DEVELOPMENT OF POLYMER- BASED DENTAL MOLD CONTAINING AMOXICILLIN TRIHYDRATE, LIDOCAINE HYDROCHLORIDE AND METRONIDAZOLE AS AN ALTERNATIVE TO MITIGATE DENTAL DISEASES

Thesis submitted in the Partial Fulfilment of the Requirements for the Degree of Master of Pharmaceutical Technology

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This is to certify that the project enititled " was carried out by **Mr. Shounak Sarkhel** based upon her work under my direct supervision at the **Department of Pharmaceutical Technology, jadavpur University, Kolkata** , for the requirement of completion of M.Pharm . I am satisfied that he has completed his work with proper care & confidence to my entire satisfaction.

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DECLARATION OF ORIGINALITY AND COMPLIANCE OF ACADEMIC ETHICS

I hereby declare that this thesis contains literature survey and orginal research work by the undersigned candidate , as part of his **Master of Pharmaceutical Technology** studies. All information in this document have been obtained and presented in accordance with academic rules and ethical conduct.

I also declare that as required by these rules and conduct, I have fully cited and referenced all materials and results that are not original to this work.

Name : Shounak Sarkhel

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Thesis title: Development of Polymer-based Dental Mold Containing Amoxicillin Trihydrate, Lidocaine Hydrochloride and Metronidazole as an alternative to mitigate Dental Diseases .

Signature:

DEDICATED

TO

MY FAMILY, ALMIGHTY

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Date:

Place: Jadavpur

Shounak Sarkhel

CONTENTS

CHAPTER 1

INTRODUCTION

1❖Introduction:

1.1▪Dental:

1.1▪Dental: A dental i.e. plural teeth,a solid calcified structure found in jaws , used to break down food. Many animals, particularly carnivores, use their teeth for hunting and fooding. Many animals also use the teeth for defensive purpose. Teeth are not made of bone.These are the multiple tissues of varying density and hardness. The cellular tissues that ultimately become teeth originate from the embryonic germ layer, the ectoderm.[1] Dental used for breaking down items of food by cutting and crushing them for a swallowing and digesting.

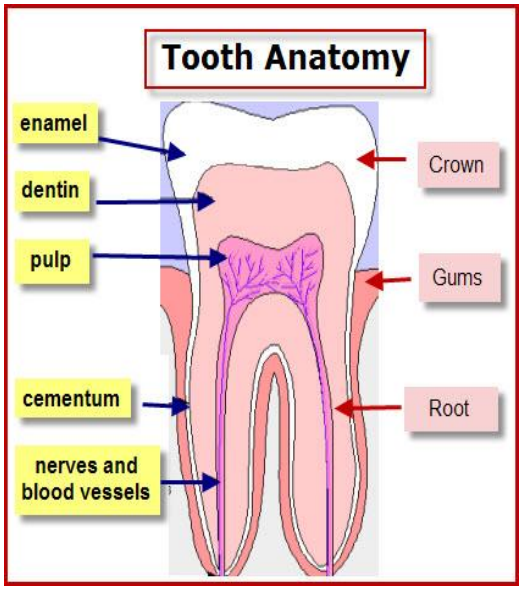
Dental health is a general term that refers to the overall health status of human mouth, which is a important factor in an oral examination of the teeth.[2] The teeth are examined for areas of decay, wear and fracture defective fillings, crowns and other restorations mobility, discoloration, missing teeth occlusion. Evaluation also made for oral hygiene and plague accumulation. For signs of gum disease it is examined and evaluated including mobility also bleeding deep areas below the gum margin , pus and quality of the tissue of gum.[3]

Dental pain mostly effected and irritated dental health, In dental pain i.e. toothache is a pain in the teeth and/or their supporting structures, caused by dental diseases or pain referred to the teeth by non-dental diseases.[4] Common causes of the dental pain includes inflammation of the pulp, usually in response to tooth decay, dental trauma or other factors, dentin hyper sensitivity (short, sharp, pain, usually associated with exposed root surfaces), apical periodontitis (inflammation of the periodontal ligament and alveolar bone around the root apex), dental abscesses (localized collections of pus, such as apical abscess, per coronal abscess, and periodontal abscess), alveolar osteitis ("dry socket", a possible complication of tooth extraction, with loss of the blood clot and

exposure of bone), acute necrotizing ulcerative gingivitis a gum infection, also called trench mouth, temporomandibular disorder and others.[5]

1.2▪ANATOMY OF TOOTH: The teeth are the toughest substances in the human body. Besides being essential for chewing, the teeth play an imperative role in speech parts of teeth include:-Enamel: The toughest white outer part of the tooth, Enamel is chiefly made of calcium phosphate a rock-hard mineral[6] Dentin: An underlying layer the enamel. It is a hard tissue that contains microscopic tubes.[7]

When the enamel is not intact, heat or cold can enter the tooth through these paths and cause sensitivity or pain. • Pulp: The softer, inner living structure of teeth. Blood vessels and nerves run though the pulp of teeth. • Cementum: A layer of connective tissue that unites the roots of the teeth firmly to the gums and jawbone. • Periodontal ligament: Tissue that helps hold the teeth firmly against the jaw. A healthy adult mouth has 32 teeth, which (except for wisdom teeth) have erupted by about age 1: • Incisors (8 total): The middlemost four teeth on the lower and upper jaw • Canines (4 total): The pointed teeth immediately outside the incisors • Premolars (8 total): Teeth between the molars and canines. • Molars (8 total): Flat teeth in the back of the mouth, best at grinding food. • Wisdom teeth or third molars (4 total): These teeth blow up at around age 18, but are often surgically taken out to prevent displacement of other teeth. [8]



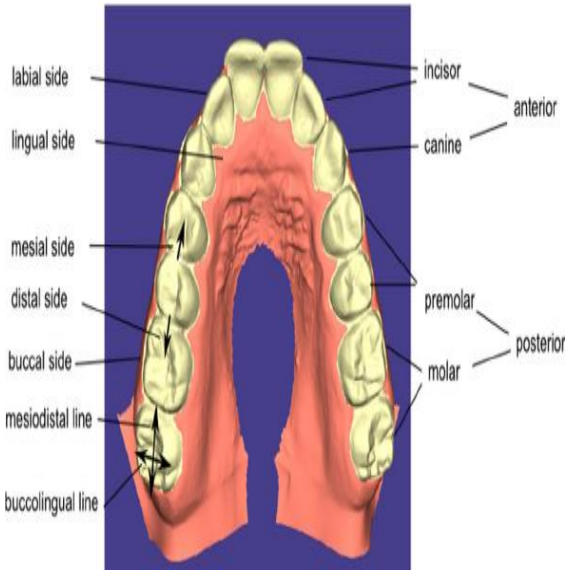


Fig. 1. Structure of tooth anatomy **Fig.2. Structure of tooth**

1.3▪Density Treatment Medicine: There are several types of medications that are used to manage a variety of diseases involving the oral cavity (mouth) that are part of good dental care. The medications mentioned in this article have pharmacological properties that are used to treat conditions such as pain, anxiety, and infections, amongst others. [9]

1.4▪MEDICATIONS USED TO CONTROL PAIN AND ANXIETY:

Non-narcotic type of analgesics are the most frequently used drugs for elevate of toothache or pain following dental cure as well as fever. The commonly-used medications used are: ibuprofen (Advil, Nuprin, Motrin), acetaminophen (Tylenol), and aspirin (for example, Bayer) such corticosteroids as Orabase-HCA, Oracort, and Oralone are anti-inflammatory medications that are used to relieve discomfort and redness of the mouth; and for severe pain conditions, narcotic analgesics such as codeine or hydrocodone (Vicodin) may be given. [10] Codeine formulations usually contain acetaminophen for increased usefulness, for example, (Vicoprofen) usually used topical anaesthetics include Anbesol and Orajel. Local anaesthetics are injected into the interior tissues of the mouth and work by inhibiting the impulses from pain-sensing nerves and hence are

used to decrease pain especially in procedures involving drilling, and cutting of the tissue.[11]Common local anaesthetics are 2% lidocaine hydrochloride and 2% mepivacaine (Carbocyanine).General anaesthetics are inhaled and include anti-anxiety agents, such as nitrous oxide, that help to ensure relaxation during dental visits and often may be used along with local anaesthetics.[12]

1.5▪Dry Mouth:- All the above mentioned medications have the shared common side effect of xerostomia or dry mouth, though medications rarely have the direct effect of tooth decay. Itis a common factor that dry mouth can lead to tooth decay and infection and drying also irritates the soft tissues in your mouth, which can make them inflamed and increase the risk for infection. [13] Saliva plays a big role to protect your teeth from bacteria. So when your mouth is dry, your risk for infection and tooth decay is increased. Here are the common medications which cause dry mouth and subsequent tooth decay and what are the ways to protect your oral health. [14]

1.6▪Tooth Decay Treatment Medication: - Firstly to look after your teeth and gums, brushing your teeth properly with a fluoride toothpaste twice a day. Using floss and an inter-dental brush at least once a day.[15] To avoid smoking or drinking alcohol excessively as tobacco can interfere with saliva production, which helps to keep your teeth clean and alcohol can contribute to the erosion of tooth enamel. Consult is needed with dentist or GP if you have a persistently dry mouth,this may be caused by certain medicines, treatment or medical conditions.[16]

1.7▪Treatment of Gingivitis and Plaque: -Flap surgery/pocket reduction surgery: In this procedure the gums are lifted back and the tarter is removed. In a few cases, irregular surfaces of the damaged bone are smoothed to certain areas where bacteria can hide causing disease. The gums are then placed so that the tissue fits snugly around the tooth. This method is used to reduce the size of the gap between the gum and tooth, which decreasing the areas where harmful bacteria can grow up. This is also decreasing the chance of serious health

problems associated with periodontal disease. **Bone grafts:**[15]This method involves using fragments of your own bone, synthetic bone, or donated bone to replace bone destroyed by gum disease. The grafts serve is a platform for the re-growth of bone, which restores stability of the teeth. Now the new technology, which is also called tissue engineering, encourages your own body to regenerate bone and tissue at an accelerated rate. **Soft tissue grafts**:[16] procedure is used to reinforce thin gums or fills in places where gums have refrained. Grafted tissue, mostly taken from the roof of the mouth, is stitched in place, adding tissue to the affected area. **Guided tissue regeneration**.:[17] It is done when the bone supporting your teeth has been destroyed. This procedure stimulates bone and gum tissue growth and it is made in combination with flap surgery, a small piece of mesh-like fabric is inserted between the bone and gum tissue. This keeps the gum tissue from growing into the area where the bone actually should be, allowing the bone and connective tissue to re-grow for better support the teeth**. Bone surgery**:[18] it is performed for Smooth shallow craters in the bone owing to moderate and advanced bone loss. Following flap surgery, the bone around the tooth is reshaped to decrease the craters. It causes harder for bacteria to collect and grow. In some patients, the non-surgical procedure of scaling and root planning is also needed to treat the gum diseases. But surgery is needed when the tissue around the teeth is unhealthy and cannot be repaired with non-surgical options.

1.8▪Dental Mold : In dental mold, dental impression is controlling a real part and it is a negative imprint of hard (teeth) and soft tissues in the mouth from which a positive reproduction (cast or model) can be formed.[19]It is made by placing an appropriate material in a stock or custom dental impression tray, which is designed to roughly fit over the dental arches. Impression material is of liquid or semi-solid nature at the time of first mixed and placed in the mouth. It then sets to become an elastic solid, leaving an imprint of person's dentition and

surrounding structures of oral cavity. and it is also border molding for shaping of the border areas with an impression by functional or manual manipulation of the size of the vestibule. [20,21]

▪**Advantages:-**

▪1) High tear strength.

▪2) Long working time.

▪3) It helps establish precision.

▪ 4) It economically cheap.

▪5) It also good Extensive shelf life.

▪6) It is also less hydrophobic.

▪7) It also reproduce the teeth, gums, and relationships between the upper and lower dental arches.

▪8) It also provide an inside the mouth view of how the teeth fit together.

▪**Disadvantages:**

▪1) It is dimensionally unstable.

▪2) It unacceptable odor.

▪3) It also Untidy and stains clothing

▪4) It also want long setting time.

▪5) It also least elastic recovery.

▪6) Its subsequent pours are less accurate. [22]

CHAPTER2

LITERATURE REVIEW

2❖ Literatures Review :-

❖**Soma Ghosh et al**- Oral administration of antibiotics to treat dental problems mostly yields slow actions due to slow onset and hepatic “first-pass.” Again, commonly used dental paints are generally washed out by saliva within few hours of application. To overcome the challenges, polymeric molds to be placed on an affected tooth (during carries and gum problems) were prepared and evaluated *in vitro* for sustained drug release for prolonged local action. Here, amoxicillin tri-hydrate and lidocaine hydrochloride were utilized as model drugs. Dental molds were made using corn zein, carbopol 934 P, gum karaya powder, and poloxamer 407 by mixing and solvent evaporation technique. Various physicochemical evaluation studies such as tooth adhesion test, surface pH, swelling index, and drug-distribution pattern were carried out.[23] Percentage swelling varied from 56% to 93%. Average tooth adhesion strength and mean initial surface pH of the formulations were found to be 50 g and 6.5, respectively. As determined by scanning electron microscopy, drug distribution was uniform throughout the matrix. Cumulative percentage release of lidocaine hydrochloride and amoxicillin tri-hydrate in simulated saliva were seen 98% and 50%, respectively. *In vitro* drug-release studies showed the sustained-release patterns of the drugs in simulated saliva at least for 24 h. The stability study indicates that the drugs were stable in the formulations following the conditions as per ICH guideline. The formulation is a novel way to deliver the drug(s) for a prolonged period for local action upon its application on an affected tooth.[24]

❖**Mukherjee B et al**- Toothache is a major problem worldwide. To give support from this intolerable toothache, doctors prescribe painkillers along with antibiotics.[25] Most of the painkillers, if not all, create hyperacidity and gastric irritation upon oral administration. Oral antibiotics have delayed onset of action and undergo hepatic "first-pass" effect. Moreover, existing dental formulations

are mostly liquid and remain only few hours upon application, before being washed out by saliva. To conquer the above-mentioned problems, a soft polymeric mold containing antibiotic and analgesic drugs and having a suitable consistency to adhere to the tooth, was built up for sustained drug release to provide better treatment in dental patients. Eudragit L 100-55, carbopol 971 P, gum karaya powder and ethyl cellulose were taken to prepare the mold "Denticaps" containing Lidocaine hydrochloride and Amoxicillin trihydrate alone and in combination, by mixing and solvent evaporation technique.[26] A variety of physicochemical characterization studies such as mucoadhesion test, water absorption capacity and swelling index were executed. In vitro drug release studies demonstrated sustained release of Lidocaine hydrochloride and Amoxicillin tri-hydrate in simulated saliva for 24 h. Further studies are justified to succeed with these formulations in humans. Upon success, this type of dosage form may open up new opportunities towards dentistry.[27]

❖**Bascones-Martínez, Figuero-Ruiz E**- The periodontal disease is established by a group of illnesses affecting the gums and dental support structures. They are due to by certain bacteria found in the bacterial plaque. These bacteria are necessary to the onset of illness; however, there are predisposing factors in both the host and the microorganisms that will have an outcome on the pathogenesis of the illness. Periodontal pathogenic bacteria micro biota is required, but by itself, it is not enough to cause the illness, involving the presence of a susceptible host.[28] These diseases have been categorized as gingivitis, when restricted to the gums, and periodontitis, when they extend to deeper tissues. Classification of periodontal disease has changed over the years. The one used in this work was accepted at the International Workshop for a Classification of Periodontal Diseases and Conditions, held in 1999. This study is an overview of the diverse periodontal disease syndromes. Later, the systematic use of antibiotic treatment consisting of amoxicillin, amoxicillin-clavulanic acid, and

metronidazole as first line co adjuvant therapy of these illnesses will be reviewed.[29]

❖**J.O. Andreasen et al**- Based on a study of the literature relating to parameters controlling the prognosis of shocking dental injuries, few studies were established to have examined possible relationships between treatment delay and pulpal and periodontal ligament healing problems. It has been generally established that all injuries should be treated on an emergency basis, for the compliance of the patient and also to reduce wound healing problems. For particularly and practical economic reasons, different approaches can be selected to fulfil such a demand, such as acute treatment (i.e. within a few hours), sub acute (i.e. within the first 24 h), and delayed (i.e. after the first 24 h). In this survey the results of treatment delay on pulpal and periodontal remedial have been analyzed for the various dental trauma groups.[30] Applying such a therapeutic approach to the a variety types of injuries, the following treatment guidelines can be suggested, based on our present rather lack of knowledge of the effect of treatment delay upon wound healing. Crown and crown/root fractures: Sub acute or late approach. Root fractures: sub acute or Acute approach. Alveolar fractures: Acute approach (evidence however uncertain). Concussion and sublimation: Sub acute method. Extrusion and lateral luxation: acute or Sub acute approach (evidence however questionable). Intrusion: Sub acute approach (evidence however disputed). Avulsion: If the tooth is not replanted at the time of injury, acute approach; or else sub acute. Primary tooth injury: Sub acute approach, unless the primary tooth is enthused into the follicle of the permanent tooth or occlusal problems are there; in the latter instance, an acute approach should be selected particular. These treatment guidelines are based on very limited evidence from the literature.[31]

❖**Perioli L et al**- Mucoadhesive tablets using different mixture of cellulose and polyacrylic derivatives were prepared in order to obtain new formulations

containing metronidazole for periodontal disease treatment. All tablets were considered by swelling studies, ex vivo and in vivo mucoadhesive time, ex vivo mucoadhesion force, in vitro and in vivo release. [32]The best mucoadhesive show the best in vitro drug release profile were achieved by using hydroxyethyl cellulose (HEC) and carbomer 940 2:2 ratio. The chosen tablet, containing 20 mg of metronidazole, performed 12 h drug sustained release with buccal concentrations always greater than its MIC.[33]

❖**Kasaj A et al-** The purpose of the present study was to evaluate clinically the effect of an anaesthetic gel (lidocaine 20 mg/g as active agent) on pain sensitivity and early wound remedial following nonsurgical periodontal therapy. A total of 40 patients with chronic periodontitis were enrolled in this randomized, double-blind, split-mouth, placebo-controlled clinical trial. Each subject had 3 sites in each of 2 contra-lateral jaw quadrants with a probing pocket depth (PPD) of > or = 5 mm and bleeding on searching (BOP+). All experimental sites received scaling and root planning without local anaesthesia followed by irrigation with sterile saline and assessment of pain sensitivity using a standardized Visual Analogue Scale (VAS).[34,35] After treatment, the patients randomly received the active or placebo gel into the periodontal pockets and overall pain was again assessed immediately after debridement and after 10, 20 and 30 minutes. The VAS showed a statistically significant ($p < or = 0.0001$) reduction in reported pain, favouring the active gel over the placebo at all 3 different points in time. After 30 minutes the median VAS score was 0.3 in the Dynexan group as opposed to 1.7 in the placebo-treated group ($p < or = 0.0001$). In terms of wound remedial no differences were found between the test and control sites after 1 week.[36,37] The results of the study showed that the anaesthetic gel was statistically more useful than the placebo in reducing pain following nonsurgical periodontal therapy. However, in terms of early wound healing no significant differences were seen between the two thearapy sites.[38]

CHAPTER 3

AIM OF THIS RESEACH

3.❖ AIM OF THIS RESEARCH :-

The main objective of the present study to develop polymer-based dental mold containing three drugs (amoxicillin trihydrate, lidocaine hydrochloride and metronidazole) to provide local drug action on the affected tooth or gum for a prolonged period of time. They could be attached removed as an when required. It's can help & avoid systemic use of drug and provide faster action due to its local action.

