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FORMULATION AND EVALUATION OF PERIODONTAL GEL OF CEFUROXIME AXETIL

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ABSTRACT

Periodontal diseases are the conditions that affect the supporting structure of teeth leading to the formation of pocket due to which tooth loss occurs, for which site specific injectable drug delivery systems are gaining importance. The present work investigates the development and optimization of periodontal gel of Cefuroxime Axetil for treatment of periodontal disease. Gel was prepared by using Sodium alginate & Carbopol 934P polymer with different drug/polymer ratios along with PEG 200 & PEG 400. The formulated gel was characterized for surface pH, viscosity, bioadhesion strength, spreadibility, extrudability & in vitro drug release studies. The results revealed that the surface pH was within the range of 6.2-6.5. The viscosity value was ranging from 15860 to 41200 dyne/cm^2. Maximum bioadhesion strength, extrudability and spreadibility based on pharmacopoeial limits was found to 6860, 7.75 and 22 respectively. *In-vitro* drug release showed that initial burst release followed by controlled release pattern showing upto 67.33% in 4 hr. The kinetic analysis of release data revealed that the zero order was the prominent release mechanism. Shelf life of gel was found to 9 months. From the study it was concluded that Cefuroxime Axetil periodontal gel containing polymers with PEG 200 showed more release and good extrudability, spreadibility and bioadhesive strength as compared to PEG 400.

KEYWORDS: Cefuroxime Axetil; Periodontal diseases; Sodium alginate; Carbopol 934P.

INTRODUCTION

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity.

Buccal mucosa

The oral mucosa lines the oral cavity, which is delineated by the lips, cheeks, hard and soft palates, tongue and floor of the mouth. The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosal as the innermost. The epithelium serves as the mechanical barrier that protects underlying tissues, where as the lamina propria provides a mechanical support and also carries the blood vessels and nerves. Some regions of the oral mucosa are keratinized. The non keratinized region such as buccal mucosa is more permeable than the keratinized regions. This is due to the composition of intercellular lipids comprising the particular region, where as keratinized regions contain predominantly neutral lipids (ceramides), non-keratinized regions are composed of glycosyl ceramide that appears to be derived from membrane coating of granules that differ morphologically from the lamellae membrane coating granules. Three different types of oral mucosa are recognized (Fig.1 & Fig.2).[1-4]

- Masticatory mucosa: Characterized a keratinized epithelium overlying thick and dense lamina propria that is bound tightly to the underlying bone (Gingival and hard palate).
- Lining mucosa: Consists of non keratinized epithelium over a lamina Propria which is elastic.(Lips, Cheeks, Alveolar mucosa, Floor of the mouth, soft palate).
- Specialized mucosa: Epithelium is keratinized and tightly bound to underlying muscle by a thin but densely fibrous lamina propria (Dorsal surface of tongue).

