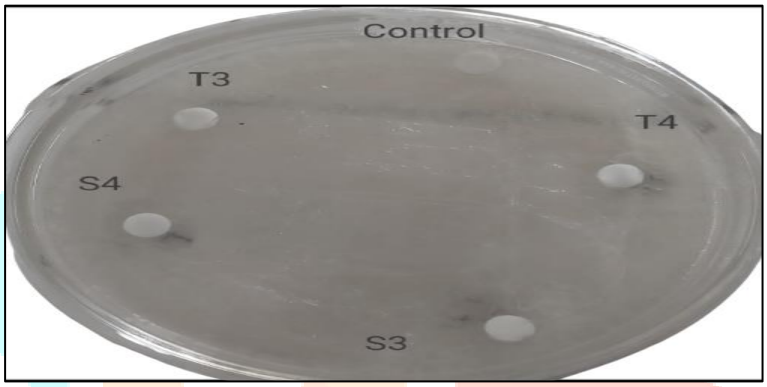


Fig no: -3.9 zone of inhibition of test and std sample

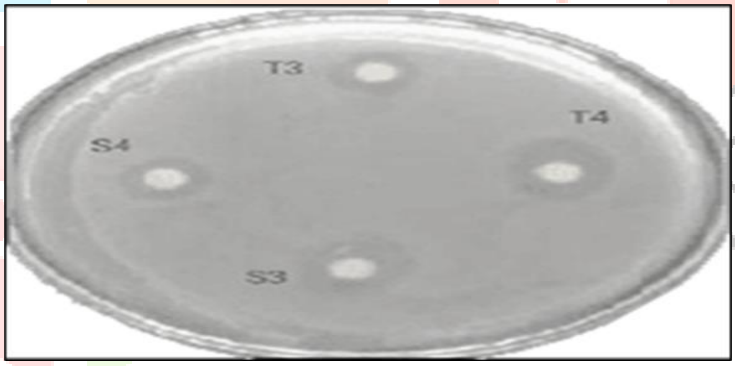


Fig no: -3.10 zone of inhibition of test and std sa

Fig no: - 3.11 control

3.1.9 Stability Study: - The stability studies of optimum formulation F9 revealed that there is slightly reduction in drug content and surface pH was observed over period of 1 month. No significant changes were observed on Physical appearance, surface pH and % Drug Content, at various storing condition 2-8^{0}C,15^{0}C. and at Stability 25^0 C±2^{0}C/60%RH±5%RH. Hence formulation F9 was found to be stable for 1 month.

Table no:- 3.6

Stability 2-8^{0}C	**Physical appearance**	**Surface pH (±SD)**	**Drug content (±SD)**
0 Day	No color change	6.46±0.15	94.67±0.27
1 week	No color change	6.32±0.15	94.49±0.21
2 week	No color change	6.47±0.28	93.10±0.27
3 week	No color change	6.46±0.25	94.20±0.15
4 week	No color change	6.27±0.15	94.37±0.49

n=3

Table no: - 3.7

Stability 15^0 C	**Physical appearance**	**Surface pH (±SD)**	**Drug content (±SD)**
0 Day	No color change	6.48±0.25	94.80±0.23
1 week	No color change	6.46±0.27	94.41±0.91
2 week	No color change	6.36±0.15	94.30±0.82
3 week	No color change	6.43±0.19	93.50±0.67
4 week	No color change	6.47±0.11	94.20±0.12

n=3

Table no: -3.8

Stability 25^0 C±2^{0}C/60%RH±5%RH	**Physical appearance**	**Surface pH(±SD)**	**Drug content (±SD)**
0 Day	No color change	6.47±0.15	94.67±0.27
1 week	No color change	6.46±0.25	94.56±0.67
2 week	No color change	6.32±0.15	94.10±0.25
3 week	No color change	6.27±0.28	93.38±0.37
4 week	No color change	6.36±0.25	93.50±0.67

n=3

The stability studies of optimum formulation F9 revealed that there is slightly reduction in drug content and surface pH was observed over period of 1 month. No significant changes were observed on Physical appearance, surface pH and % Drug Content, at various storing condition 2-8^{0}C, 15^{0}C. and at Stability 25^0 C±2^{0}C/60%RH±5%RH. Hence formulation F9 was found to be stable for 1 month.

CONCLUSION: - In the present work, an attempt was made to formulate dental cones containing antibacterial agent for the treatment of periodontitis was fulfilled. The developed dosage form was satisfactory in terms of drug release. The drug polymer interaction study was done by FTIR and DSC analysis of physical mixtures of drug and polymer. The compatibility of azithromycin with polymers studies of FTIR shows that all above characteristic peaks of Azithromycin dihydrate observed near about their respective values so it has been concluded that there is no incompatibility between polymer and pure drug. The formulated dental cones were prepared by combination of polymers such as gelatin and sodium alginate. F9 is considered as optimized formulation based on the evaluation tests. In the above findings, effect of polymers shows better results in terms of swelling index, drug content and high drug release. On the basis of all evaluation, it may concluded that dental cones containing biodegradable polymers with antibacterial were successfully prepared and it is better alternative to conventional drug delivery for the management of periodontitis.

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