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DESIGN AND CHARACTERISATION OF AMOXYCILLIN LOADED DENTICAP USING MUCOADHESIVE GUM ISOLATED FROM FRUIT PULP OF *ZIZIPHUS MAURITIANA* L.

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Keywords:

Denticap, Natural polysaccharides, *Ziziphus mauritiana* L., Antimicrobial property

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ABSTRACT: Novel drug delivery approach by using natural polymers is a newer area of formulation development. The oral drug delivery in the buccal cavity to treat the dental infections has some limitations such as slow onset of actions and is also affected by the first pass metabolism. In order to overcome these challenges plant derived mucoadhesive gum from the fruit pulp of *Ziziphus mauritiana L.*(ZM) is used in the preparation of Denticap and evaluated *in vitro* for to analysis its sustained release action. Antibacterial drug Amoxycillin Trihydrate has been taken as the model drug. The denticap was formulated using Carbopol 934P, Z Mgum, Ethyl cellulose and ethanol by solvent evaporation technique. The physicochemical parameters such as swelling index, surface pH, tooth adhesion test etc were carried out. The swelling % ranges from 40-55%. The tooth adhesive strength and pH was 45g and 6.7 respectively. The cumulative drug release from the ZM denticap was found to be 67% at 30 hr. The drug release kinetic study shows that formulation follows diffusion mechanism. The antibacterial study against various oral infection pathogens like *Lactobacillus acidophillus*, *Staphylococcus aureus*, *Porphyromonas Gingivalis* and *Streptococcus mutans* showed that the ZM gum possess certain antibacterial activity. SEM study shows the surface morphology of the denticap. The stability study following ICH guidelines shows that the formulation is stable. The formulated Denticap using ZM gum is a newer approach for sustained delivery of drug for treatment of dental infections.

INTRODUCTION: Plants have been used in the traditional system of medicine for several thousand years. The development of various excipients that can be used in formulation development is moving toward utilizing natural sources in the modern world [1, 2]. Presently, many polysaccharides are identified and isolated from various plant sources [3, 4]. They are used in various formulations such as tablets, emulsions, suspensions, microparticle nanoparticles *etc*. Thus, to fulfill the increasing industrial demands for plant polysaccharides, it is vital to explore newer sources [5].

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The fact that plant sources are renewable and may provide a steady supply of raw materials provided they are grown or harvested sustainably is the reason for the development in importance of plant polysaccharides in the forms of gums, mucilage, and starches [6]. Natural polysaccharides can replace synthetic polymers for the development of various novel formulations. Nowadays, various novel dental formulation is developed with the aim of local action, which will release the drug for a prolonged duration [7].

One common dental problem is infection due to microbial attack, which can be cured by antibiotic drug use. However, due to their delayed onset of action and "first pass" hepatic effect, most antibiotics cannot produce sustained and immediate effects [8]. The formulation of a soft, gummy dental mold consisting of antibiotic drugs can show a

prolonged release of drugs. The polymers used for the formulation should have proper adhesiveness to get attached to the tooth, and at the same time, it should not be washed away from the saliva. The ripe fruits of *Ziziphus mauritiana* from Rhamnaceae family show mucilagenous exudation [9].

The fruits can be used to isolate mucoadhesive gum, and if it shows good mucoadhesive strength, it can be further applied for the formulation of mucoadhesive drug delivery system [10]. Amoxycillin trihydrate a β – lactam antibiotic prevents Gram-positive and Gram-negative bacteria from cross-linking their linear peptidoglycan polymer chains in the cell wall [11]. Periodontal diseases and oral microbial plaques have both been treated with the drug [12].

MATERIALS AND METHODS:

Materials: Carbopol 934P (Hi media), *Ziziphus mauritiana*(ZM) ripe fruit, Amoxycillin trihydrate (Caplet India Pvt Ltd), Ethyl cellulose (S.D fine chemicals), disodium hydrogen phosphate (Merck), potassium dihydrogen phosphate, Tween 20 and absolute ethanol.

Methods:

Isolation of ZM Gum: *Ziziphus mauritiana* ripened fruits were collected from the local market of the East Burdwan district. The fruits were appropriately washed and crushed in a mortar pestle to separate the seeds from the pulp.