Toothaches, periodontal disease, bacterial and fungal infection, periodontal diseases are the infection and inflammatory conditions, including gingivitis and periodontitis that affect teeth and create dental pain and decay. The diseases occur when bacteria from dental plaque invade surrounding tissues. Tooth decay is a destruction of tooth enamel protects the soft tissue and nerves underlying dentine bacteria thrive on the foods left on the teeth and produce acids ,which destroy tooth enable and resulting in tooth decay.[23] For treatment of dental problem such as dental pain due to carries periodontitis, gingivitis other gum, infection painkillers with antibiotics are prescribed by dentist at initial stage.[24]Oral administration of antibiotics to treat dental problems mostly yields slow actions due to slow onset and hepatic "first-pass." Again, commonly used dental paints are generally washed out by saliva within a short span of application. To overcome the challenges, polymeric molds to be placed on an affected tooth (during carries and gum problems) were prepared and evaluated in vitro for sustained drug release for prolonged local action the formulation is a novel approach to deliver the drug(s) for a prolonged period for local action upon its application on an affected tooth. [25]

CHAPTER 4

MATERIALS

4.❖Materials

4.1.Chemicals

Chemicals	Source
Cron Zein	Sigma, St. Louis,USA
Carbopol 934P	Corel Pharma-Chem, Ahmedabad,India
Gum Acacia Powder	Nutriroma, Hyderabad, India
Ethyl Cellulose	s. d Fine-chem Ltd, Boisar, India
Poloxamer 407	Sciencelab.com,Houston, Texaxs
Absolute ethanol	Merck Ltd., Mumbai,India
Amoxicillin trihydrate	Deys Medical,West Bengal, India
Lidocaine hydrochloride	Heer Pharmaceutical Pvt, Ltd., Mumbai,India
Metronidazole	Gluconate, West Bengal,India
Disodiumhydrogen orthophosphate anhydrous	Process Chemical Industries,Kolkata,India
Sodium Chloride	Process Chemical Industries,Kolkata,India
Potassium dihydrogen phosphate	Process Chemical Industries,Kolkata,India
EDTA(Disodium salt)	Process Chemical Industries,Kolkata,India
Aspartate Aminotransferase(AST)	Span Diagnostics Ltd., Surat, India
Alanine Aminotransferase(ALT)	Span Diagnostics Ltd., Surat, India

4.2.❖Equipments

Equipments	Source
Magnetic stirrer	Remi Equipments, Mumnai,India
Electronic Balance	Satorius, Geottingen,Germany
Hot-air gun	Philips India Ltd. Mumbai,Maharashtra,India
1mL micropipette	Ependrof India Limited, Chennai, India
5mL micropipette	Ependrof India Limited, Chennai, India
Scanning Electron Microscope	JSM 6100 JEOL, Tokyo Japan
FTIR Instrument	Magna IR 750 series II (Nicolet, Wisconsin,USA)
Pyris Diamond TG/DTA Thermogravimetric/ Differential/Thermal Analyzer	Perkin Elmer Inc, Boston,MA,USA
Uv-spectrophotometer	Varian, Palo Alto,USA
Dissolution apparatus	Electro- lab, Chennai, India
PH meter	Toshniwal Instruments Mfg. Pvt. Ltd., Ajmer, Rajasthan, India
Centrifuge	Remi Equipments, Mumbai ,Maharashtra,India
Stability chambers	Themolab Scientific Equipments Pvt.Ltd, Mumbai,India

4.3. Polymer

4.3.1.Crown Zein

Nanoparticles name:

USP: Zein

Chemical Name:

Zein

Molecular weight:

>>38000

Functional category:

Coating agent; extended release agent; tablet binder.

Application in pharmaceutical formulation or technology

Zein is used as a tablet binder in weight granulation process or as a tablet coating agent. It's primarily used as an enteric coating agent or in extended release oral tablet formulation. Zein is also used in food application as a coating agent.

Use.	Concentration(%)
Tablet coating agent.	15
Tablet sealer	20
Wet granulation binder.	30

Description

Zein is polymeric obtained from cron.It occurs as granular,straw to plate yellow-colored amorphous powder or fine flakes and has a charcteristic odor and bland taste.

Typical properties

Density:1.23 g/cm_3

Melting point : when completely dry it may be heated to 200°c without visible signs of decomposition.

Particle size distribution: 100%,< 840 micro m in size.

Solubility, partially insoluble in acetone; soluble in aqueous alcohol solutions; aqueous acetone solutions(60-80% v/v) and glycols. Also soluble in aqueous alkaline solutions of pH 11.5 & above.

Stability and storage conditions:

Zein should be stored in an airtight container,in a cool dry place.It has not been reported to polymmerize.

Incompatibilities:-

Incompatible with oxidizing agent.

4.3.2. Carbopol

Nonproprietary Names

BP: carbomer

PhEur : carbomer

USP : Carbomer

Note that the USP contains several carbomer monographs.

Synonyms

Acritamer, acrylic acid polymer, carbopol, carboxyviniyl polymer, carboxypolymethylene, polyacrylic acid.

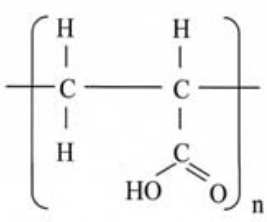
Chemical Name

Carbomer 910,934,934A 940,941,971P and 974P resins.

Empirical formula and molecular weight

Carbomers are synthetic High molecular weight polymers of acrylic acid that are crosslinked with either allylsucrose or allyl ethers of pentaerythritol. They contain between 56-86% of carboxylic acid (-COOH) groups as calculated on the dry basis.The PhEur has a single monographs describing carbomer in composition with the USP that contain several monographs describing individual carbomer grades that vary in aqueous viscosity and in lebeling for oral ana nanoral use.The molecular weight of carbomer resins is theoretically estimated at 700,000 to 4 billion.In an effort to measure the molecular weight between crosslinkes (Mc) researchers have extended the network theory of elasticity to swollen gels have utilized the inverse relationship between the elastic modulus and Mc. Estimated Mc of 237,600 gm/mole for carbopol 941 and of 104,000 viscosity and lower rigidity will have higher Mc and conversly, higher viscosity,more rigid carbomer resins will have lower Mc.

Structural Formula



Acrylic acid monomer unit in carbomer resins.

Carbomer polymer formed from repeating unit of acrylic acid.The polymer chains are crosslinked with allylsucrose of allylpentaerythritol.

Functional category

Bio adhesive, emulsifying agent, release modifying agent, suspending agent, tablet binder, viscosity increasing agent.

Application in pharmaceutical formulation or technology

Carbomer are used mainly in liquid or semi-solid pharmaceutical formulations as suspending or viscosity increasing agent. Formulation include creams,gels and ointments for use in opthalmic,rectal and topical preparation. Carbomer grades with a low residual benzene contant,such as carbomer 934P or 974P low residual ethyl acetate levels such as carbomer 974P,may additionally be used in oral preparations in suspension tables, or sustaind- release tablet preparation. In tablet formulation carbomer are used as dry or wet binders and as a rate controlling excipient.In wet granulation process,water or an alcohol/water blend is used as the granulating fluid.The tackiness of wet mass can be reduced with the addition of certain cationic species to the granulating fluid. Carbomers resins have also been investigated in the preparation of sustained release, matrix beads,as enzyme inhibitors of intestinal proteases in peptide containing dosage forms,as a bioadhesive for a cervical patch for intranasally administered microspheres and in magnetic granules for site specific drug delivery to the esophagus. Carbomer are also employed as emulsifying agent in the preparation of oil-in water emulsions for external use. For the purpose, the carbomer is netralized party with sodium hydroxide and party with a long chain amine such as stearylamine. Carbomer 951 has been investigated as a viscosity increasing aid in the preparation of multiple emulsion microspheres. Carbomer are also used in cosmetics.

Use	Concentration(%)
Emulsifying agent.	0.1-0.5%
Gelling agent.	0.5-2.0%
Suspending agent.	0.5-1.0%
Tablet binder.	5.0-10.0%

Description

Carbomer are white coloured,'fulffy', acidic hygroscopic powder with a slight characteristic order.

Typical properties

Acidity/Alkalinity : pH = 2.7-3.5 for a 0.5% w/v aqueous dispersion; pH = 2.5-3.0 for a 1% w/v aqueous dispersion.

Density (bulk): 0.163 g/cm_3

Density (tapped) :0.260 g/cm_3

Glass transition temperature :100-105 °C

Melting point: decomposition occurs within 30 min at 260 °c.

Moisture content: normal water content is up to 2% w/w However carbomer are hygroscopic and a typical equilibrium moisture content at 25 °c and relative humidity is 8% w/w.The moisture content of a carbomer more difficult to handle, i.e it is readily dispersed.

Particle size: primary particles average about 0.2 µm in diameter. The flocculated powder particles average 2-7 µm in diameter and cannot be broken down into the primary particles.

Solubility:- soluble in water in after neutralization, in ethanol and glycerin.

Specific gravity: 1.41

Viscosity(dynamic): carbomers disperse in water to from acidic colloidal solution of low viscosity that when neutralized produce highly viscous gels. Carbomers powder should first be dispersed into vigorously stirred water, taking care to avoid the formation of a base. BF Goodrich has introduced the carbopol ETD and ultrez 10 series of carbomer to help overcome some of the problem of dispersing the powder into aqueous solvents. The line of carbomer resins wets quickly, yet hydrates slowly while processing a lower unneutrilized dispersion viscosity. Agents that may be used to be neutralized carbomers polymers include amino acid,borax , potassium hydroxide , sodium bicarbonate, sodium hydroxide and polar organic amines such as triethanolamine. Lauryl and stearyl amines may be used as gelling agents in nonpolar systems. One gram of carbomer is netralized by approximately 0.4 gm of sodium hydroxide. During preparation of the gel the solution bubbles. Neutralized aqueous gels are more viscous at pH 6-11. The viscosity is considerably reduced at pH values less than 3 or greater than 12 or in the presence of strong elctrolytes. Gels rapidly lose viscosity on exposure to ultraviolet light but this can be minimized by the addition of a suitable antioxidant.

4.3.3. Ethyl cellulose

Nano proprietary name

BP : Ethyl cellulose

PhEur : Ethylcellulosum

USP : Ethyl cellulose

Synonyms

Aquacoat; E462 ;Ethocel ; Surelease

Chemical Name

Cellulose ethyl ether

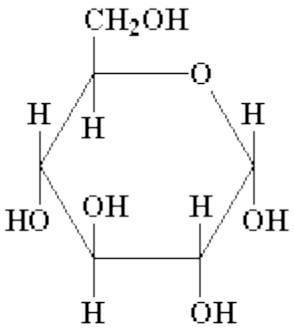
Empirical formula and molecular weight

Ethyl cellulose with complete ethoxyl substitution (DS=3) is $C_{12}H_{23}O_6(C_{12}H_{22}0_5)nC_{12}H_{23}O_5$

Where n can provide a wide variety of molecular weight . Ethyl cellulose, an ethyl ether of cellulose ,is a long chain polymer b- anhydroglucose units join together by acetal linkages.

Structural Formula

The structure with complete ethoxyl substitution is given below.



glucose

Functional category

Coating agent, favouring fixative tablet binder, tablet filter, viscosity increasing agent.

Application in pharmaceutical formulation and technology

Ethyl cellulose is widely used in oral and topical pharmaceutical formulation.

The main use of ethyl cellulose in oral formulations is a hydrophobic cotting agent for tablet and granules. Ethyl cellulose coating are used to modified release drug , to mask an unpleasant taste ,or to improve the stability of formulation, as is the case the granules are coated to ethylcellulose to inhibit oxidation. Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.

Ethylcellulose disolve in an organic solvent or solvent mixture can be used on its own to produce water insoluble flims. High viscosity ethylcellulose grades tends to produce stronger and most durable flims. Ethylcellulose flims may be modified to alter their solubility, by the addition of hydroxpropyl methylcellulose or a plasticizer. An aqueous polymer dispersion of ethylcellulose such as Aquacoat (FMC Crop) or Surelease may also be used to produce ethylcellulose flims without the need for organic solvents. Drug release thought the film coat. This can be slow process unless a large surface area is utilized.In those instances, aqueous ethylcellulose dispersions tend therefore to be used to coat granules or pellets. Ethylcellulose- coated beads/ granules have also demonstrated the ability to absorb pressure and hence protect the coating from facture during compression.

High viscosity grades of ethylcellulose are used in drug microencapsulation.

Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area.

In tablet formulations , ethylcellulose may additionally be employed as a binder the ethylcellulose being blended dry or wet granulated with a solvent such as ethanol (95%).Ethylcellulose produces hard tablets with low fribility; however, they may demonstrate poor dissolution.

Ethylcellulose has also been used as an agent for delivering therapeutic agent from oral appliances.

In topical fromulations, ethylcellulose is used as a thickening agent in creams.lotions , or gels, provided an appropriate solvent is used.

Description:-

Ethylcellulose is a tasteless, free- flowing, white to light tan coloured powder.

Typical properties:-

Density (bulk): 0.4 g/cm_3

Glass transition temperature: 129-133 °c

Specific gravity:1.12-1.15 g/cm_3

In addition, nonpharmaceutical grades of ethylcellulose which differ in their ethoxyl content and degree of polymerization are also available.

Storage and storage conditions:-

Ethylcellulose should be stored as a temperature not exceeding 90°F(32°c) in a dry area away from all sources of heat.It should not be stored next to preoxides or other oxidizing agents.

Incompatibilities:-

Incompatible with paraffin wax and microcrystalline wax.

Safety:-

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is used in food products. Ethylcellulose is not metabolised following oral consumption and is therefore a noncaloric substance. It is generally regarded as a nontoxic, non-allergic and nonirritating material. Ethylcellulose is not metabolised and therefore is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

Handling precautions:-

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and therefore eye protection should be worn.

Regulatory status:-

Ethylcellulose is GRAS listed and is included in the FDA inactive ingredients guide (oral capsules, suspensions and tablets topical emulsions and viginal preparations).

4.3.4.Gum Acacia

B.P.- Gum Acacia

U.S.P.-:Gum Acacia

Synonyms:-

Gum arabic, Acacia, Gum (ACACIA SENEGAL (L.) WILLD.)

Australian gum

Chemical Name: N-(8-(2-Hydroxybenzoyl)amino)caprylate MeSH

N-(8-(2-Hydroxybenzoyl)amino)caprylate sodium

Chemical Formula: $C_{15}H_{20}NNaO_4$

IUPAC name:

sodium 2-[(7-carboxyheptyl)-C-hydroxycarbonimidoyl]benzen-1-olate

Average Molecular Weight-301.318

Monoisotopic Molecular Weight-301.12900241

Description:

This compound belongs to the class of organic compounds known as medium-chain fatty acids. These are fatty acids with an aliphatic tail that contains between 4 and 12 carbon atoms.

Application & usage:-

Gum arabic's mixture of polysaccharides and glycoproteins gives it the properties of a glue and binder that is edible by humans. Other substances have replaced it where toxicity is not an issue, and as the proportions of the various chemicals in gum arabic vary widely and make it unpredictable. Still, it remains an important ingredient in soft drink syrup and "hard" gummy candies such as gumdrops, marshmallows, and M&M's chocolate candies. For artists, it is the traditional binder in watercolor paint, in photography for gum printing, and it is used as a binder in pyrotechnic compositions. Pharmaceutical drugs and cosmetics also use the gum as a binder, emulsifying agent, and a suspending or viscosity increasing agent. Wine makers have used gum arabic as a wine fining agent.