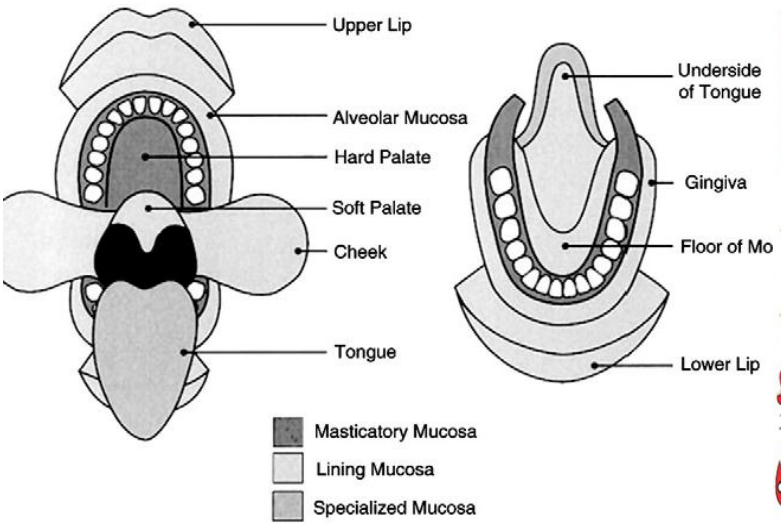


Figure.1 Schematic representation of the Different linings of mucosa in mouth

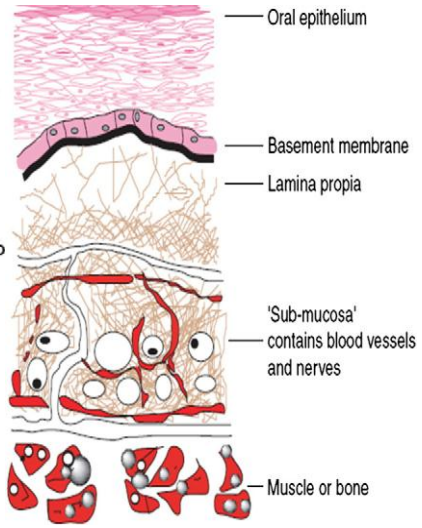


Figure.2 Diagram of buccal mucosa

The cells of the oral epithelia are surrounded by intercellular ground substance mucus. Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the Pathphysiological state. However, it has the following general composition Water - 95%, Glycoproteins and Lipids - 0.5 to 5%, Mineral salts - 0.5 to 1%, Free Proteins - 0.5 to 1%. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralization of the tooth enamel after eruption and helps in demineralization of the enamel in the early stages of dental caries. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Periodontitis

Periodontitis, which means "inflammation around the tooth". In periodontitis, gums pull away from the teeth and form "pockets" that are infected. The body's immune system fights the bacteria as the plaque spreads and grows below the gum line. Bacterial toxins and the body's enzymes fighting the infection actually start to break down the bone and connective tissue that hold teeth in place. If not treated, the bones, gums, and connective tissue that

support the teeth are destroyed. The teeth may eventually become loose and have to be removed.[3]

Local administration of antibiotics necessarily involves insertion of drug loaded device in periodontal pocket to achieve effective concentration at the target site. The enhancement of antibiotic penetration into biofilms is of particular importance to prevent microbial colonization in periodontal pockets and dental root canals, since the drug should reach sites of difficult access. The use of sustained drug delivery systems may also provide drug delivery over a prolonged period in periodontal pockets.[4]

Bioadhesive buccal drug delivery system

The term bioadhesion refers to either adhesion between two biological materials or adhesion between some biological material (including cells, cellular secretions, mucus, extracellular, matrix etc) and an artificial substrate. Bioadhesion refers to the adhesion between a polymer based delivery system and soft tissue in the presence of water. The immobilization of drug carrying particles at the mucosal surfaces would result in,

- Prolonged residence time at the site of action or absorption.
- Localization of the drug delivery system at a given target site.

Mechanism of bioadhesion

The forces that are responsible for adhesive bond formation must be understood to develop ideal bioadhesive drug delivery system. The processes involved in formation of such bonds are as given below:

- Wetting and swelling of polymer to permit intimate contact with biological tissue
- Interpenetration of bioadhesive polymer chains and entanglement of polymer & mucin chains.
- Formation of weak chemical bonds.

Several polymer characteristics are required to obtain adhesion which includes:

- Sufficient quantities of hydrogen-bonding chemical groups (-OH & COOH).
- Anionic surface charge.
- High molecular weight.
- High chain flexibility.
- Surface tensions that will induce spreading into the mucus.

The above characteristics favors the formation of bonds that are either mechanical or chemical in nature.

Theories of bioadhesion: Several theories have been proposed to explain the fundamental mechanisms of adhesion.

Electronic theory: According to this theory, electron transfer occurs upon the contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structure. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

Absorption theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds are

i) Primary chemical bonds of covalent nature.

ii) Secondary chemical bonds including electrostatic forces, Vander Waals forces and Hydrogen and hydrophobic bonds.

Wetting theory: Wetting theory predominantly is applicable to liquid bioadhesive systems and analyses adhesive and contact behavior in terms of the ability of a liquid or a paste to spread over a biological system.

Diffusion theory: According to this theory, the polymer chain and the mucus mix to sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucous depends on the diffusion coefficient and the time of contact.

Formulation considerations

The buccal mucosa has a very limited area for application of the buccal delivery system, thus it depends upon the size of dosage form. Generally, a device with size of 1-3cm^2 and a daily dose of 25mg or less would be preferred for buccal delivery. The maximal duration of buccal drug delivery is approximately 6-8 hr. The period that a drug is in contact with particular substrate in the oral cavity is defined as substantivity. Drugs that have prolonged duration of contact are considered to have high substantivity. Oral cavity substantivity depends upon two pharmacokinetic features:

i) Degree of reversible, non-specific binding to oral reservoirs.

ii) Rate of clearance by salivary flow

The oral compartments that accumulate drug must be able to reversibly bind large proportions of the administered dose and release therapeutic concentration of free drug to the site of action over long periods of time.