About 250 g of fruit pulp was taken, and distilled water was added around 500 ml to prepare a slurry-like consistency [13]. It then continues to boil at a temperature between 80 and 100°C while constantly stirring until a viscous solution is formed. The thickened slurry is filtered through a muslin cloth. The extract obtained is allowed to stand overnight to separate the cell and debris through sedimentation. The extract is then centrifuged for 20 min at 5000 rpm [14].

To obtain the residue, the resulting supernatant is treated with twice as much ethanol. The precipitate is separated through filtration and dried for 5-6 hours at 40-45°C [15]. The ZM gum is obtained in the form of a dried film which is then powdered and stored in desiccator for further use [10, 16].

Formulation Development: Optimization of the formulation was carried out by mixing the polymers at different ratios. The optimal formulation considering the physicochemical characteristics and drug release is considered. The dental molds were formed using a variety of polymers, including ZM gum and Carbopol 934 P. Carbopol, in combination with both natural mucoadhesive were used for adhesion [8]. Tween 20 was used as a wetting agents. Ethyl cellulose was used as a coating agent [17]. The formulation was prepared as per the method discussed by Ghosh *et al.* [18, 19].

Drug Excipient Interaction Study using FTIR Spectroscopy: The FTIR study for drug interaction was carried out as a part of the pre-formulation study to check the interaction of the drug with the excipients. The drug Amoxycillin trihydrate is mixed with the polymer mixture. The ATR-FTIR analysis for the drug-polymer mixture was carried out as described by Wood *et al.* [20, 21].

Tooth Adhesion test: The study was carried out on extracted goat tooth fixed on clay to prepare the teeth model **Fig. 1A-C**.

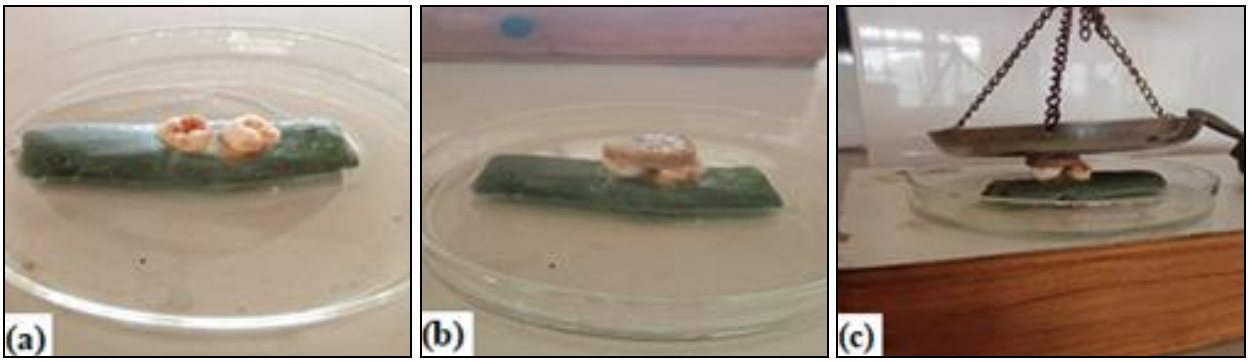

FIG. 1: TOOTH ADHESION TEST SETUP

Before being fixed, teeth were sterilized and cleansed with distilled water. Then, the formulation was affixed to the dental setup that had been moistened with simulated saliva (pH 6.8). A physical balance was used for the set up. One of the pans was attached to the denticap placed on the tooth, and the other on the other pan weight was placed continuously till it gets separated from the tooth model. The simulated saliva was formulated by mixing 2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8 g of NaCl in a litre of distilled water [11, 22].

Percent Swelling: The formed denticap underwent the percent swelling test. This approach involves weighing the denticap at its initial weight, recording it and storing it in a petri dish filled with artificial saliva with a pH of 6.8 and kept at room temperature.

The weight of the denticap was taken at a predetermined time interval ranging from 1-5 hours. The increase in weight was reported, and it continued till the weight became constant, which is noted. After this, the percent swelling was calculated by applying the formula given below, where W_t is the weight of the denticap at time t and W_0 is the weight at time 0 [23].