It is an important ingredient in shoe polish, and can be used in making homemade incense cones. It is also used as a lickable adhesive, for example on postage stamps, envelopes, and cigarette papers. Lithographic printers employ it to keep the non-image areas of the plate receptive to water. This treatment also helps to stop oxidation of aluminium printing plates in the interval between processing of the plate and its use on a printing press.

Gum arabic is used in the food industry as a stabilizer, emulsifier and thickening agent in icing, fillings, soft candy, chewing gum and other confectionery and to bind the sweeteners and flavorings in soft drinks.A solution of sugar and gum arabic in water, gomme syrup, is sometimes used in cocktails to prevent the sugar from crystallizing and provide a smooth texture.

Gum arabic is a soluble dietary fibre, a complex polysaccharide, primarily indigestible to both humans and animals. It is considere non-toxic and safe for human consumption. There is indication of harmless flatulence in some people taking large doses of 30g or more per day. It is not degraded in the intestine, but fermented in the colon under the influence of microorganisms—it is a prebiotic (as distinct from a probiotic). There is no regulatory or scientific consensus about its caloric value; an upper limit of 2 kcal/g was set for rats, but this is not valid for humans. The US FDA initially set a value of 4 kcal/g for food labelling, but in Europe no value was assigned for soluble dietary fibre. A 1998 review concluded that "based on present scientific knowledge only an arbitrary value can be used for regulatory purposes". In 2008 the FDA sent a letter of no objection in response to an application to reduce the rated caloric value of gum arabic to 1.7 kcal/g.

Storage:

The crude gum arabic is stored and exported either in burlap or jute sacks. The graded gum is packed in heavy duty bags of about 80 kg each. The US regulations require that only new, unused jute sacks are used. Semi-processed and processed kibbled variety, granules and powdered gum arabic is exported in drums, polyethylene lined multi-wall paper bags or polyethylene lined cardboard boxes. Gum arabic, when stored in cool (21 -24°C) and dry place, has an unlimited shelf life.

Typical properties:

Optical rotation: provides assurances that the gum has not come from other tree species

Moisture content: not more than 12-14% is permitted

Foreign matter content: no more than 3-5 % is permitted

Color(specific parameters)

Viscosity (specific parameters)

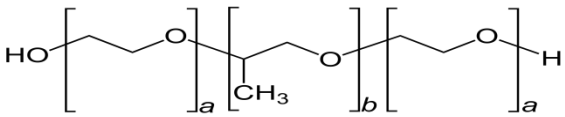
Microbiological count: tests for Salmonella,Escherichia coli and Staphyloccus aureus should be negative.

4.3.5.Poloxamer

Nanoproprietary Names

BP: Poloxamer 188

USP: Poloxamer



Synonyms:

lutrol, Monolon, pluronic, poloxalkol, polyethylene-propylene glycol copolymer, polyoxyethelene-polyoxypropylene copolymer, supronic, synperonic.

Chemical Name:

a-hydro w-hydroxypoly(oxythelene)poly(oxypropylene) poly(oxythelene) block copolymer.

Empirical formula and molecular weight:

The Poloxamer propyl are a series of closely related block copolymers of ethylene oxide or propylene oxide confirming to the general formula.

$HO(C_2H_2O)_a(C_3H_6O)_b(C_2H_4O)_aH$

The BP includes only poloxamer 188, where “a” is about 75 and “b” about 30; it has an average molecular weight of 8350.

Functional category

Dispersing agent, emulsifying agent, and solubilizing agent, tablet lubricant, wetting agent.

Application in pharmaceutical formulation and technology:

Poloxamer are nonionic polyoxyethelene-polyoxypropylene copolymer used primarily in pharmaceutical formulation as emulsifying and solubilizing agents.The polyoxyethelene segment is hydrophilic while the polyoxethelene segment is hydrophobic. All of the Poloxamers are chemically similar in composition, differing only in the relative amounts of propylene ethylene oxides added during manufacture Their physical and surface active properties very over a wide range and a number of different types are commercially available.

Poloxamer are used as emulsifying agent in intervenous fat emulsion and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups, poloxamer may also be used as wetting agents, in ointments, suppositories bases, gels and tablet binders and coating.

Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid dispersion system.

Poloxamer 338 and 447 are used in solution for contact lens care.

Use.	Concentration (%)
Fat emulsifier.	0.3
Flavour solubilizer.	0.3

Fluorocarbon emulsifier.	2.5
Gelling agent	15-50
Spreading agent.	1
Stabilizing agent	1-5
Suppositories base.	4-6 or 90
Tablet coating.	10
Tablet excipient.	5-10
Wetting agent.	0.01-5

Description

Poloxamers generally occur as white-colored, waxy, free flowing prilled granules or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

Typical Properties

Acidity/alkalinity: pH 5.0-7.4 for a 2.5% w aqueous solution.

Cloud point: > 100°C for a 1 % w/y aqueous solution and a 10% w/v aqueous solution of poloxamer 188.

Density: 1.06 g/cm at 25°C

Flash point: 260°C

Flowability: solid poloxamers are free flowing.

HLB value: 0.5-30; 29 for poloxamer 188.

Melting point: 16°C for poloxamer 124; 52-57°C for poloxamer 188; 49°C for poloxamer 237; 57°C for poloxamer 338; 52-57°C for poloxamer 407.

Moisture content: poloxamers generally contain less than 0.5% w/w water and are hygroscopic only at greater than 80% relative humidity.

Solubility: solubility varies according to the poloxamer type.

Surface tension: 19.8 mN/m (19.3 dynes/cm) for a 0.1% w/w aqueous poloxamer 188

solution at 25°C: 24.0 mN/m (24.0 dynes/cm) for a 0.01% w/v aqueous poloxamer 188

solution at 25°C: 26.0 mN/m (26.0 dynes/cm) for a 0.001% w/v aqueous poloxamer solution at 25°c

Viscosity (dynamic): 1000 mPa s (1000 cP) as a melt at 77°C.

Stability and Storage Conditions:-

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis and metal ions. However, aqueous solutions do support mold growth.

The bluk meterial should be stored in a well closed container in a cool, dry, place.

Acute animals toxicity data for poloxamer 188

LD50(mouse, IV): 1g/kg

LD50(mouse, oral): 15 g/kg

LD5o (mouse, SC): 5.5 g/kg

LD5o (rat, IV): 7.5 g/kg

LD5o (rat, oral): 9.4 g/kg

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material

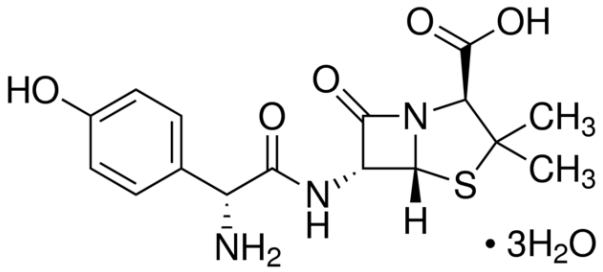
handled. Eye protection and gloves are recommended.

Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections, inhalations, ophthalmic preparations, oral powders, solutions, suspensions and syrups, also topical preparations) Included in nonparenteral medicines licensed in the UK.

4.4 Drug profile

4.4.1.Amoxicillin trihydrate



Molecular Formula C16H19N3O5,S,3H2O

Molecular Weight 419.45

Amoxicillin trihydrate contains not less than 95.0 per cent and not more than the equivalent of 102.0 per cent of (2S,5R,6R)-6-LI(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3.3 dimethyl-7-oxo -4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, calculated with reference to the anhydrous substane.

Physico-chemical Properties

A white or alnost whil, erstlline powder, sighly silable in water, very slightly soluble in alcohol, practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Mechanisms of action

An aminopenicillin that inhibits cell-wall synthesis during bacterial multiplication.Bacteria resist amoxicillin by producing penicillinases- enzymes that hydrolyze amoxicillin.

Pharmacokinetics

Bioavailability	95% oral
Metabolism.	less than 30% biotransformed in liver
Half life.	61.3 minutes
Excretion.	renal

Available forms

Tablets: 500 , 875 mg

Tablets (chewable): 125 mg, 250 mg

Capsules: 250 mg, 500 mg

Oral suspenson: 50 mg/mL (pediatric drops), 125 mg/5 mL, 250 mg/5 mL (after reconstitution)

Storage

Store in an airtight container.

Adverse reactions

CNS: lethargy, hallucinations, Seizures, anxiety, confusion, agitation, depression,dizziness, fatigue.

Gl nausea, vomiting, diarrhea, glossitis, stomatitis, gastritis, enterocolitis, abdominal pain, pseudomembranous colitis, black hairy tongue.

GU: interstitial nephritis, nephropathy, vaginitis.

Hematologic: anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia,

leukopenia, hemolytic anemia, agranulocytosis

Other: hyperseusitivity reactions, anaphylaxis, overgrowth of nonsusceptible organisms.

Interactions

Drug-drug. Alopurinol: Increased risk of rash. Monitor patient.

contraceptives: May decrease efficaey of oral contraceptives. Recommend additional form of contraception during penicillin therapy.

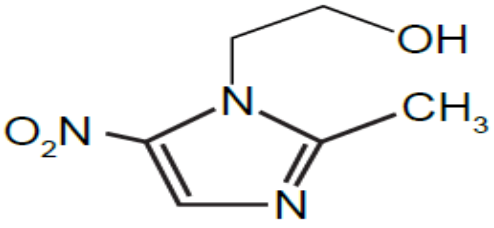
Probenecid: Increased blood levels of amoxicilin and other penicillins. Probenecid may be used for this purpose.

Drug-herb.khat: May decrease antimicrobial effect of certain penicillins. Avoid khat chewing or give amoxicillin 2 hours after khat chewing.

contraindications

contraindicated in patients hypersensitive to dug or oither penicillins.

4.4.2. Metronidazole



Molecular weight: 171.16 g/ml

IUPAC Name: 2-(2-methyl-5-nitroimidazol-1-yl)ethanol.

Physical Description:

White to pale-yellow crystalline powder with a slight odor. Bitter and saline taste. pH (saturated aqueous solution) about 6.5.

Cream:colored crystals

Odor: Odourless

Melting Point: 316 to 320 ° F , 160°c

Solubility:less than 1 mg/mL at 68° F

Water Solubility: 9500 mg/L (at 25 °C)

Solubilities: g/100 ml at 20 deg C: 1.0 in water, 0.5 in ethanol, less than 0.05 in ether, chloroform; sol in dilute acids; sparingly sol in dimethylformamide

Children: Neonatal (<28 Days) Anaerobic Infection

<1.2 kg 7.5 mg/kg IV/PO q48hr

<7 days 1.2-2 kg: 7.5 mg/kg IV/PO qDay

>2 kg 15 mg/kg/day IV/PO divided q12hr

>7 days. 1.2-2 kg: 15 mg/kg/day IV/PO divided q12hr>2 kg: 30 mg/kg/day IV/PO divided q12hr

Infants and Children:30 mg/kg/day PO/IV divided q6hr; not to exceed 4 g/day

Clostridium Difficile Colitis:30 mg/kg/day IV/PO divided q6hr IV/PO for 7-10 days (American Academy of Pediatrics)

Amebiasis:35-50 mg/kg PO divided q8hr for 10 days

Giardiasis:15 mg/kg/day IV/PO divided q8hr for 5 days

Trichomoniasis:< 45 kg body weight: 15 mg/kg/day IV/PO divided q8hr for 7 days; not to exceed 2 g/day

Helicobacter Pylori-Associated Peptic Ulcer Disease (Off-label):With amoxicillin and bismuth subsalicylate: 15-20 mg/kg/day PO divided q12hr for 4 weeks

In Adults

Anaerobic Bacterial Infections
Loading dose: 15 mg/kg IV; not to exceed 4 g/day

Maintenance dose: 7.5 mg/kg PO/IV (over 1 h) q6hr x 7-10 days (or 2-3 weeks if severe)

Sexually Transmitted Disease: Prevention following sexual assault:2 g PO as a single dose; 3-drug regimen that also includes ceftriaxone or cefixime, PLUS azithromycin or doxycycline (CDC STD guidelines, 2010)

Bacterial Vaginosis

Nonpregnant women

500 mg PO BID x 7 days, OR

2 g PO qDay single dose, OR

Extended-release: 750 mg PO qDay x 7 days

Pregnant women

500 mg PO BID x 7 days, OR

250 mg PO TID x 7 days

Colorectal Surgical Infection

Prophylaxis; start after mechanical bowel preparation the afternoon and evening before surgery

1 g PO q6-8hr for 3 doses

15 mg/kg IV over 30-60 min; complete approximately 1 hr before surgery; may administer 7.5 mg/kg IV over 30-60 min at 6 and 12 hr after initial dose for maintenance; discontinue within 12 hr after surgery

Trichomoniasis

250 mg PO q8hr for 7 days; alternatively, 375 mg PO q12hr for 7 days

2 g PO qDay single dose; alternatively, 1g PO q12hr for 2 doses

Amebiasis:500-750 mg PO q8hr for 5-10 days

Giardiasis (Off-label):500 mg PO q12hr for 5-7 days

Gardnerella Infection:

Immediate release: 500 mg PO q12hr

Extended-release: 750 mg PO qDay for 7 days; take on empty stomach

Helicobacter Pylori Infection (Off-label):250-500 mg PO QID in combination with tetracycline (500 mg) and bismuth subsalicylate (525 mg) x 14 days

Nongonococcal Urethritis (Off-label):2 g PO qDay single dose with erythromycin (500 mg QID) or erythromycin ethylsuccinate (800 mg QID) x 7 days

Pelvic Inflammatory Disease (Off-label):500 mg PO q12hr for 14 days in conjunction with ofloxacin or levofloxacin

Dosing Considerations

Hepatic failure Mild to moderate hapatic impairment (Child-Pugh A or B): No dosage adjustment needed but patients should be monitored for metronidazole associated adverse events

Severe hepatic impairment: Reduce dose of by 50%

Renal failure

✓Mild to moderate renal impairment: Dose adjustment not considered necessary as elimination half-life not significantly altered

✓Severe renal impairment or end stage of renal disease: Metronidazole and metronidazole metabolites may accumulate significantly because of reduced urinary excretion; monitor in severe renal impairment or end stage of renal disease, not undergoing hemodialysis

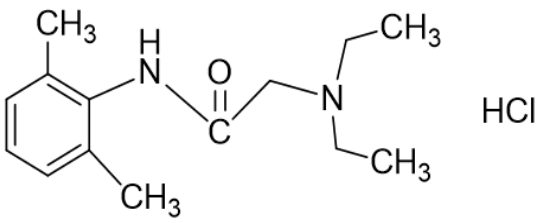
✓Hemodialysis removes significant amounts of metronidazole and its metabolites from systemic circulation; supplementation may be necessary

✓Peritoneal dialysis: Monitor for signs of toxicity due to potential accumulation of metronidazole metabolites.

Pouchitis (Orphan):Orphan indication sponsor

Crohn Disease (Orphan):Topical treatment of active perianal Crohn disease

4.4.3. Lidocaine hydrochtoride



Molecular Formula $C_{14}H_{22}N_2O.HCI$

Molecular Weight 270.80

Lidocaine hydrochloride is chemically designated as 2-(diethyl amino)-N-(2,6 dimethyl/pheny) acetamide.

Physico-chemical Properties:

Pyical state and appearance: White crystalline powder.

Odor Odorles

Color: White.

Solubility: Soluble in water.

Melting Point: 77°C (170.6°F)

Mechanism of Action

It decreses automaticity by slowing the rate of spontaneous phase IV depolarization.Terminates re-enty by decreasing conduction in re-entrant pathways (by showing conditions in ischemic tissue, equalizers conduction speed among fibers). Increases Ventricular fibrillation threshold.

Pharmacokinetics.

Bioavailability	35%(oral)
	3%(topical)
Metabolism	Hepatic. 90 CYPIA2-mediated
Half-life.	1.5-2 hours
Excretion.	renal

Indications and Usage

Acute management of ventricular artythmias topical anesthesia in local skin disorders; local anaesthesia of acecessible mucous membranes.

Dosage and Administration

Adults

Adult im, dose is 300 mg. May be repeated aftr 60 to 90 min and i.v. bolus varies between 50 and 100 mg at rate of 25 to 50 mg/min; may be repeated, but should not exceed 200 to 300 mg/h. It has a continaous infusion 1 to 4 mg/min. Patch applied and allowed to remain in place until the desired ane sthetic effect is produced for up to 15 min.

The lowest dosage for effectiveness is generally used.

Children

IV bolus/intratracheal I mg/kg/dose every 5 to 10 min max dose. 5 mg/kg). Maintenance dose is 20 to 50 mcg/kg/min. Topical Apply as needed to affected area.

Drug Interactions

Beta-adrenergic blockers: Increased lidocaine levels.

Cimetidine:Decreased lidocaine Cl.

Class I antiarriythmic agents (eg. tocainide, mexiletine): Toxic effects are additive and potentially synergistic.

Procainamide: Additive neurological and cardiac effects.

Suciylcholine: Prolongation of neuromuscalar blockade.

Incompatibility

It has reported incompatibility with Amphotericin B, parenteral cephalosporins, doxycycline, epinephrine, isoproterenol, methohexital, nitroprusside, norepinephrine,phenytoin, sodium bicarbonate, sulfadiazine,

Storage/Stability

All forms of drug may be stored at room temperature.

Adverse Reactions

Cardiovascular: Hypotension; bradycardia, CV collapse, cardiac arrest.

CNS: Dizziness lightheadedness;, nervousness, drowsiness, apprehension; confusion, mood changes;hallucinations, tremors.

EENT: Visual disturbances; diplopia; tinnitus.