Buccal dosage forms include:

- Hollow Fibres
- Muco-adhesive tablets
- Films and patches
- Chewing gums
- Liquid crystalline phase of glyceryl mono-oleate (GMO)
- Microparticles
- Lectins
- Semisolids/Gels

Gels

Gels are defined by the USP as: "semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid, where the gel mass consist of a network of small discrete particles".

Gels are also defined as semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macro-molecules in the dispersed phase. Physical and /or chemical cross-linking may be involved. The interlacing and consequential internal friction is responsible for increased viscosity and the semisolid state.

Some gel systems are clear and others are turbid, since the ingredients involved may not be completely soluble or insoluble, or they may form aggregates, which disperse light. They can be applied using the finger (or syringe) to a target region and tend to be more acceptable in terms of mouth feel to patients relative to a solid dosage form. The concentration of the gelling agents is generally less than 10% and usually in 0.5 to 2.0% range.[1,9-12] A compilation of some drugs formulated & incorporated in mucoadhesive gels is presented in Table 1.

Advantages of bioadhesive gels

Advantages of mucoadhesive gels as a drug delivery system include:

a. Improved performance of drugs as they are having prolonged intimate contact with mucosal membrane.
b. There is no requirement of medical practitioner to apply the dosage form.
c. Good patient compliance.
d. Don't hinder the talking function of patient.
e. Provide rapid release of drugs at the absorption site.
f. Applied using the finger (or syringe) to a target region and tend to be more acceptable in terms of mouth feel to patients relative to a solid dosage form.
g. By pass the first pass-effect and non-exposure of the drugs to the gastrointestinal fluids.
h. Additionally significant cost reductions may be achieved and dose related side effects may be reduced due to drug localization at the disease site.

MATERIALS AND METHODS

Cefuroxime axetil

Rationale

Cefuroxime axetil is a second generation oral cephalosporin antibiotic. It is an acetoxyethyl ester prodrug of cefuroxime which is effective orally. The activity depends on *in vivo* hydrolysis and release of cefuroxime.

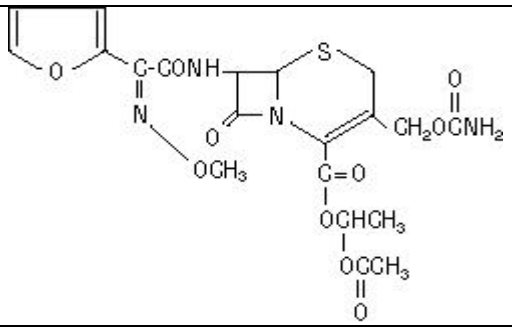
Cefuroxime is effective against a wide variety of bacteria, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *E. coli*, *N. gonorrhea*, and many others.[1]

Unlike other second generation cephalosporins, cefuroxime can cross the blood brain barrier. Cefuroxime is generally well tolerated and side effects are usually transient. In the treatment of periodontitis, cefuroxime axetil is used systemically and topically.

Drug profile

Profile of cefuroxime axetil is presented in a following table.

Table 1: Profile of cefuroxime axetil.

Parameters	Description
a.Analytical profile	
CAS Number	55268-75-2
Chemical structure	
Chemical formula	$C_{16}H_{16}N_4O_8S$
Molecular Weight(g/mo)	Average: 424.385
Λmax	278nm in water
b.Pharmaceutic profile	
Appearance	Solid
Melting point	218-225^{0}C
Solubility	Sparingly soluble in water
c. Pharmacodynamic profile	
Therapeutic category	a.Anti-Bacterial agents b.Cephalosporins
Mechanism of action	Cefuroxime, like the penicillins, is a beta-lactam antibiotic. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that cefuroxime interferes with an autolysin inhibitor.
Indication	For the treatment of many different types of bacterial infections such as bronchitis, sinusitis, tonsillitis, ear infections, skin infections, gonorrhea, periodontitis and urinary tract infections.
d. Pharmacokinetic profile	
Absorption	Absorbed from the gastrointestinal tract. Absorption is greater when taken after food (absolute bioavailability increases from 37% to 52%).
Half life	Approximately 80 minutes following intramuscular or intravenous injection.
Protein binding	50% to serum protein
Bioavailability	>90%
e. Marketed formulations	