Percent Swelling = (Wt-W0) x 100 / W0

***In-vitro* Drug Release Study:** The USP Type II equipment was used to release amoxycillin trihydrate from the tooth mold in simulated saliva (pH 6.8) at a temperature of 37.5 ±0.5°C as described by Hassan *et al.* [24].

Antibacterial Study of the Denticaps: The denticaps were assessed for antibacterial properties and also analyzed if there is any additive effect of the isolated polysaccharides on *Lactobacillus acidophillus*, *Staphyloccocus aureus*, *Porphyromonas gingivitis* and *Streptococcus mutans* [25]. The agar cup plate method using Muller Hilton Agar media was employed to carry out the assay. The sample of denticap A after 24-hour release was taken and compared with the sample of blank denticaps without drug. Standard Amoxycillin was taken as the positive control and 0.1% DMSO as the negative control [26, 27].

SEM Analysis of the Denticaps: The morphological characters of the formulated Denticaps were studied using Scanning Electron Microscope (ZEISS EVO 18 special edition).

RESULT AND DISCUSSION: The different combinations of the polymers were screened for the appropriate physicochemical property and drug release patterns. The best formulation is reported here using the isolated ZM gum along with Carbopol 934, Tween 20, and Ethylcellulose. The ratio of the ingredients is represented in **Table 1.**

TABLE 1: DRUG POLYMER COMPOSITION OF DENTAL MOLD FORMULATIONS

Formulations	Ingredients (Ratio by weight)	Amount of Drug (mg)
Denticap A-(ZM + Drug)	Carbopol 934: ZM gum: Tween 20 (8:6:1) Ethyl cellulose (it is used as coating material)	70 mg

FTIR spectra of amoxycillin trihydrate showed that the characteristic peak of the drug is present in the peak (12). The infrared spectrum of the Amoxycillin trihydrate showed strong absorption at 1,776 cm^{-1}, characteristic of the β-lactam ring [28].

When the drug was mixed with the isolated polysaccharides, minor variations in the peak were noticed, as shown in **Fig. 2** (Drug +polymer peak).

The comparison was carried out between 3700 cm^{-1} and 2400 cm^{-1} and between 1800 cm^{-1} and 1000 cm^{-1}. Alkenyl (>C=C); 3,020–3,100 cm^{-1}; and amide (>NH; 1,000–1,250 cm^{-1}) Phenolic (-OH; 970-1,250 cm^{-1}) and ketone (>C=O; 1,710-1,720 cm^{-1}) stretches are the primary functional groupings in charge of certain areas [28, 29]. The FTIR data reveals the formation of weak to medium intensity bonds, which may be caused by the development of Vander Waal forces and dipole moments due to the interaction of the drug and excipient. The major shift in the peak was not present [30].

The swelling percentage was expressed with respect to the water uptake at room temperature. **Fig. 3** shows the % swelling of the different formulations of denticap. The percent swelling of the formulations varied from 10.20 % to 46.0 % at a duration of 1-5 hr.