GI: Nausea; vomiting.

Respiratory: Respiratory depression or arrest.

Miscellaneous: Hypersensitivity reactions. Local reactions, including soreness at i.m. injection site; venous thrombosis or phlebitis; extravasation; burning, stinging, sloughing,tenderness (with topical application). Difficulty in speaking, breathing and swallowing;numbness of lips or tongue and other paresthesias, including heat and cold.

Contraindications

✓Known hypersensitivity/allergy.

✓Use extreme caution in patients with conduction disturbance (second or third degree block).

CHAPTER 5

METHODOLOGIES

5. Methodologies

5.1.Preparation of calibration curve

Amoxicillin trihydrate, lidocaine hydrochloride and metronidazole solutions(100µg/ml) were prepared individually in simulated saliva .pH 6.8 (prepared by dissolving 2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8 g of Nacl in a liter of distilled water)[39] and water –ethanol mixture (1:1) and scanned from wave length 200 nm to 400 nm with Cary 50 UV-Vis spectrophotometer with respect to their solvent blanks. In simulated saliva the absorption maxima(λ max) values of amoxicillin trihydrate, lidocaine hydrochloride and metronidazole were 269 nm , 273 nm and 318 nm, respectively. On the other hand ,in 1:1 water- ethanol mixture the values were 269 nm, 273 nm and 318 nm for amoxicillin trihydrate, lidocaine hydrochloride, respectively.

10 mg of each drug was dissolved separately in 100 ml of each solvent by continuous stirring and resulted in stock solutions of 100 µg/ml. Six sets of stock solutions were prepared and different dilutions(20,40,60,80 and 100 µg/ml) were made by adding required volume of respective medium, The individual absorbance was determined spectrophotometrically at their respective wavelengths.The calibration curves were prepared by plotting with their average value of the absorbances against concentration for the every individual drugs.

5.1.1.Molar absorptivity

Molar absorpitivity can be defined as follows:

$$\varepsilon = A/c\ L$$

(where A= absorbance, C= sample concentration in moles/ liter and L= length of light path though the cuvette in cm.)

$$c = A/\varepsilon\ L (= A/\varepsilon \text{ when } L = 1 \text{ cm})$$

Application of a molar extinction coefficient in the calculation of concentration in terms of molarity:

$$A / \varepsilon \text{ molar} = \text{molar concentration}$$

However, for1% (=1g/100 mL) solutions measured in a 1 cm cuvette. These values can be understood as percent solution extinction coefficients(ε percent) having units of $(g/100\ mL)^{-1}cm^{-1}$ instead of $M^{-1}\ cm^{-1}$.

Consequently, when these values are applied as extinction coefficients in the general formula, the units for concentration, c, are present solution (i.e; 1%=1 g/100 mL=10 mg/ mL).

$$A/ \varepsilon\text{percent} = \text{percent concentration}$$

If concentration is in terms of mg/ mL, then an adjustment factor of 10 must be made when using these percent solution extinction coefficients (i.e; 10mg/ mL units must be converted to 1 mg/mL concentration units),

$$(A /\varepsilon \text{ percent})10= \text{concentration in mg/ mL})$$

The relationship between molar extinction coefficient (ε molar) and percent extinction coefficient(ε percent) is as follows:

$$(\varepsilon \text{ molar }) = (\varepsilon \text{ percent }) \times (\text{ molecular weight of the test compound})$$

5.2.Preparation of denticaps

5.2.1 Formulation of dental molds

For developing dental molds, primary primarily several polymers mixed were screened at different ratio. The best formulation depends on physicochemical properties and drug release has been reported here. Moldable “denticaps” will formulated with combination of polymers such as corn zein, carbopol, gum karaya, poloxamer, ethyl cellulose,(Table:6) Here, corn zein was used to form

drug matrix for sustained release[40] of drugs Carbopol and gum karaya were used for achieving adhesiveness in the formulations since they are known to possess mucoadhesive property[41,42] Poloxamer to be a wetting agent,[43] Ethyl cellulose to be used for coating purpose.[44]

To from a paste, drugs and polymers is mixed in ethanol using homogenizer. Then mixture to be poured in a cap-shaped ethanol-proof plastic molds and will subjected to evaporation of solvent at 37°C for 2h attached before coating the formulation. Finally, the formulations will coated from all the sides except the side for drug release on the affected tooth. Prior to coating, the formulations to be removed from the plastic molds. The coating done using ethanolic solution of ethyl cellulose following the method available keeping drug release side-covered.

Fig:3 Diagram of prepared Denticap (internal diameter 1 cm, height 1 cm) before coating

Table 1: Composition of prepared denticaps

Formulation	Ingredients (ratio by weight)*	Weight of drug(mg)
Denticap-L	Cron Zein, Carbopol 934 P,Gum karaya and poloxamer 407(8:8:4:1) (Ethyl cellulose was used for coating only)	Lidocaine hydrochloride 50mg

Denticap-A	Corn zein,Carbopol 934P,Gum karaya and poloxamer 407(8:8:4:1) (Ethyl cellulose was used for coating only)	Amoxicillin trihydrate 70 mg
Denticap-M	Corn zein,Carbopol 934P,Gum karaya and poloxamer 407(8:8:4:1) (Ethyl cellulose was used for coating only)	Metronidazole 67 mg
Denticap-ALM	Corn zein,Carbopol 934P,Gum karaya and poloxamer 407(8:8:4:1) (Ethyl cellulose was used for coating only)	Lidocaine hydrochloride 50mg, Amoxicillin trihydrate 70 mg, Metronidazole 67 mg

Total weight of the polymer blend is g 449.5 g

L, A, M and ALM stand for lidocaine hydrochloride, amoxicillin trihydrate, metronidazole and lidocaine hydrochloride -amoxicillin trihydrate - metronidazole , respectively

5.2.2.Coating Procedure

The denticaps were coated from all the sides except the side for drug release on the affected tooth (Fig:4). The coating was done using 5% ethano.lic solution of ethyl cellulose[45] by immersing (for 2 minutes) the denticaps into the coating solution keeping the drug release side adhered on a glass slide using both side gummed adhesive tape After withdrawal from coating solution the denticaps were dired at 37ºc for 30 min.

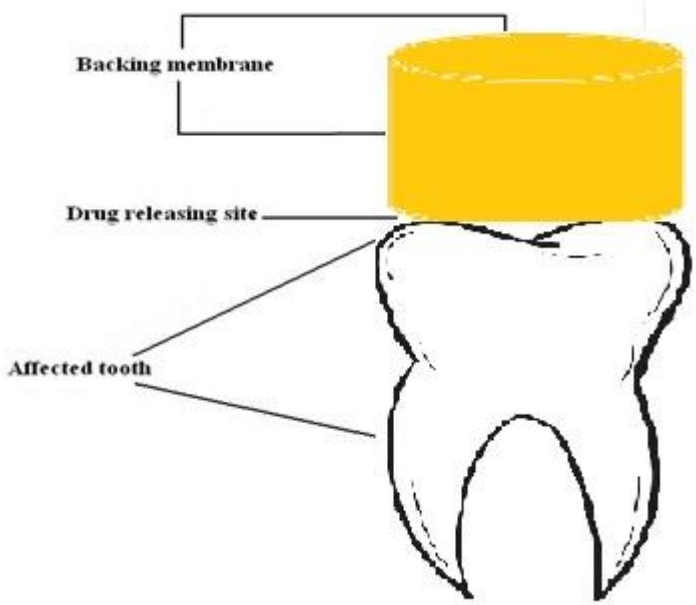


Fig:4 Outline Diagram of a Denticap on an affected Tooth

5.3. Physciochemical Characterization of denticaps

5.3.1. Drug-Excipient Interaction Study Using FTIR Spectroscopy

For pre-formulation experiment drug –excipient interaction study[46] is needed to confirm whether the excipients of a formulation interact chemically among themselves as well as with drug, present in the formulation. FTIR spectroscopy was used here for the purpose. Pure drug separately with poly-meric combinations; and polymeric combinations alone were mixed separately with IR grade K Br in the ratio 1:100 and corresponding pellets were prepared by applying pressure in a hydraulic press the pellets were scanned over a wave number range of 4,000–400 cm−1 in Magna IR 750 Series II FTIR spectroscope.

5.3.2Tooth Adhesion Test

To prepare a tooth model, some teeth of goats collected will fixed on a plaster of paris base. Teeth will be cleaned with distilled water before fixing. The

individual experimental formulation to be attached to the tooth model after being made wet with simulated saliva (pH 6.8, viscosity 0.740 cp at 37 ± 0.5°C). A physical balance with two circular pans, balanced with a fulcrum on a stand,(Fig:5).hanged from a rod was used as a modified tooth adhesion test assembly. Lower surface of a pan will be fixed to the denticap attached to the tooth model as described above, by both-side adhesive tape. Weights were given on the other pan continuously until the denticap[47] will be detached from the tooth model. Simulated saliva to be prepared by dissolving in Na2HPO4, KH2PO4, and NaCl in a litre of distilled water.

5.3.3.Percent Swelling

For swelling the original weights of the denticaps will be determined and allowed on a petri dish in stimulated saliva PH 6.8. At predetermined time intervals (1–5 h), increase in weights (wet weight) to be reported after removal of excess saliva with filter paper. When the weight became constant, percent swelling was calculated in terms of water uptake.[48,49]

$$Percent\ Swelling = \frac{(Wt - W0)}{W0}\ X\ 100$$

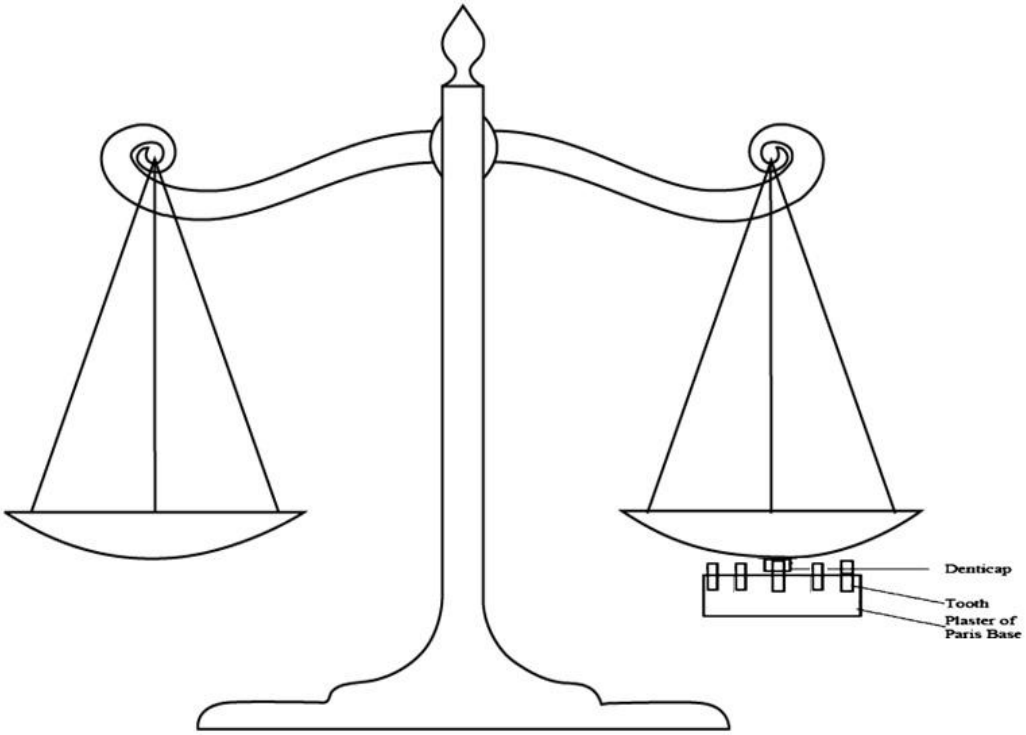


Fig:5 Mucoadhesive strength test assembly

5.3.4.Surface pH

The denticaps will be incubated in a Petri dish in simulated saliva, for 2 h. Then, the surface pH will be determined by touching the electrode of a pH meter in the excess simulated saliva present at the surface of the denticaps.[50]

5.3.5.Scanning electron microscopy (SEM)

The drug distribution patterns of denticaps (before and after drug release) were studied using scanning electron microscope (GerminiSEM-450, JEOL,Tokyo , Japan). Experimental samples were cut and mounted onto stubs and then platinum sputtered under vacuum. They were visualized at an acceleration voltage of 20KV.

5.3.6.Drug Content analysis

After dental mold was taken in 100 ml stimulated saliva, PH 6.8 in a volumetric flask, the mixture will stir for forty-eight hours at a room temperature using a magnetic stirrer. The drug will be done by simultaneous equation UV method[51] as described above. Initially, the time of analysis of the method to be standardized by taking formulation with measured amount of drug in simulated saliva and determination of amount of drug released with the duration. It will find that 100% release of the drug was achieved in 48 h. Therefore, the time of drug content analysis will be chosen up to 48 h.

5.4.In vitro drug release study of denticaps

Drug release study is to evaluate the release characteristic of drug from denticaps. Release of individual drug and combination of lidocaine hydrochloride – amoxicillin trihydrate from denticaps was carried out in aUSP apparatus I .In this apparatus denticaps were placed inside the basket and the drug release occurs from only one side of the formulation , which remains open towards the reservoir containing 100 ml of stimulated saliva , pH 6.8 as a dissolution media at 37±0.5ºC and 50 rpm The flow rate of saliva was maintained by replacing the dissolution medium time to time at a predetermined time intervals (every hour up to 6 h).Amoxicillin trihydrate , lidocaine hydrochloride and metronidazole were assayed by simultaneous equation UV method[52] at 269 nm,273 nm and 318 repectively.Both the drugs obeyed linearity at the concentration of 10-100 µg/ml. The difference between the test (denticap with drug) control (denticap without drug) reading was considered as the absorbance due to drug.

CHAPTER 6

RESULTS AND DISCUSSION

6❖Results and Discussion

6.1. Calibration curve

6.1.1.Calibration curve of amoxicillin trihydrate

Absorbance maxima (λmax) of amoxicillin trihydrate in stimulated saliva, pH6.8 and water-ethanol mixture (1:1) showed the abosorption maxima of the drug are at 269 nm in both the cases (Fig,4A and B) . The mean drug absorbances (n=6) against different concentrations were plotted for both solvents as shown in Figs.7A-D.

6.1.2.Calibration curve of Lidocaine hydrochloride

lidocaine hydrochloride in stimulated saliva, pH6.8 and water-ethanol mixture (1:1) showed that the abosorption maxima of the drug are at 273 nm. In both of the media (Fig,4A and B) .The mean drug absorbances (n=6) against different concentrations were plotted for each case as shown in Figs. 8A-D

6.1.3.Calibration curve of Metronidazole

Scanning of Metronidazole in stimulated saliva, pH6.8 and water-ethanol mixture (1:1) showed that the abosorption maxima of the drug was at 318nm. in each case (Fig.4A and B).The mean drug absorbances (n=6) against different concentrations were plotted for both the solvents as shown in Figs. 9A-B

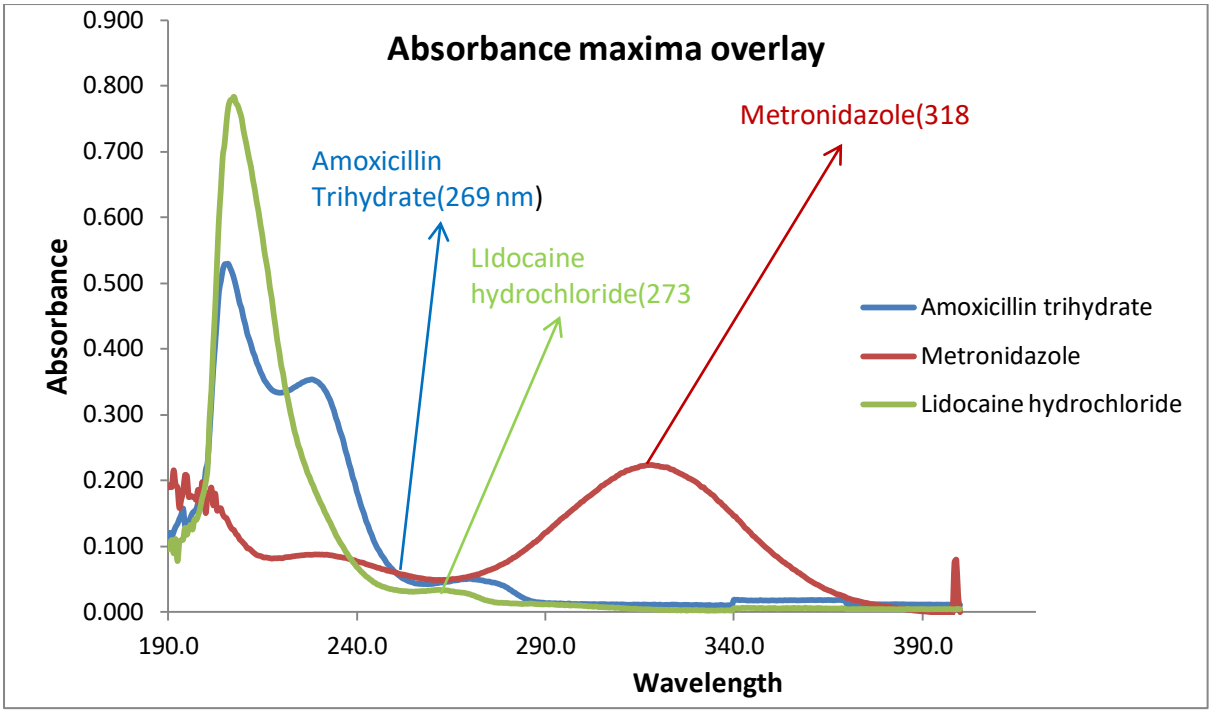


Fig. 4A λmax of the overly amoxicillin trihydrate , lidocaine hydrochloride and metronidazole in simulated saliva, pH 6.8 and 1:1 ethaonl- water mixture.