Brand	Dosage Form	Strength	Company
Ceftin	Tablet	250mg-500mg	Glaxosmithkline Pharmaceuticals
Zinacef	Injection	750 mg	Glaxosmithkline Pharmaceuticals

Selection of polymers: Sodium alginate and Carbopol 934p

Rationale

To increase the adherence between the bases and the oral tissues, polymers with bioadhesive properties are selected as gelling agent. Mucoadhesive polymers of natural, semi synthetic or synthetic origin are able to form hydro gel which swell in presence of water and physically entrap drug molecules for subsequent release by diffusion or erosion. Among bioadhesive polymers sodium alginate and carbopol 934p have been selected.[9-11]

Profile of polymers

Profiles of sodium alginate and Carbopol 934p are presented in Table 3 and 4 respectively.

Table 2: Profile of sodium alginate.

CAS No.	9005-38-3
Chemical name	Sodium alginate
Pa Parameters	**De Description**
Chemical formula	$(C_6H_7NaO_6)_n$
Description	Occurs as white to yellowish brown filamentous, grainy, granular or powdered forms
Functional category	Stabilizer, thickener, gelling agent and as emulsifier
Solubility	Dissolves slowly in water, forming a viscous solution; insoluble in ethanol and ether
Molecular weight	30,000 to 40,000g/mol
Melting point	$>300^0$C

Table 4: Profile of Carbopol 934p.

Polymer	Properties	Characteristics
Carbopol 934p	• Mw 1×106–4×106 • η 29,400-39,400 cps • at 25°C with 0.5% neutralized aqueous solution. • κ 5 g/cm^3 in bulk, 1.4g/cm^{3}tapped . • pH 2.5–3.0 • φ water, alcohol • White, fluffy, acidic, hygroscopic powder.	• Emulsifying, suspending, gelling agent. • Gel looses viscosity on exposure to sunlight. • It is unaffected by temperature variations, hydrolysis, oxidation and resistant to bacterial growth. • It contributes no off- taste and may mask the undesirable taste of formulation. • Incompatible with phenols, cationic polymers, high concentration of electrolytes and resorcinol.

Aim & Objectives

It is proposed to incorporate cefuroxime axetil into a mucoadehesive periodontal gel with a view to localize and sustain the release of cefuroxime axetil. In the present desertation work, aim would be to study the influence of type and concentration of polymers namely sodium alginate and Carbopol 934p on mucoadehesion and additionally the influence of PEG 200 & 400 on release of cefuroxime axetil from the periodontal gel.

Plan of work

In order to achieve the aim, the dissertation work was carried out as follows:

Preformulation studies of cefuroxime axetil

a) Identification of cefuroxime axetil by IR spectroscopy

b) Solubility determination of cefuroxime axetil

c) Melting point determination

d) Drug-excipient compatibility study

e) Preparation of calibration curve

Formulation development of cefuroxime axetil periodontal gel

a) Process flow chart
b) Formulation development variables
c) Formulation composition
d) Method of preparation

Evaluation of the developed cefuroxime axetil periodontal gel formulations

a) pH measurement
b) Determination of drug content and content uniformity
c) Determination of viscosity
d) Extrudability
e) Spreadability
f) *In vitro* buccoadhesive studies
g) *In vitro* release study and model fitting

Method

- **Materials used**

Details of A.P.I used

S.No.	Drug Name	Supplier
1	Cefuroxime axetil	Hirals Lab Limited

Chemical used

All the chemicals used were of IP/AR or equivalent grade.

S.No.	Name	Manufacturer/ Supplier
1	Carbopol 934p	Loba Chemicals, Mumbai
2	Sodium alginate	Loba Chemicals, Mumbai
3	PEG 400	S. D. Fine-chem Ltd., Mumbai
4	PEG 200	S. D. Fine-chem Ltd., Mumbai

Glassware used

S.No	Name of Item	Specification
1	Beaker	Borosil glass, 50ml, 100ml, 1000ml
2	Measuring cylinder	Borosil glass, 10ml, 100ml
3	Petri dish	Borosil glass, 4"
4	Volumetric flask	Borosil glass, 10ml, 100ml, 1000ml
5	Pipette	Borosil glass, 1ml, 2ml, 10ml
6	Conical flask	Borosil glass 25 ml
7	Funnel	Borosil glass
8	Spatula	Stainless steel