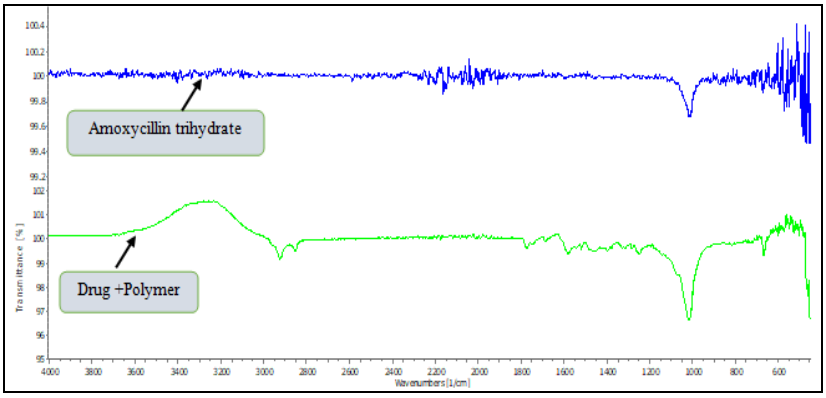

FIG. 2: FTIR SPECTRA (FROM TOP TO BOTTOM) OF AMOXYCILLIN TRIHYDRATE, DRUG + ZM GUM

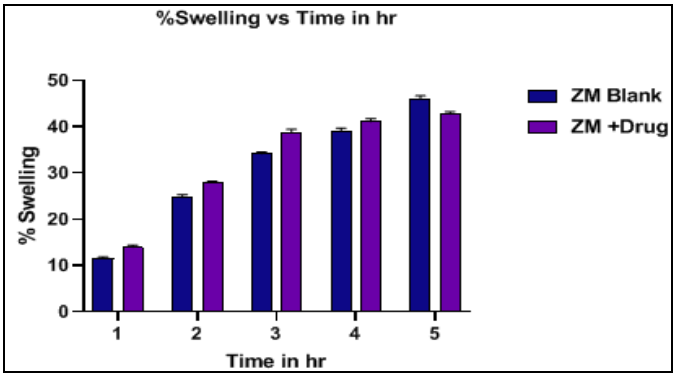

FIG. 3: PERCENTAGE SWELLING OF DIFFERENT FORMULATIONS OF DENTICAP. Data shows mean (n=3) ±SEM. Values were significant as accessed by two-way ANOVA test ($p<0.0001$)

The average initial mucoadhesive strength was found to be 30 g. The formulation's mean adhesive strength is 45 g ± 0.471(n=3). This proves to be advantageous because more adhesive strength is required to attach a formulation to the tooth surface [31]. The formulation was easily removed from the tooth. The surface pH at room temperature was found to be around 6.66 ± 0.054, which is within limits and hence reduces the chances of irritation to the buccal cavity. Denticap A's tooth adhesive strength was discovered to be 48g. The mean adhesive strength of the developed denticap is discovered to be 48g, which is higher than the average mucoadhesive strength necessary for mucoadhesion, which is stated to be 30g. This was useful since the buccal cavity's mucous layer surface is uneven compared to tooth surfaces, requiring more adhesive strength to link the formulation to the tooth surface [31]. In addition, it was observed that the tooth's adhesive power was adequate to keep the compounds in place. The adhesiveness of our formulations also made it simple to remove them from the tooth. The *in-vitro* drug release of the generated denticap was examined in simulated saliva with a pH of 6.8. **Fig. 4** shows the std calibration curve of Amoxycillin. The cumulative % drug release from both the Denticap A was about 67.63% over a time period of 24 h.