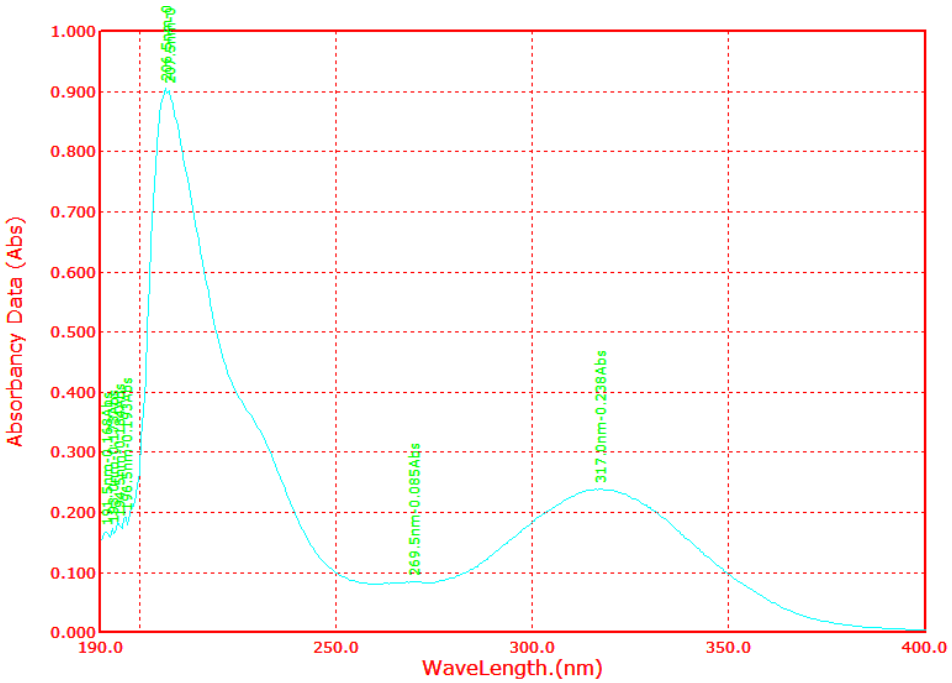
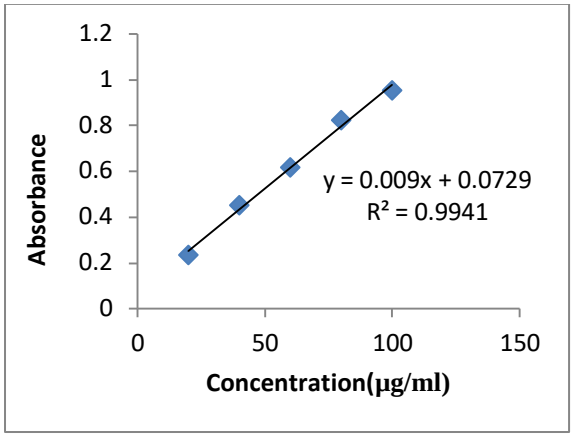
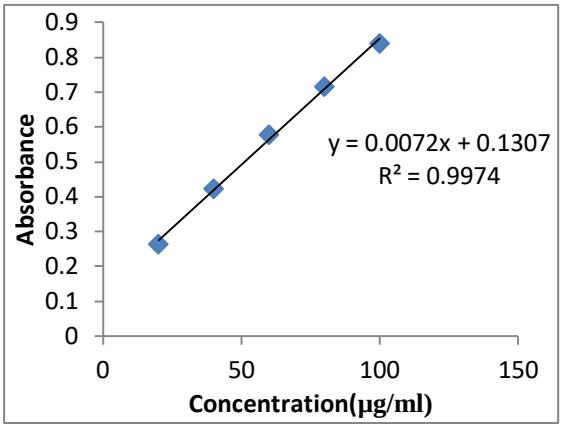


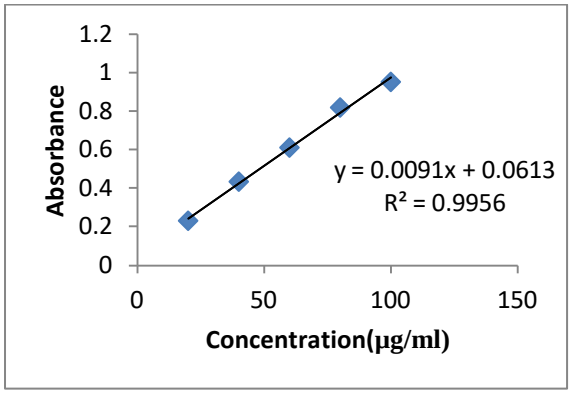
Fig. 4B. UV Scan of amoxicillin trihydrate , lidocaine hydrochloride and metronidazole in simulated saliva, pH 6.8 and 1:1 ethaonl- water mixture.



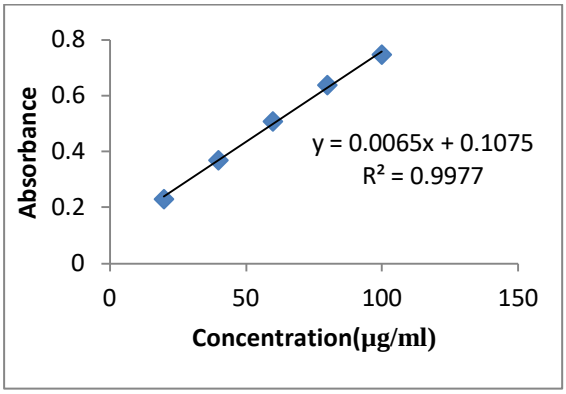
A



B

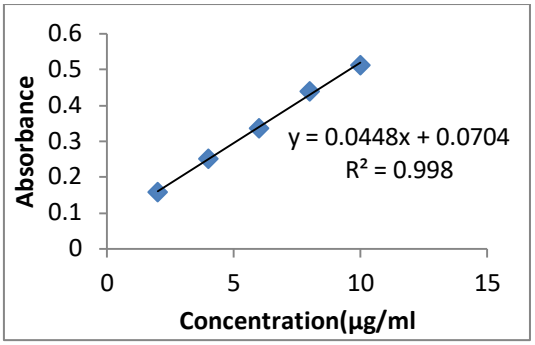


C

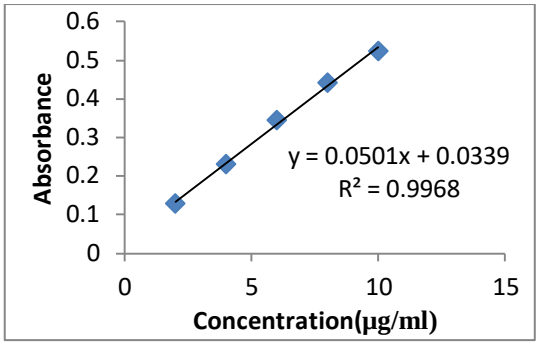


D

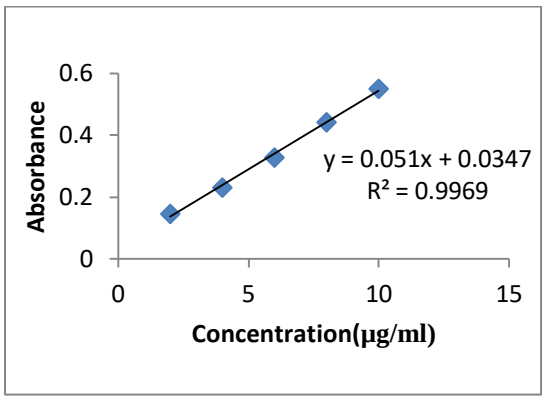
Fig:5 Calibration curve of amoxicillin trihydrate ; (A) in stimulated saliva, pH6.8 at 269nm; (B) in stimulated saliva, pH6.8 at 273 nm; (C) in 1:1 ethanol- water mixture at 269 nm; and (D) in 1:1 ethanol- water mixture at 273 nm.



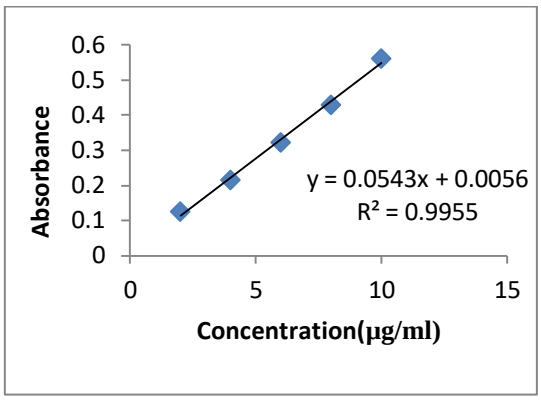
A



B



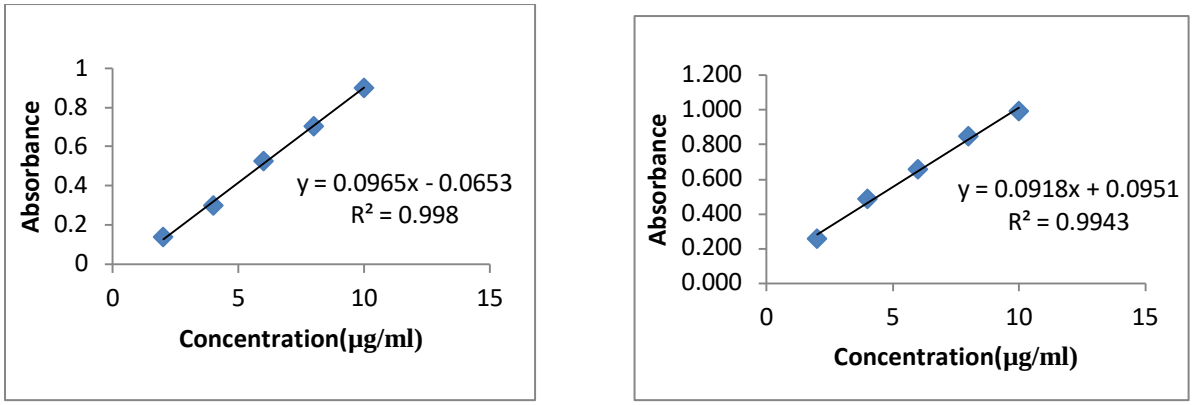
C



D

Fig:6 Calibration curve of lidocaine hydrochloride; (A) in stimulated saliva, pH6.8 at 273nm; (B) in stimulated saliva, pH6.8 at 269 nm; (C) in 1:1 ethanol- water mixture at 273 nm; and (D) in 1:1 Ethanol- water mixture at 269 nm.

Regression values (R^2 values) of all the calibration curves showed the good linearity of the curves and accuracy of the data obtained.



A **B**

Fig:7 Calibration curve of metronidazole ;(A) in 1:1 ethanol- water mixture at 318 nm (B) in stimulated saliva, pH 6.8 at 318nm

6.1.3.Molar absorptivity

Molar absorptivities of amoxicillin trihydrate[53] , lidocaine hydrochloride[54] and metronidazole both in stimulated saliva,pH6.8 and 1:1 ethanol-water mixture were determined at respective wavelengths by the method decribed earlier and reported in table 2

Table 2 Molar absorptivity of drug in the experimental media

Drug	Concentration range(µg/ml)	Wavelength(nm)	Media	Molar absorptivity (ε molar)
Amoxicillin trihydrate	10-100	269 273	Simulated saliva (pH 6.8)	377.32 301.86
		269 273	Ethanol-water (1:1)	381.51 272.51
Lidocaine hydrochloride	10-100	269 273	Simulated saliva (pH 6.8)	1213.18 1356.70
		269 273	Ethanol-water (1:1)	1381.08 1470.44
Metronidazole	10-100	318	Simulated saliva (pH 6.8)	1651.69
		318	Ethanol-Water	1572.96

6.2.FTIR

Here drug-excipient interaction was determined using FTIR-spectroscopy. Figs. 10A-T show the FTIR spectra of each of the polymers; amoxicilin tribydrate; lidocainehydrochloride, Metronidazole and a mixture of amoxicillin trihydrate and lidocaine hydrochloride; a mixture amoxicillin trihydrate and metronidazole, a mixture of lidocaine hydrochloride and metronidazole a mixture of the polymers corn zein (1636,1647), carbopol 934P (1706,1455), gum acacia(1020, 977) poloxamer 407 (1466,1659,1341) and ethyl cellulose (3970, 3420), a mixture of amoxicillin trihydrate with the polymers; a mixture of lidocaine hydrochloride with the polymers, a mixture of metronidazole with the polymers , a mixture of amoxiciln tihydrate and lidocaine hydrachloride and metronidazole with those polymers, respectively. The FTIR spectra of pure amoxicillin trihlydrate lidocaine hydrochloride and metronidazole show that all the characteristic peaks of amoxicilin tritydrate at the wave no (1790,1700,1590 cm^{-1}) lidocaine hydrochloride at the wave no (1650,1550,1480 $cm^{-1)}$ and metronidazole at the wave no (1580,1520,1480 cm^{-1}) were present.[55,56] Again, FTIR spectra of the combination of both the drugs showed the presence of their characteristic peaks. This indicates that the drugs did not intract chemicaly in their physical mixture.When the drugs were mixed with the excipients variation of some peaks was noticed. Between 3200cm-1 and 2800 cm^{-1} and between 1800 cm^{-1} and 1000 cm^{-1} wave numbers, variations at transmission spectroscopy data were noted. Alienyl (>C=C<)(3020 cm^{-1} -3100 cm^{-1}) amide(>NH) (1000 cm-1-1250cm^{-1}) ketonyl(>C=O)(1720 cm^{-1} -1720cm^{-1}), phenolic (-OH) at the wave no (970 cm^{-1}- 1250 cm^{-1}) stretches were mainly responsible for those regions.They suggested that formation of weak to medium intensity bonds due to the forces such as van der Waals force, dipole moment and electrostatic force between drugs and the excipients in those regions there physical interactions

might be responsible for providing the structure of the formulation and sustained drug release patterns from it.