Equipments/instruments used

S.No.	Name of equipment	Make and Model
1	Electronic weighing balance	Adair Dutt, AD-200E
2	Attenuated total reflectance (A.T.R.) spectrophotometer	ATR-Alpha, Alpha Bruker
3	UV spectrophotometer	Shimadzu. Corp., UV1800.
4	Digital pH meter	Hanna, PHep®
5	Brook Field viscometer	Brook Field, DV-II +PRO
6	Magnetic stirrer	Remi, 1MLH
7	Analytical weighing balance	General laboratory equipment
8	Franz-diffusion cell	Orchid, DEMDC 06 PLUS

Preformulation studies of cefuroxime axetil and selected polymers

Identification of cefuroxime axetil by I.R. spectroscopy

The IR analysis of the sample was carried out for qualitative compound identification. Cefuroxime axetil was placed in the cell and scanned over the wavelength 4000 cm^{-1} - 500 cm^{-1} and spectrum was recorded using powder dispersive technique. The recorded and

reference spectra as per IP 2010 are presented in Figure 3 and 4 respectively. The recorded peaks were compared with the reference peaks.

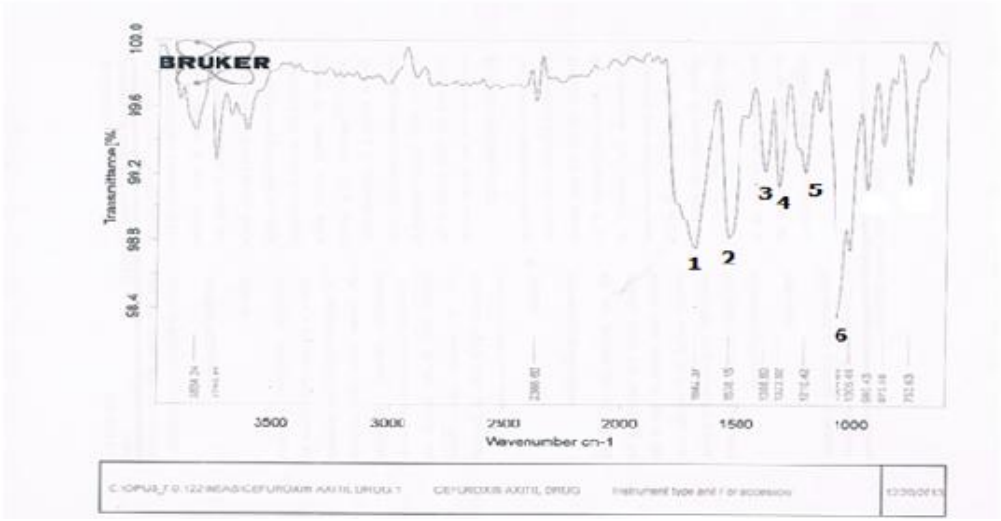


Figure 3: Recorded IR spectrum of cefuroxime axetil.

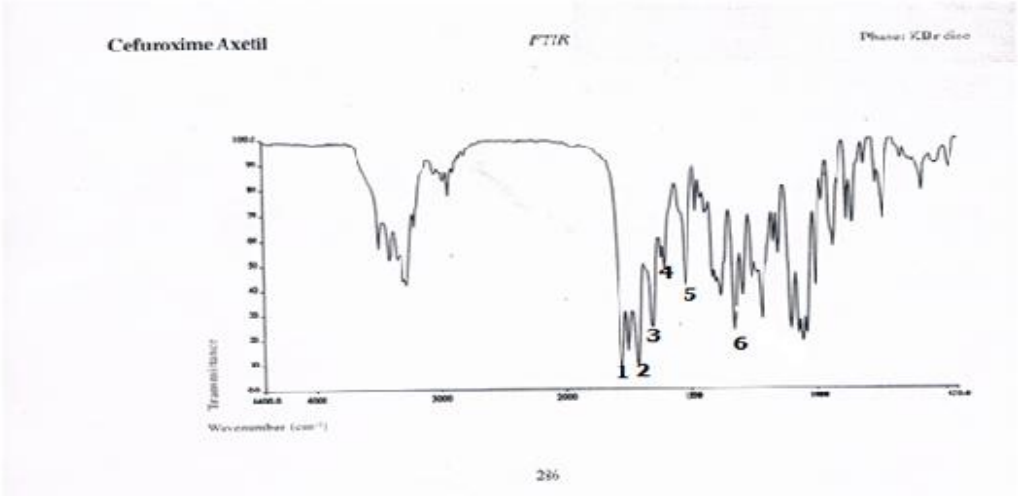


Figure 4: Reference IR spectrum of cefuroxime axetil as per IP 2010.