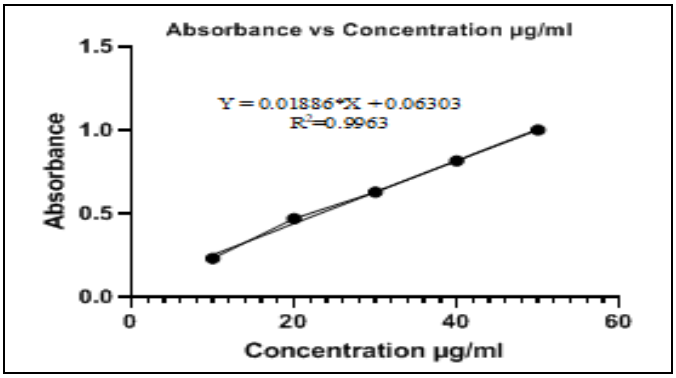

FIG. 4: STANDARD CALIBRATION CURVE OF AMOXYCILLIN TRIHYDRATE

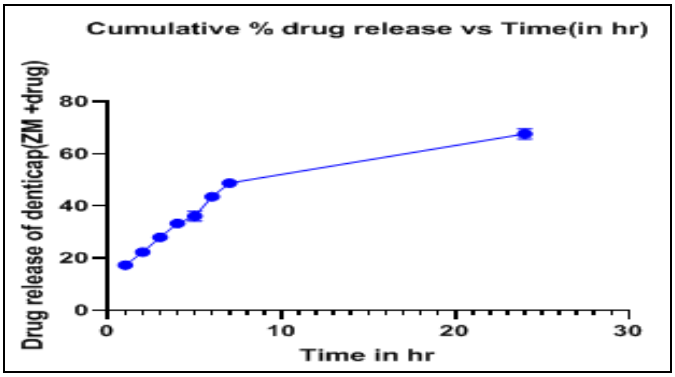

FIG. 5: CUMULATIVE % DRUG RELEASE FROM THE DENTICAP. Data shows mean (N=3) ±Sem

The zero order, first order, Higuchi, and Korsmeyer -Peppas kinetic models were used to analyse the drug release kinetic pattern. **Table 2** displays the R^2 values for the kinetics. **Fig. 6** depicts the graph for the kinetic models for both denticaps.

TABLE 2: DRUG RELEASE KINETICS OF DENTICAPS

Formulation	Zero-order Kinetics	First-order kinetics	Higuchi Kinetics	Korsmeyer *et al* kinetics
Denticap A	y = 7.9898x + 6.0961 R^2 = 0.9745	y = -0.0611x + 2.0193 R^2 = 0.9166	y = 23.231x + 5.8381 R^2 = 0.921 2	y = 1.3842x + 0.7062 R^2 = 0.637

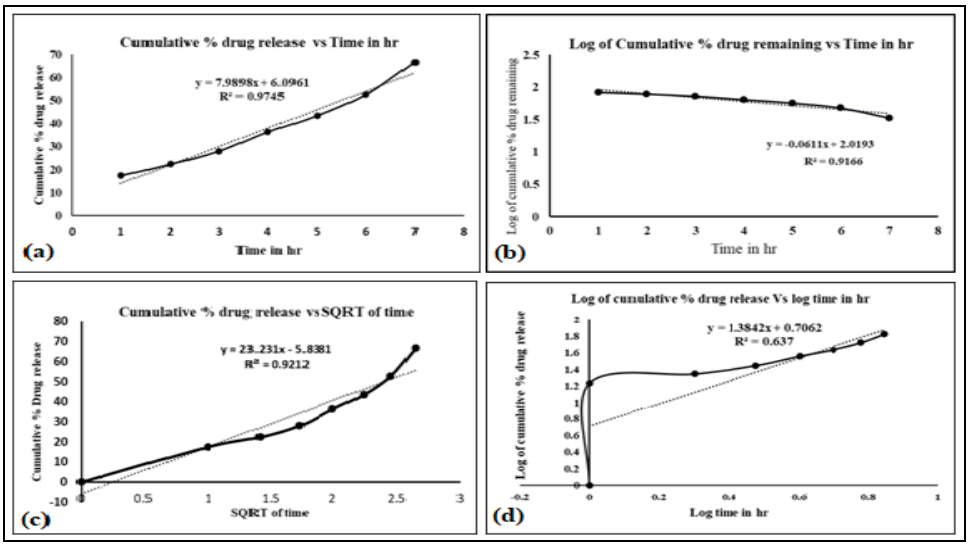

FIG. 6: VARIOUS KINETIC RELEASES OF DENTICAP A A) ZERO ORDER KINETICS RELEASE B) FIRST ORDER KINETICRELEASE C) HIGUCHI MODEL KINETIC RELEASE D) KORSMEYERPEPPAS KINETIC RELEASE

TABLE 3: PERCENT DRUG CONTENT OF THE DENTAL MOLD (CONTAINING AMOXYCILLIN TRIHYDRATE) STORED AT DIFFERENT TEMPERATURE AND HUMIDITY CONDITIONS: DENTICAP A

Storage Condition	30± 2°C/60 % RH	45± 2°C /75 % RH	2-8 °C
	% Drug content ±SEM (n=3)		
Initial	99.40 %±0.0047	99.56 %± 0.0011	99.08 %±0.0026
1 month	99.08 %±0.0035	98.76 %±0.0039	98.76%±0.0018
3 months	97.64 %±0.0020	98.28 %±0.0031	98.60 %±0.0015
6 months	97.07 %±0.0023	98.12 %±0.0017	98.44 % ±0.0032