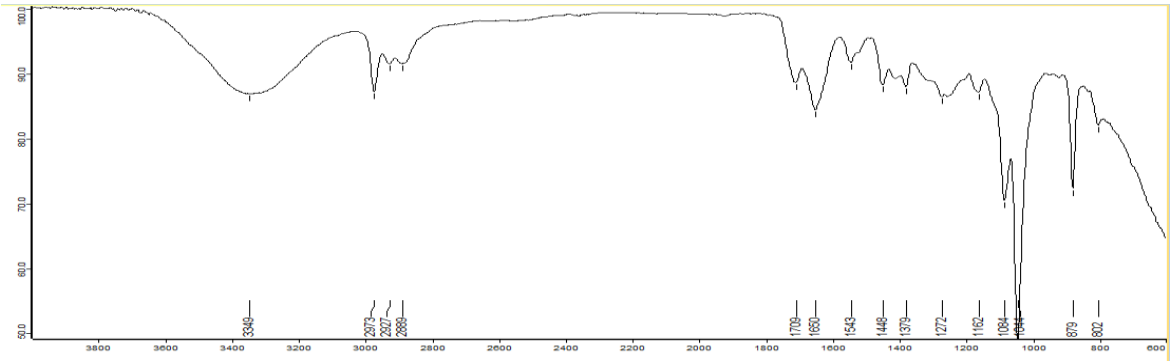


Fig:10A FTIR spectra of polymer mixture

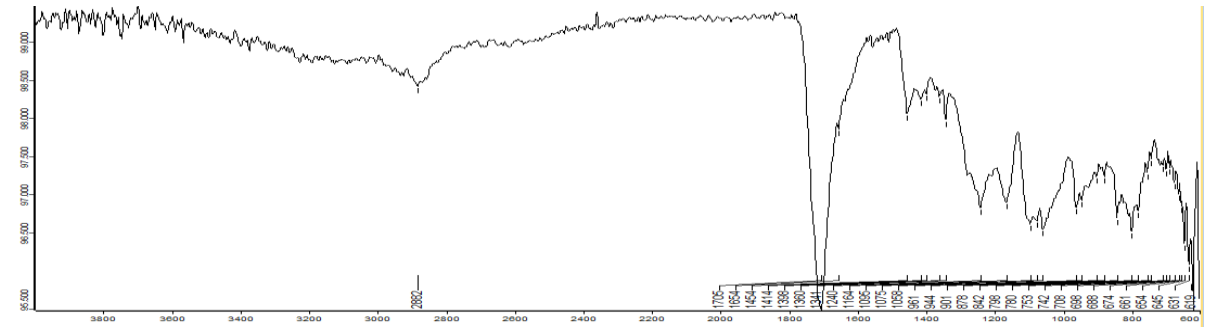


Fig:10B FTIR spectra of carbopol 934P

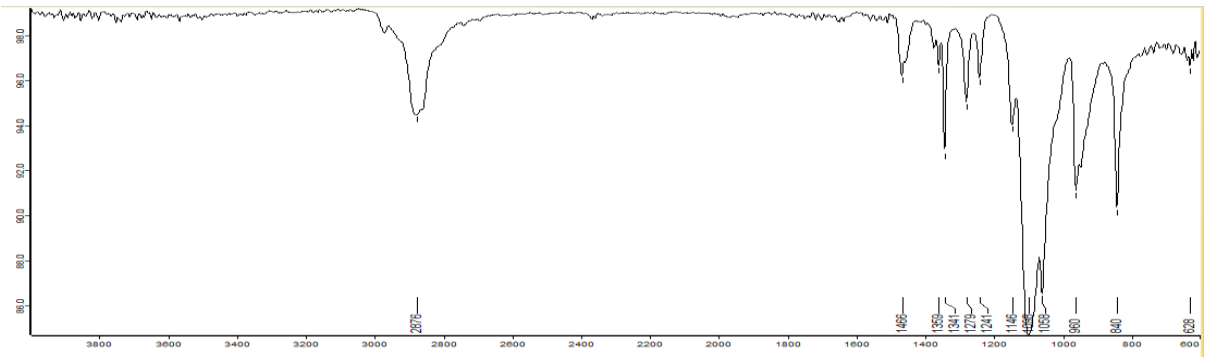


Fig:10C FTIR spectra of cron zein

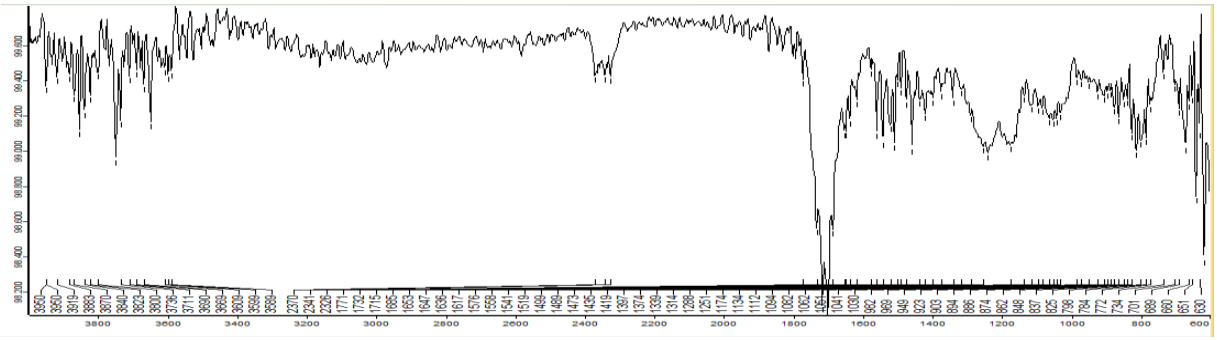


Fig:10D FTIR spectra of amoxicillin trihydrate and polymers

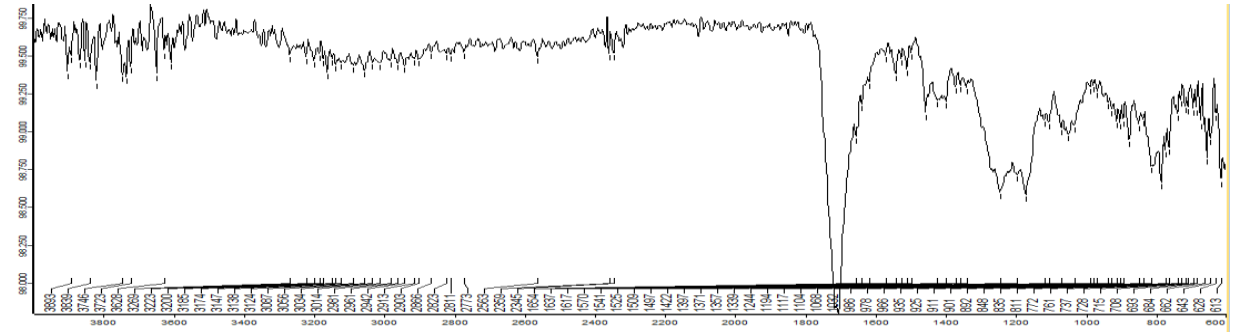


Fig:10E FTIR spectra of mixture of amoxicillin trihydrate , lidocaine hydrochloride and metronidazole and polymers

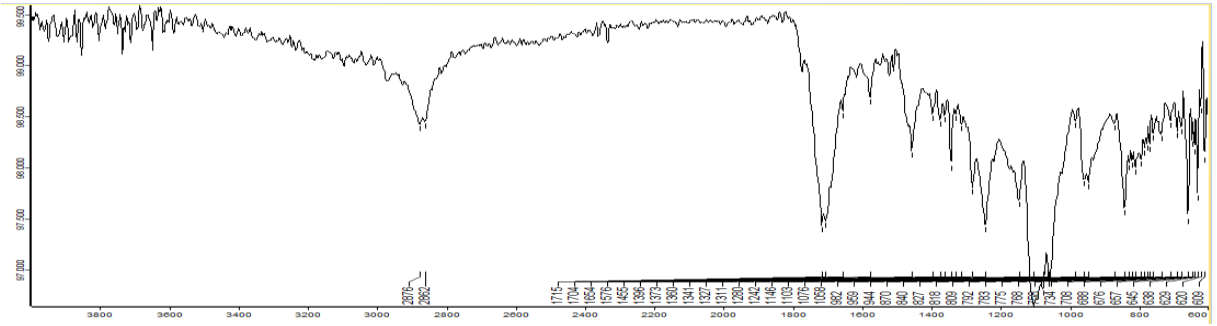


Fig:10F FTIR spectra of lidocaine hydrochloride

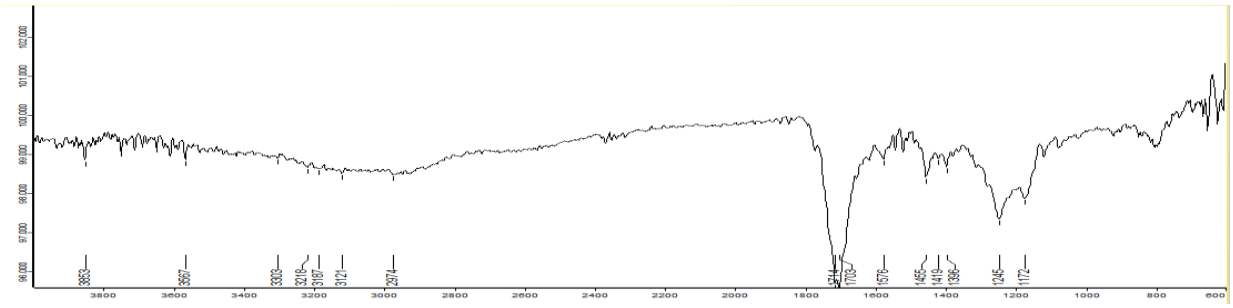


Fig:10G FTIR spectra of metronidazole

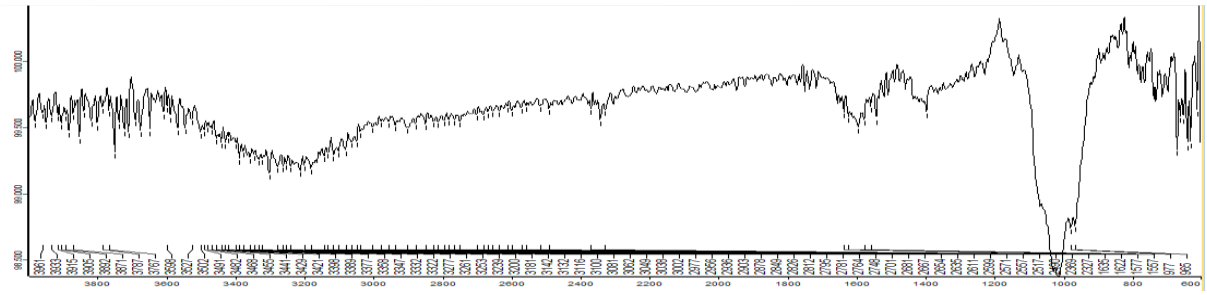


Fig:10H FTIR spectra of gum acacia

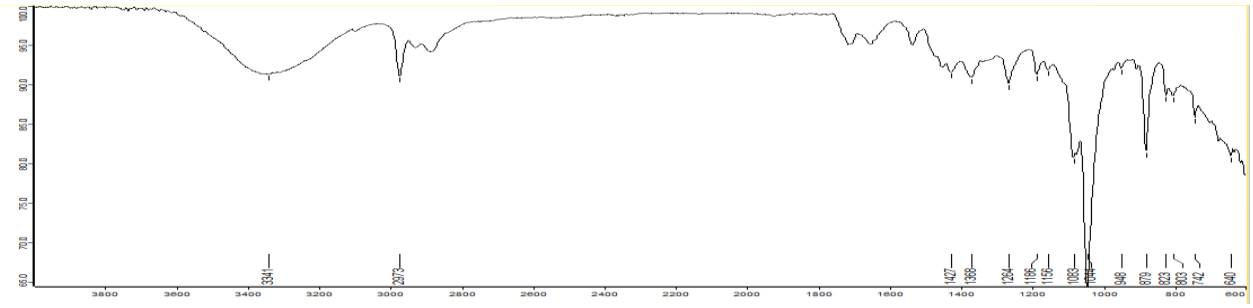


Fig:10I FTIR spectra of physical mixture of amoxicillin trihydrate and ethyl cellulose

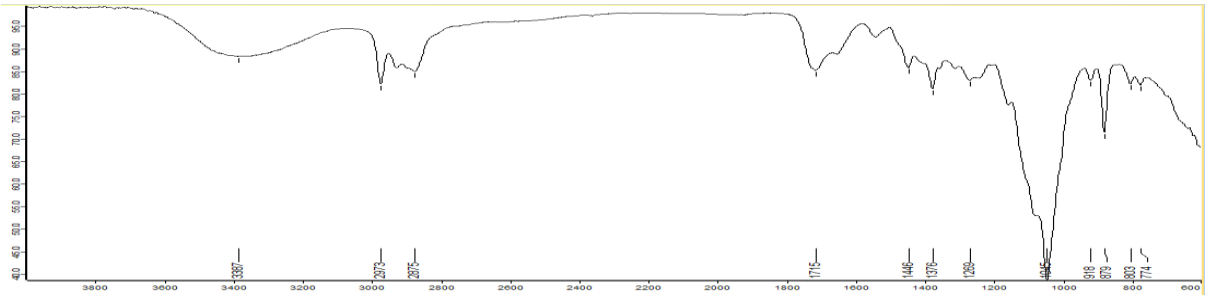


Fig:10J FTIR spectra of physical mixture of amoxicillin trihydrate , lidocaine hydrochloride, metronidazole and polymers

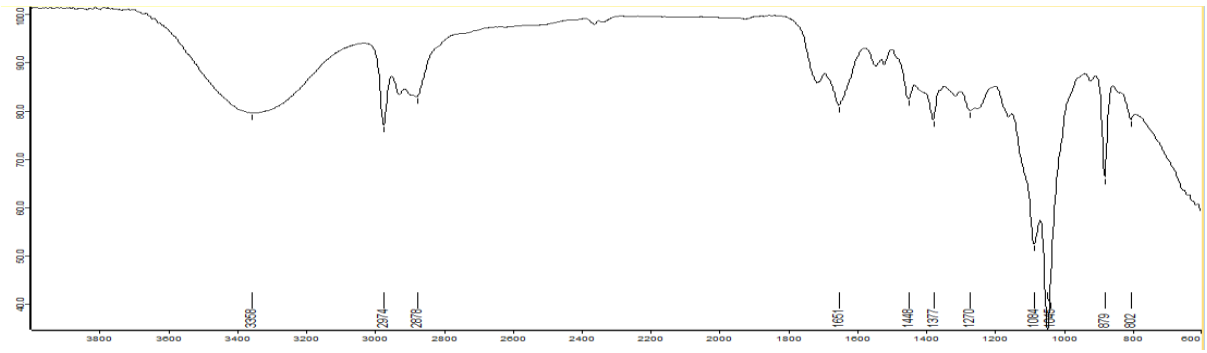


Fig:10K FTIR spectra of physical mixture of lidocaine hydrochloride, ethyl Cellulose and polymers

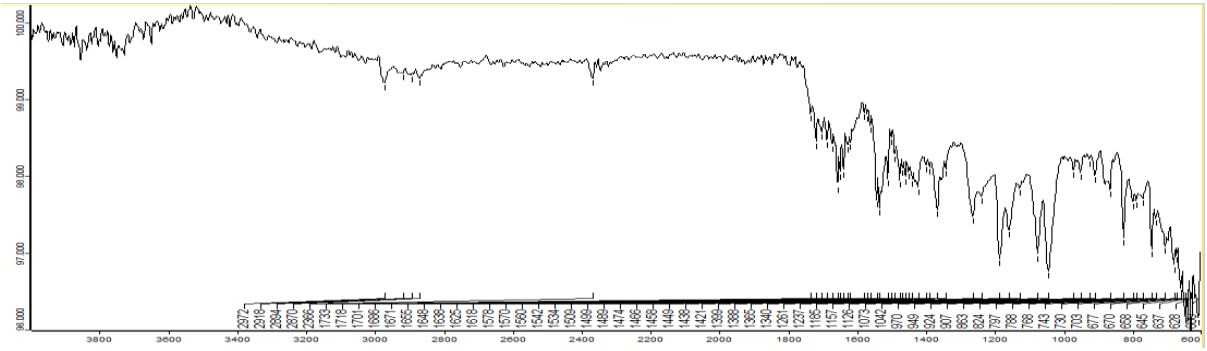


Fig:10L FTIR spectra of physical mixture of metronidazole, ethyl cellulose and polymers