Table-3: Peak table for comparison of IR spectra of cefuroxime axetil

Peak No.	Wave no. (cm^{-1})	Band width (cm^{-1})	Characteristic vibration / functional group
1	1612	1600-1800	C=N, C=O
2	1528	1510-1550	N-H
3	1323	1300-1400	C-H_3
4	1210	1300-800	C-C Streching
5	940	900-1000	C-H Bending
6	753	750-810	C-H out of plane bending m-disubstituted

RESULTS

Result and Discussion

The observed wave numbers of cefuroxime axetil were in range of theoretical band width of cefuroxime axetil functional groups. Identity of cefuroxime axetil is confirmed.

Solubility determination

Solubility was determined by using shake flask method. In this cefuroxime axetil was added in excess to the medium such as water, simulated saliva fluid pH 6.5 and PEG 400 and 200 and shaken for few hrs. The saturation was confirmed by observation of the presence of un-dissolved cefuroxime axetil. The solution with excess amount of cefuroxime axetil was allowed to equilibrate for 24hrs. Solution was filtered; sample was suitably diluted and analyzed spectrophotometerically at 278 nm. The result is shown in Table 6.

Table 4: Solubility of cefuroxime axetil.

Solvent	Solubility (mg/ml)	Volume of the solvent required to dissolve 1 dose (7.5 mg) of cefuroxime axetil (ml)	Parts of solvent required to dissolve 1 part of cefuroxime Axetil
SSF	17.8	0.421	56.17 ml (30-100)

Result & Discussion

Cefuroxime axetil was found to be sparingly soluble (Appendix A1) in SSF. Volume of solution required to dissolve cefuroxime axetil equivalent to its single dose was found to be 0.421 in SSF.

Melting point determination

Melting point of cefuroxime axetil was determined by capillary method using melting point apparatus. Comparison of the observed and reported melting point of cefuroxime axetil is given in Table 5.

Table 5: Melting point of cefuroxime axetil.

Drug	Reported melting point in I.P.2010	Observed melting point
Cefuroxime axetil	218-225 ºC	211^0C

Result & Discussion

Melting point of cefuroxime axetil was found to be 211^0C which is with in the specified range indicating that the sample of cefuroxime axetil is free of impurities.

Drug-excipient compatibility studies

Physical mixture of cefuroxime axetil and polymers (Sodium alginate and Carbopol 934P) was prepared in the ratio of 1:1 and IR spectrum was recorded in the range from 4,000 to 500 cm^{-1}. This mixture was kept for 14 days at 37^0C and IR spectrum was again recorded. The spectra are shown in the Figure 5, 6 respectively.