The antimicrobial study was carried out for the formulated denticap (both blank and drug-loaded) using strains of *S. aureus, L.acidophillus, Pgingivalis* and *S. mutans*. The image of the petri plates showing the zone of inhibition is shown in **Fig. 7.** The comparative result with the positive control Amoxycillin and negative control DMSO has been shown in **Fig. 8.**

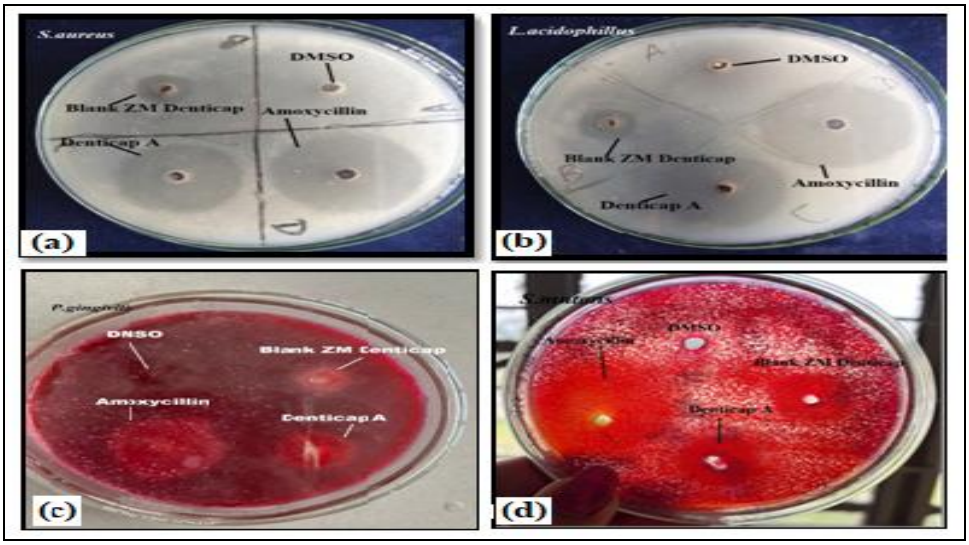

FIG. 7: INHIBITORY EFFECT OF BLANK DENTICAP ZM ALONG WITH DENTICAP A ON A) *S. AUREUS*, B) *L. ACIDOPHILLUS* C) *P. GINGIVITIS* D) *S. MUTANS*