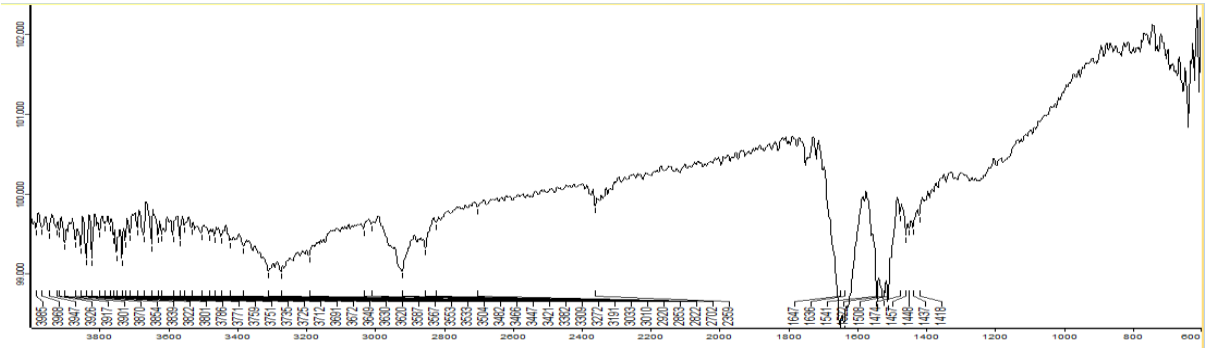


Fig:10M FTIR spectra of poloxamer 407

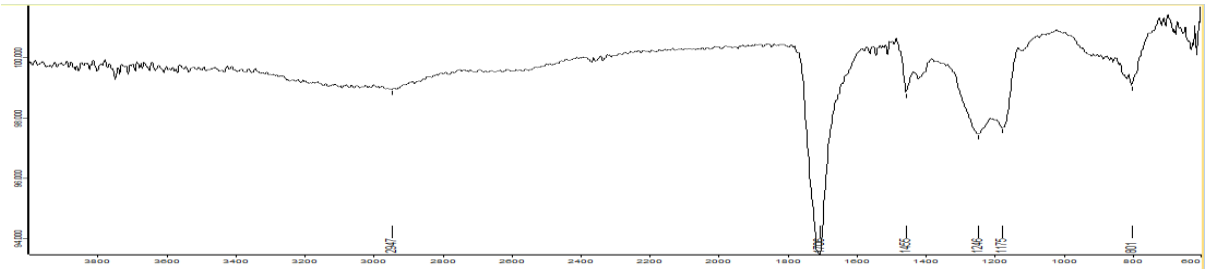


Fig:10N FTIR spectra of mixture of polymers and ethyl cellulose

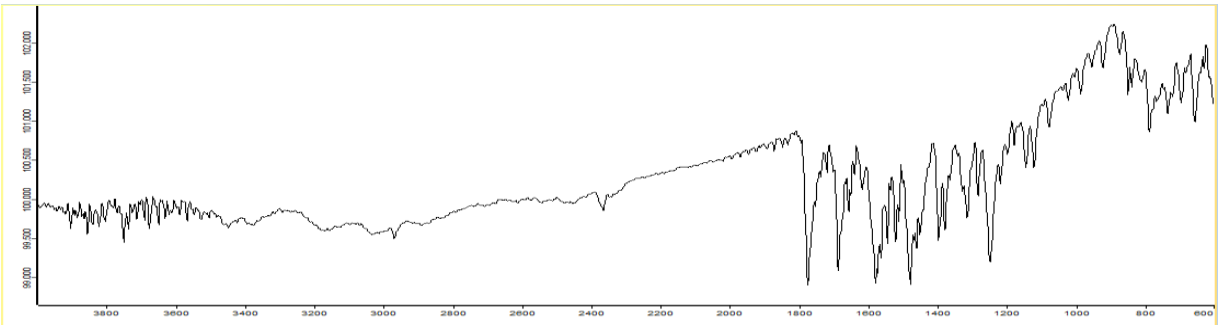


Fig:10O FTIR spectra of amoxicillin trihydrate

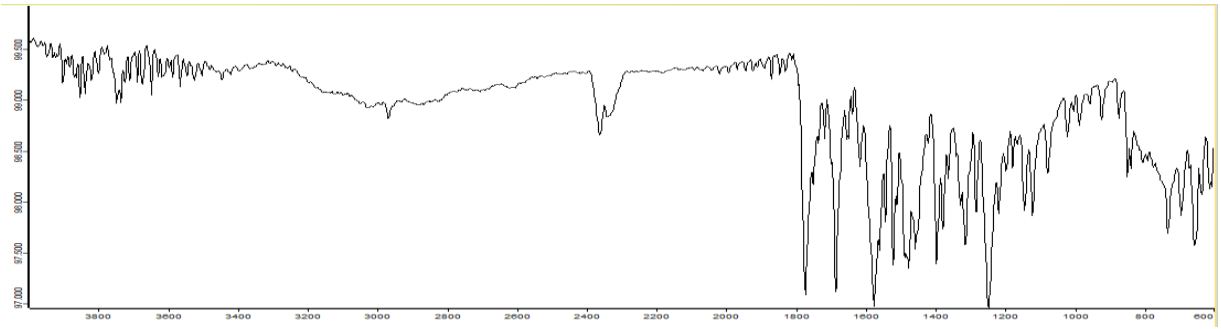


Fig:10P FTIR spectra of amoxicillin trihydrate and lidocaine hydrochloride

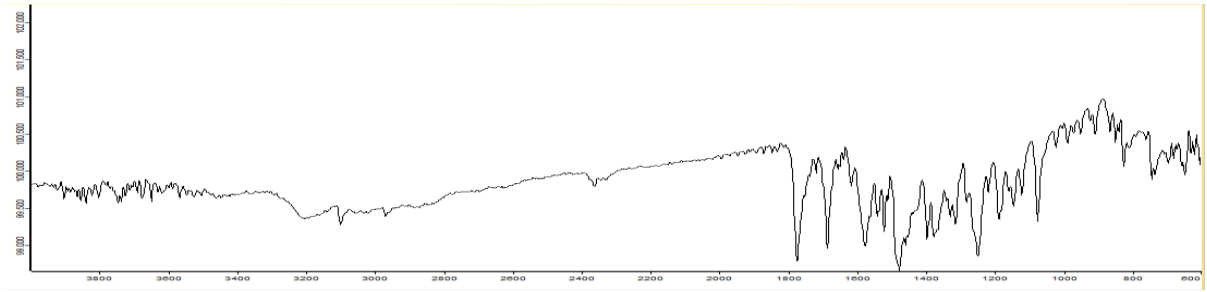


Fig:10Q FTIR spectra of lidocaine hydrochloride

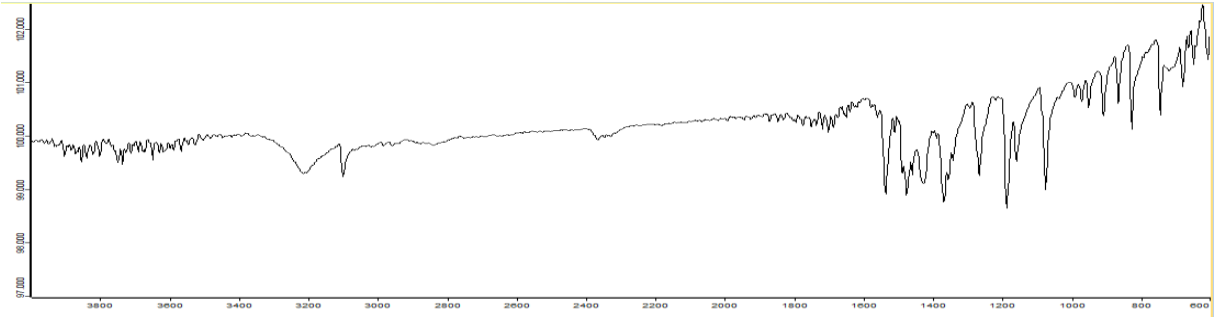


Fig:10R FTIR spectra of metronidazole

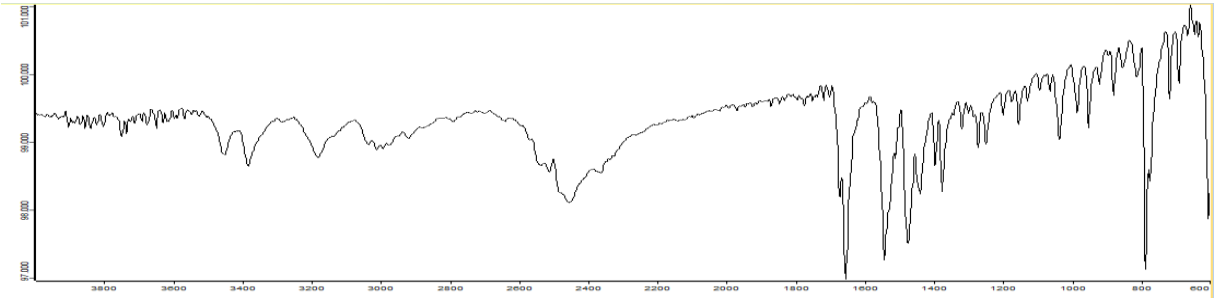


Fig:10S FTIR spectra of metronidazole and amoxicillin trihydrate

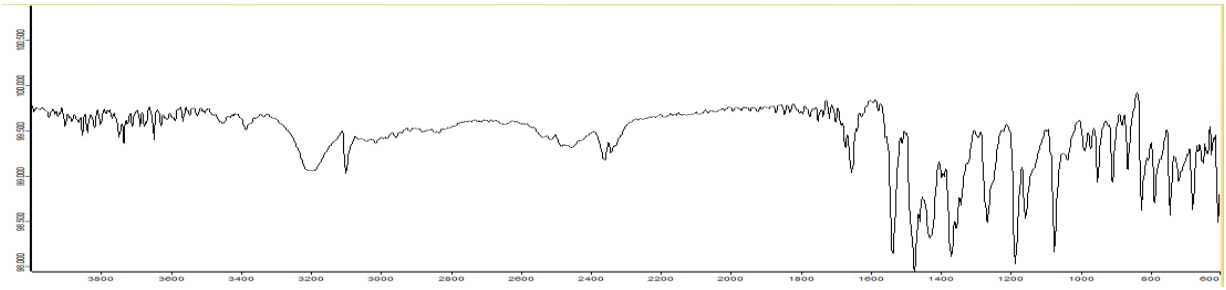


Fig:10T FTIR spectra of amoxicillin trihydrate , lidocaine hydrochloride and metronidazole

6.3.Tooth adhesion test and surface pH

Table 3 represents the tooth adhesive strength and surface pH of the experimental denticaps containing no drugs and containing drugs Amoxicillin trihydrate, lidocaine hydrochloride and metronidazole. The average initial tooth adhesive strength varied between 40-15g. In case of mucoadhesive polymers desired strength was reported to be about 30 g.[57],wheres the mean adhesive strength obtained in our formulation was 46.5g.This was advantageous because the surface of mucus layer of buccal cavity is uneven compared to tooth surface and hence more adhesion strength is required to attach the formulation on tooth surface [58,59]. The surface pH obtained in this study was within the limits of buccal pH and therefore omits the chances of irritation in the mucosal membrane upon application.

FORMULATION	Tooth adhesive Strength(g/ cm^2) ± SD(n=3)	Surface pH ±SD(n=3)
Denticap- B	41.5(±2.57)	6.47(±0.33)
Denticap-ALM	46.5(±1.89)	6.5(±0.75)

Table 3 Initial tooth adhesive strength and surface pH

6.4.Percent swelling

The percent swelling results were expressed in terms of percentage water uptake 37°C.[60] Fig 11 shows the swelling pattern of denticaps. The percent swelling of the denticaps can be arranged as follows : blank(only polymers)< amoxicillin trihydrate- metronidazole- lidocaine hydrochloride denticaps. The results show that the percentage swelling of the various denticaps varied from 70% to 91% in 4 h.

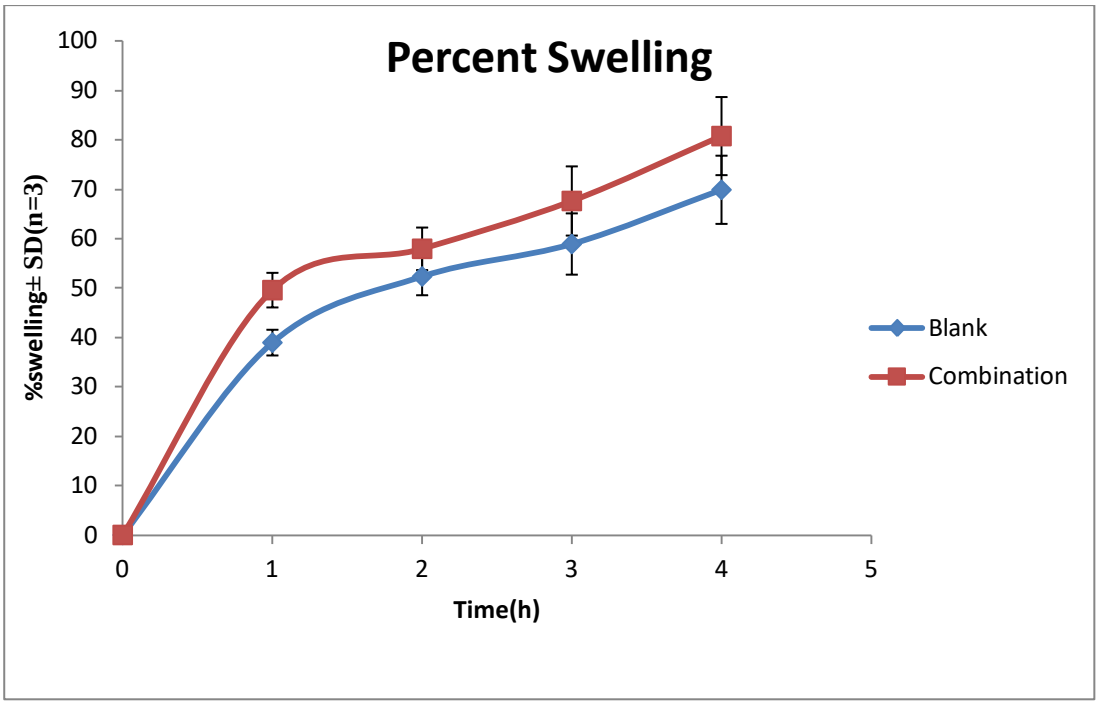


Fig: 11 Percent swelling in terms of water absorption capacity of Denticaps. Data show mean(n=3)±SD

6.5. SEM

Fig.12 shows the SEM photographs of denticaps containing amoxicillin trihydrate, lidocaine hydrochloride, metronidazole that before and after release,of the drugs respectively.SEM photographs show that drug particles were very small and different sizes and shapes based on the types of drugs in size and was distributed uniformly throughout the matrix.

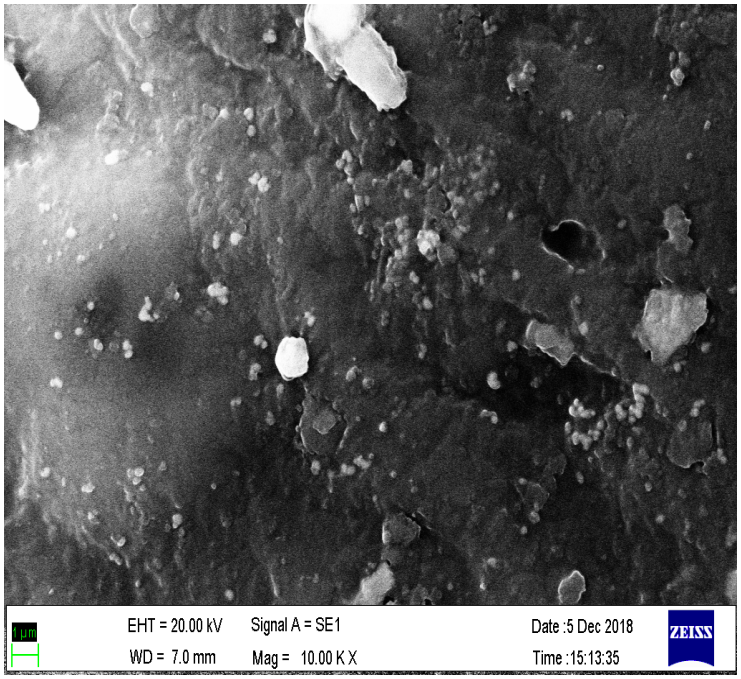


Fig:12A SEM photograph of Denticap containing amoxicillin trihydrate, lidocaine hydrochloride and metronidazole before release

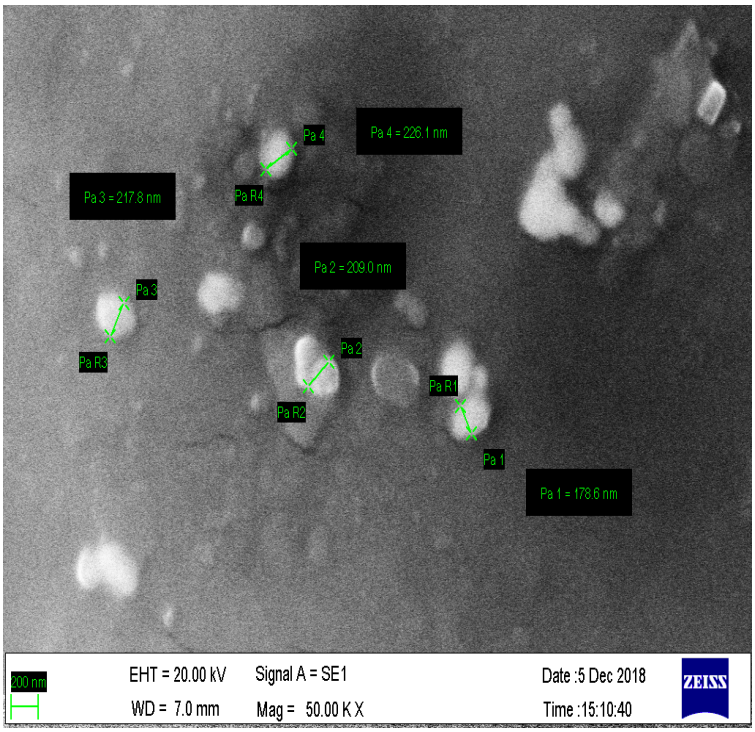


Fig:12B SEM photograph of Denticap containing amoxicillin trihydrate, lidocaine hydrochloride and metronidazole before release

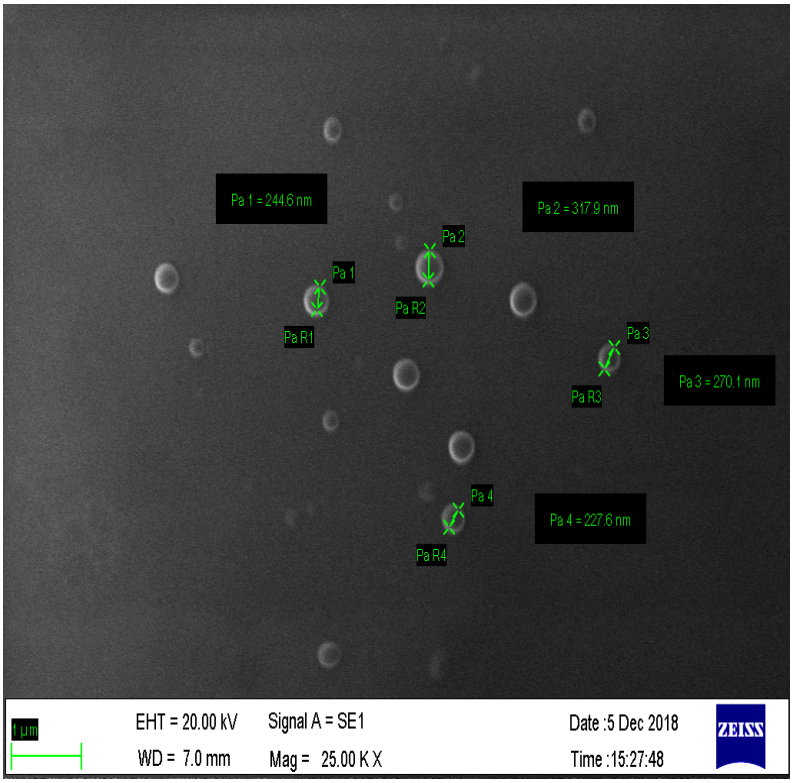


Fig:12C SEM photograph of Denticap containing lidocaine hydrochloride before release

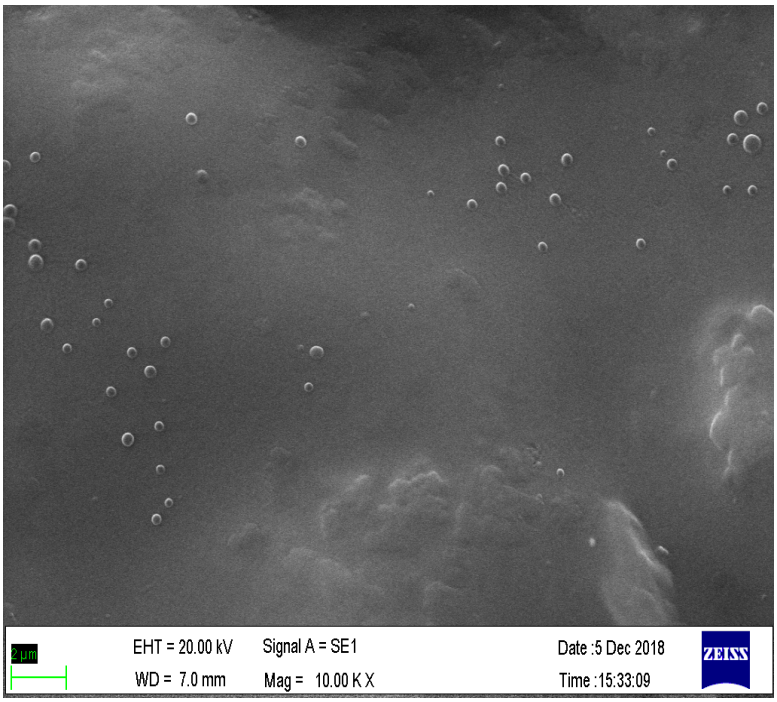


Fig:12D SEM photograph of Denticap containing lidocaine hydrochloride before release