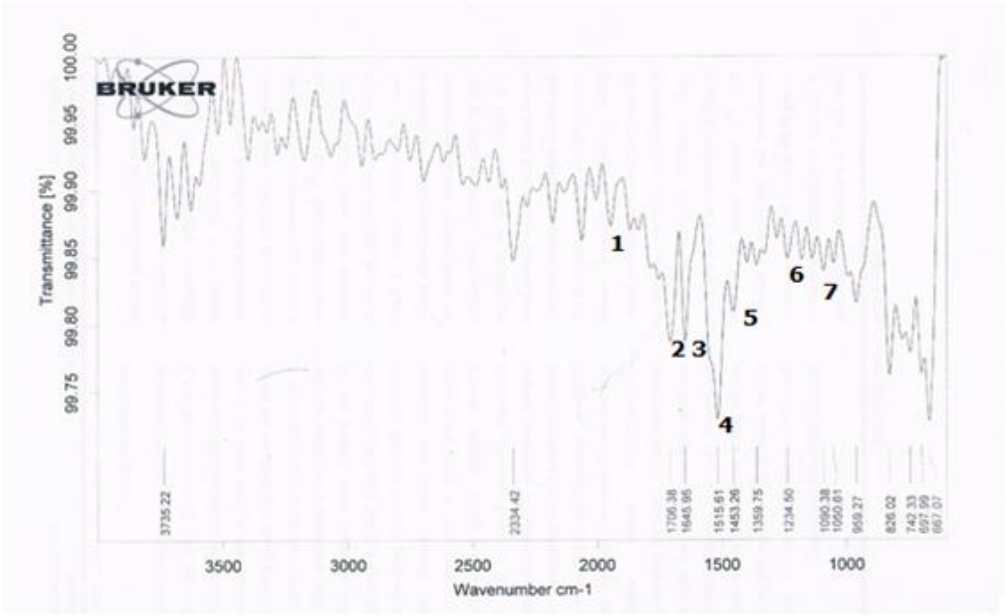


Figure 5: IR spectrum of cefuroxime axetil + sodium alginate + Carbopol 934P (Day 0).

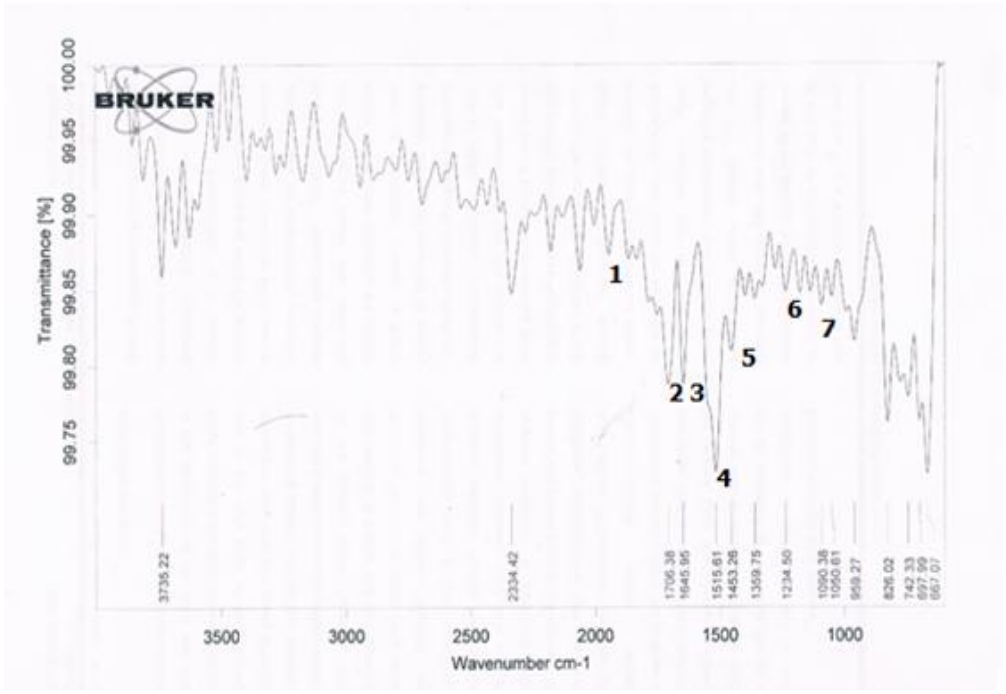


Figure 6: IR spectrum of cefuroxime axetil + sodium alginate + Carbopol 934P (Day 14).

Result & Discussion

The spectra of physical mixture as on day 0, day 14 and gel were compared with the peaks of cefuroxime axetil. It was found that there was no disappearance of peaks and no appearance of new peaks in physical mixture.

Preparation of calibration curve

- **Preparation of stock solution:** 125 mg of cefuroxime axetil was accurately weighed and transferred to previously dried 250 ml volumetric flask. Cefuroxime axetil was dissolved in PEG 400 or 200 and volume was made up to mark with SSF solvent. The resultant solution contained 500 µg of Cefuroxime axetil perml.
- **Determination of λ_{max}:** From stock solution, 20 µg/ml of cefuroxime axetil solution was prepared in simulated saliva fluid pH 6.5 and scanned the wavelengths of 200nm to 800nm. The spectrum is shown in Figure 7.