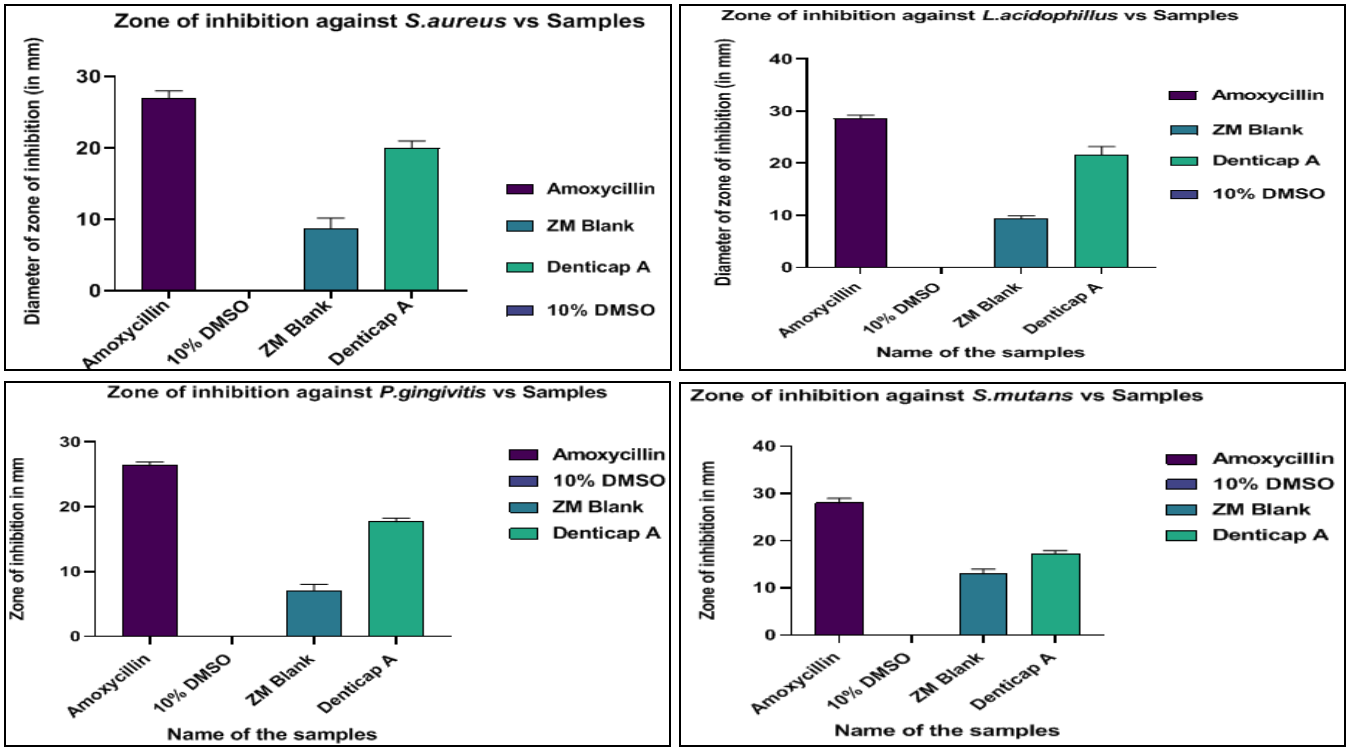

FIG. 8: ZONE OF INHIBITION OF A) DENTICAP A ON *S. AUREUS.* B) DENTICAP A ON *L. ACIDOPHILLUS*C) DENTICAP A ON *P. GINGIVITIS*D) DENTICAP A ON *S. MUTANS* DATA SHOWS MEAN (N=3) ±SEM. Values were significant as accessed by one-way ANOVA test ($p<0.0001$)