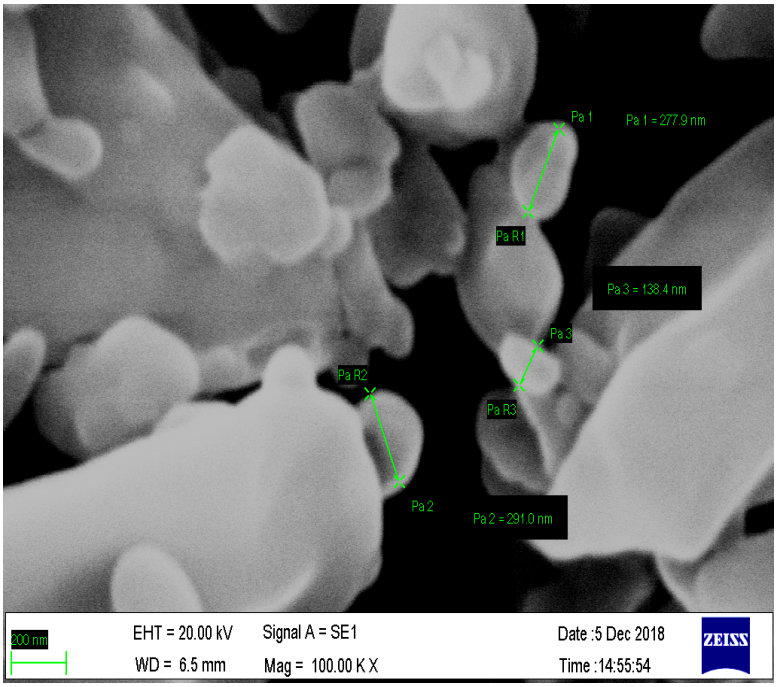


Fig:12E SEM photograph of Denticap containing metronidazole before release

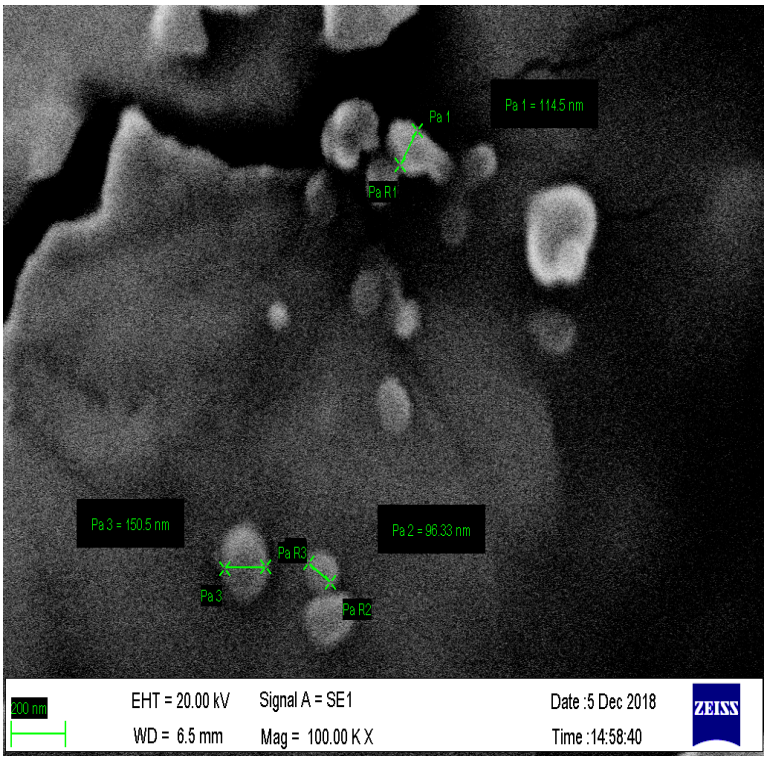


Fig:12F SEM photograph of Denticap containing metronidazole before release

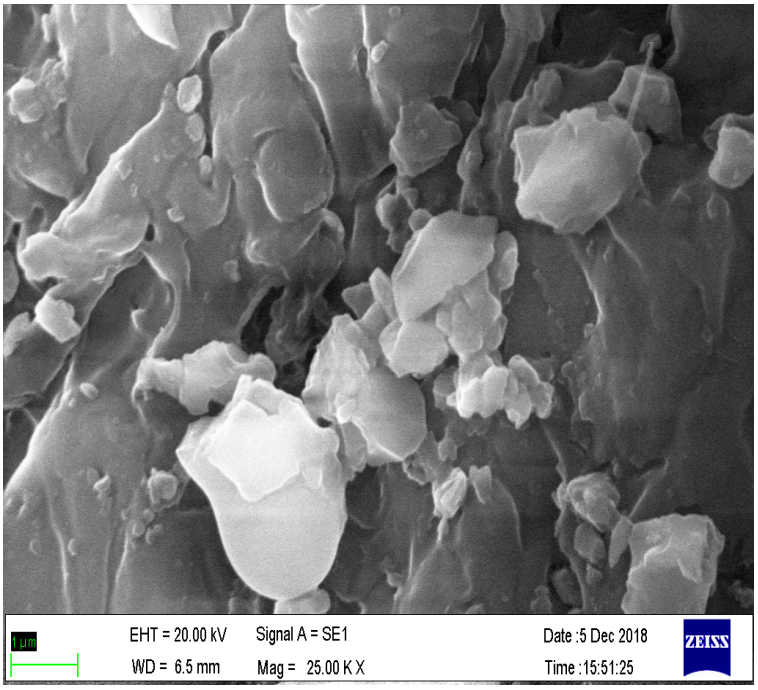


Fig:12G SEM photograph of Denticap containing amoxicillin trihydrate before release

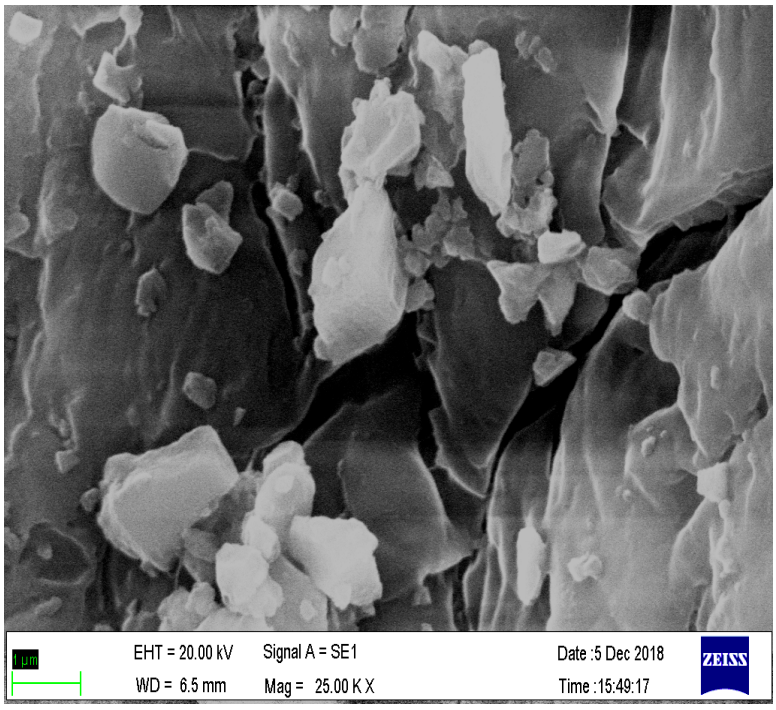


Fig:12H SEM photograph of Denticap containing amoxicillin trihydrate before release

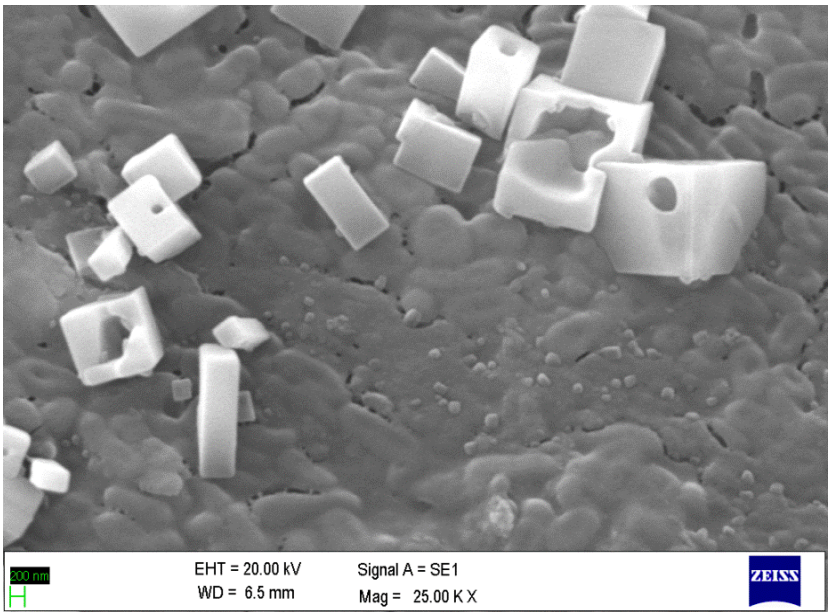


Fig:12I SEM photograph of Denticap containing amoxicillin trihydrate, lidocaine hydrochloride and metronidazole after 24 hr release

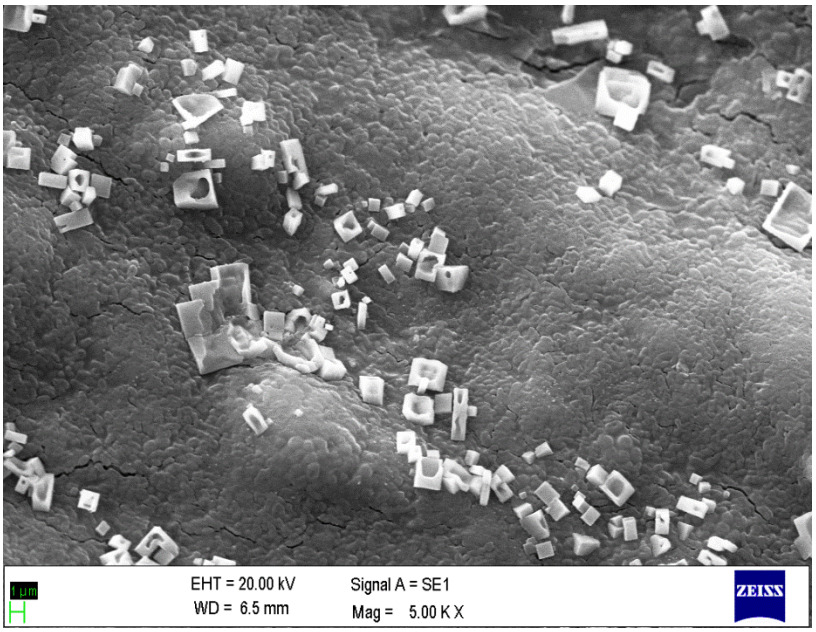


Fig:12J SEM photograph of Denticap containing amoxicillin trihydrate, lidocaine hydrochloride and metronidazole after 24 hr release

6.6. Drug loading (%)

The Drug loading content analysis of denticaps containing lidocaine hydrochloride, amoxicillin trihydrate, metronidazole in the combination of mixture shown in the table 4 Drug loading were high and reproducible.

Table 4 Initial drug content in the formulation

Formulation		% drug loading
Denticap- combination	Amoxicillin trihydrate	99.30 ±0.63
	Lidocaine hydrochloride	97.1 ±1.32
	Metronidazole	99.20 ±0.89

6.7. In vitro drug release

Release patterns of lidocaine hydrochloride, amoxicillin trihydrate, metronidazole were studied in simulated saliva (pH 6.8). Figs 13 show the release of amoxicillin trihydrate, lidocaine hydrochloride and metronidazole from denticaps for 24 h. The cumulative % release of lidocaine hydrochloride, amoxicillin trihydrate and metronidazole were about 93.6%,56.69%,38.60% respectively, from the denticaps containing the combination of three drugs over a time period of 24 h.

To investigate the drug release kinetic pattern, data were tested First order, Higuchi , korsmeyer-peppas and Hixson-crowell kinetic models. R^2 value for the studied kinetics have been included as Table 6.The release of lidocaine hydrochloride from the denticap showed to follow Korsmeyer peppas (Table 6) Amoxicillin trihydrate release was found to obey apparent frist order.(Table 6) Metronidazole release was found to obey apparent Korsmeyer peppas, kinetics.

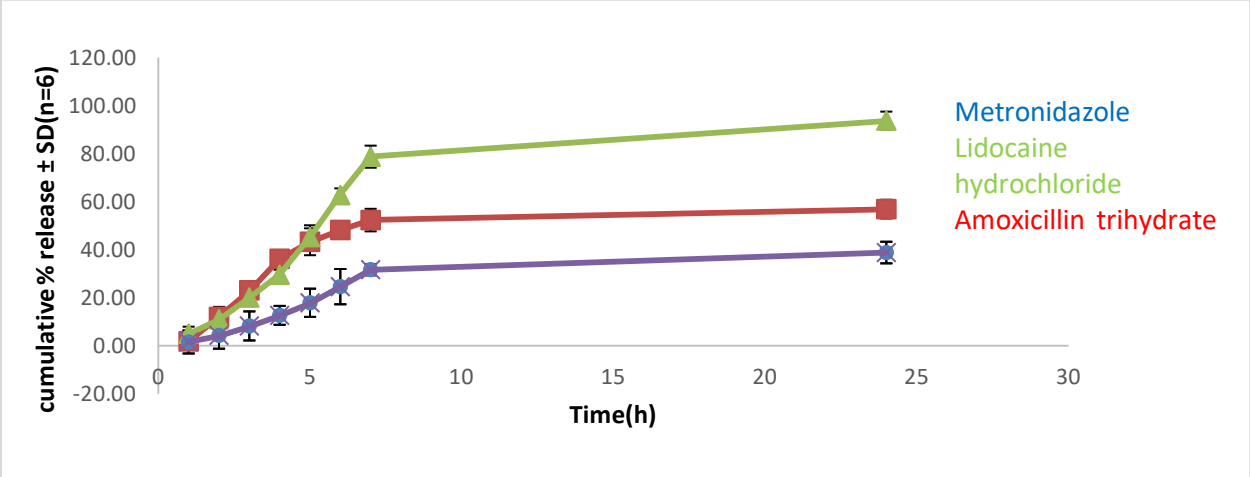


Fig 13 Initial Release pattern of amoxicillin trihydrate, lidocaine hydrochloride and metronidazole from Denticaps containing combination of Drugs

Formulation	Zero order kinetics	First order kinetics	Higuchi kinetics	Korsmeyer peppas kinetics	Hixon-Crowell kinetics
Combination Denticap(Lidocaine hydrochloride release)	y=3.5991x+19.669 R^2 =0.6597	Y=0.0518x+1.9783 R^2 = 0.8976	y=44.715x-50.25 R^2 = 0.9104	y=1.455x+0.6341 R^2 = 0.9927	Y=0.1168x+0.2245 R^2=0.8225
Combination Denticap(Amoxicillin trihydrate release)	Y=1.8458x+22.017 R^2=0.0.461	y=0.0546x+2.0447 R^2 = 0.9865	y=44.715x-50.25 R^2 = 0.9104	y=1.455x+0.6341 R^2 = 0.9927	y=0.0389x+0.3815 R^2 =0.5098
Combination Denticap (Metronidazole release)	Y=1.5014x+7.4946 R^2=0.6852	y=0.026x+2.0345 R^2 = 0.9597	y=18.034x-20.51 R^2 = 0.9228	y=1.6135x+0.1285 R^2 = 0.9999	Y=0.2777x+0.1139 R^2=0.7155

Table-5 Initial release kinetics of denticaps containing both amoxicillin trihydrate, lidocaine hydrochloride and metronidazole

CHAPTER 7

CONCLUSION

❖7 Conclusion

Dental pastes and paints were the most commonly used topical dental formulations for management of dental caries and gum problems., Use of mouth wash is also a popular another approach to maintain oral hygiene over the past few decades. However, drug released from them acts for few hours only, since the formulations are washed out quickly by saliva. Sustained-released devices are a very interesting and high demanding area of research in dentistry. Many efforts are taken on to develop the formulations. But they are mostly on the experimental level. Sustained-release delivery systems allocate extended drug action to treat dental and periodontal diseases compared to the conventional dosage forms. Better patient compliance in terms of application frequency, better relief for longer period of time, reduction in dose of drug leads to overcome the adverse reactions due to higher dose to achieve the same effectiveness when given orally. Besides faster local action as compared to slow onset of action by oral route and avoidance of hepatic "first-pass" effect is an important advantage of this formulation.

On of the important preformulation studies to prevent the tooth decay, ”Denticap” is a novel approach to local drug usage for a long time by applying it on the affected tooth. More patient compliance over the conventional dosage forms is the expected outcome of such approach. In the root canal treatment and in different gum therapies denticap could be more effective to the patients to use this type of dosage from. Denticap or Dental mold may open a new area in dentistry in future endeavour. However , further studies are required to be carried out.

CHAPTER 8

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