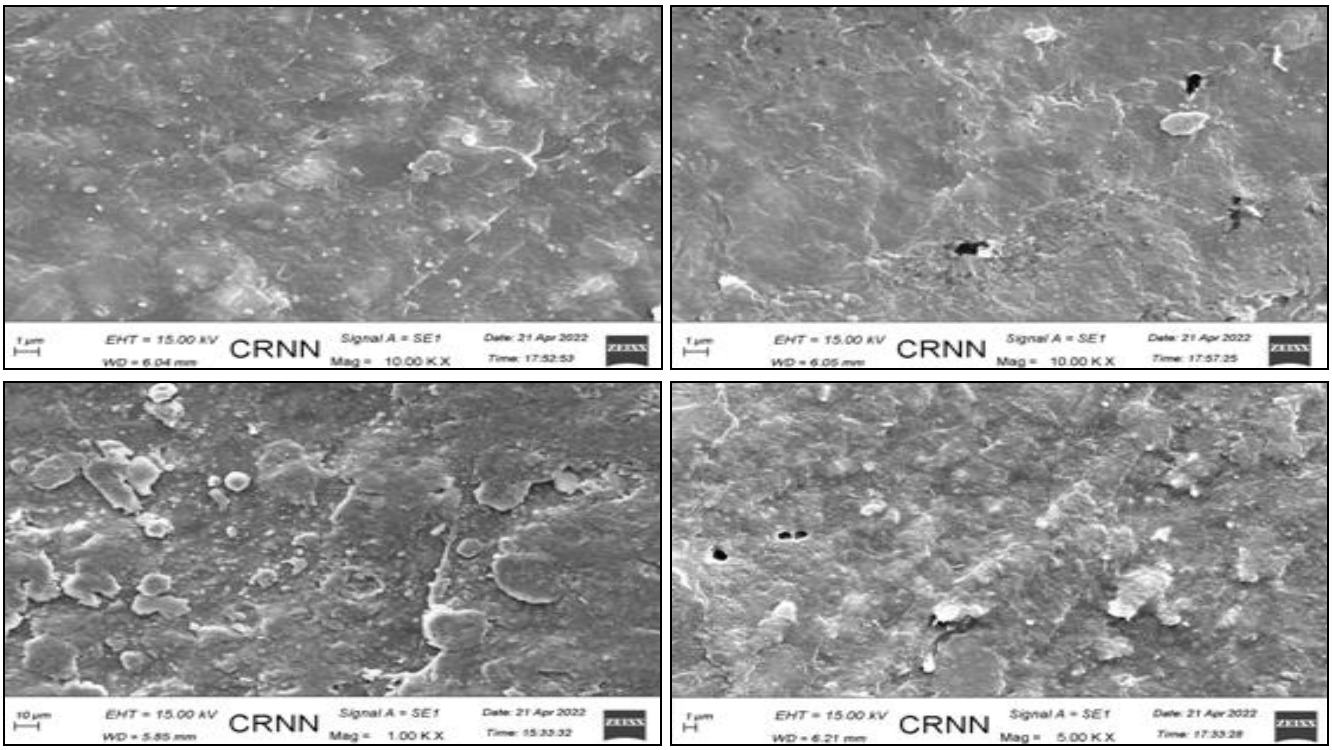

FIG. 9: SEM IMAGES OF ZM DENTICAP BEFORE DRUG RELEASE

A mold was developed, which resembles a cap (Denticap) and is soft and gummy in nature, for releasing the drug for a prolonged period of time by its application on the effected tooth. The dose of the drug was selected as per earlier investigations [33]. The isolated polysaccharide from ZM gum has shown potential adhesive character when used for the formulation. Further preformulation studies and evaluation of the Amoxycillin-loaded denticap was carried out.

The FTIR analysis demonstrates the presence of interaction between functional group levels [34, 35]. The FTIR data indicates that weak to medium-intensity bonds are forming, and no significant changes in the peak were seen. The polymer matrix usually swells due to moisture uptake [36].

The swelling % is dependent on the concentration of the polymer and the moisture absorption capacity. Denticap A shows potent % swelling. However, the % swelling of the Denticaps containing the drug was more than the blank polymer denticaps, which might be due to the presence of water of crystallinity in Amoxycillin trihydra [37, 38].

The tooth adhesion test was used to evaluate the formulation's stickiness and adhesiveness. The formulation could be easily removed from the tooth with minimal effort, and the adhesive strength was sufficient to hold it to the tooth. The drug kinetic formulation for both formulations was studied up to 7 hr and extended to 24 hrs. Based on the correlation coefficient, the Higuchi and zero-order drug release kinetic models were determined to be the best model for the two formulations. Therefore, it is concluded that the drug release takes place through diffusion mechanisms [39, 40].

The antibacterial study on the predominant bacteria of tooth decay *L.acidophillus, S. aureus, P. gingiviis and S.mutans* shows that the blank dental molds made up of isolated polysaccharides ZM gum also shows zone of inhibition [41, 42]. Blank ZM gum denticap shows 8.66 mm against *S. aureus*, 9.33 mm against *L.acidophillus,*7.2mm against *P. gingivitis* and 13.2 mm against *S. mutans.* Denticap A shows 20 mm against *S. aureus*, 21.66 mm against *L. acidophillus,* 17.66 mm against *P. gingivitis* and 17.33 mm against *S. mutans* [43, 44].

The presence of antibacterial activity in the blank denticap shows that the isolated polysaccharide possesses antibacterial properties, which act as an additive property in the formulated antibacterial Denticap [45].

The information currently available on mucosal permeability and Amoxicillin trihydrate lead to the conclusion that the formulations can exert both local and systemic effects. However, the current work was only intended for local action, and no research was done to assess how well the formulation absorbs drugs systemically [46].

CONCLUSION: The isolated polysaccharide was used for the formulation of dental molds, a novel drug delivery system for local drug delivery for a prolonged period by its application on the affected tooth. The drug release kinetic study also shows that the formulation follows the diffusion mechanism, and matrix formation has occurred as it follows the Higuchi model kinetic release. The presence of ZM gum in denticap shows added antibacterial properties. Therefore, the various synthetic mucoadhesive agents can be replaced with natural polysaccharides such as ZM gum for developing the formulations. Establishing-deplant-derived the steps involved, from collecting raw material to processing, might provide employment to the local people.

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CONFLICTS OF INTEREST: None declared

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