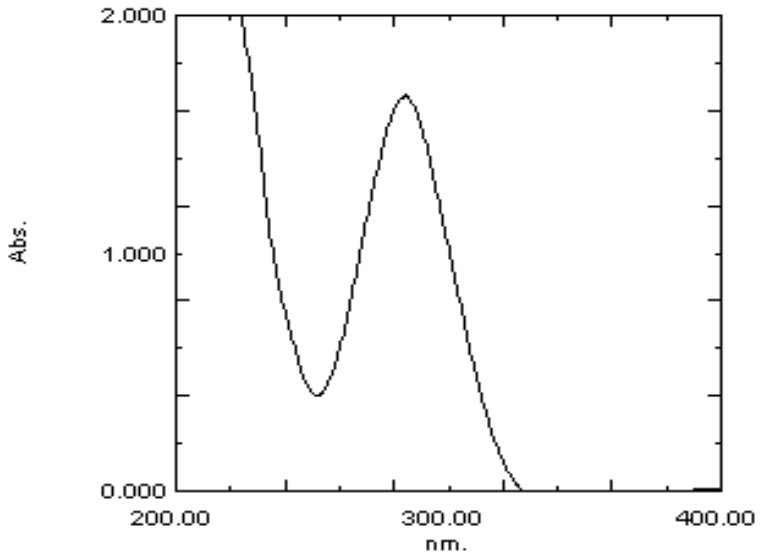


Figure 7: UV spectrum of cefuroxime axetil.

The cefuroxime axetil was scanned using UV spectrophotometer and its wavelength of maximum absorption was found to be 278nm.

Standard curve of cefuroxime axetil in simulated saliva fluid pH 6.5

From stock solution (500µg/ml), 20ml was transferred into 100ml volumetric flask and volume was made up to mark with simulated saliva fluid pH 6.5. Further 20ml of solution was transferred to 100ml of volumetric flask and volume was made up to mark with the simulated saliva fluid pH 6.5 (20 µg/ml). From this solution aliquots of 1ml, 2ml, 3ml, 4ml,

5ml, 6 ml, 7ml, 8ml, 9ml were transferred to a series of 10ml volumetric flasks and volume was made up to mark with the simulated saliva fluid pH 6.5. The absorbance of these solutions was measured at 278nm. The concentration ranges and the absorbance data are reported in Table 6. Standard curve was plotted using this data and the same is shown in Figure 8.

Table-6: Data for standard curve of cefuroxime axetil in simulated saliva fluid pH 6.5 at 278 nm.

S.No.	Concentration (µg/ml)	Absorbance			Average absorbance
		A_1	A_2	A_3	
1	2	0.1232	0.1234	0.1233	0.1233
2	4	0.2142	0.2142	0.2141	0.2142
3	6	0.3222	0.3223	0.3224	0.3223
4	8	0.4230	0.4231	0.4231	0.4231
5	10	0.5192	0.5191	0.5190	0.5191
6	12	0.6240	0.6242	0.6242	0.6242
7	14	0.7511	0.7518	0.7520	0.7516
8	16	0.8533	0.8532	0.8528	0.8531
9	18	0.9678	0.9671	0.9680	0.9676
10	20	1.0568	1.0560	1.0568	1.0565

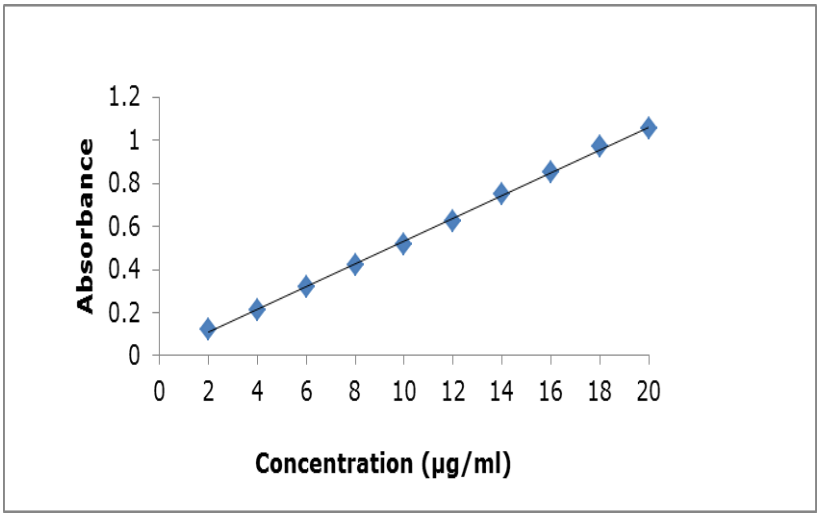


Figure 8: Standard curve of cefuroxime axetil at 278 nm.

RESULT AND DISCUSSION

The cefuroxime axetil was scanned using UV spectrophotometer and its wavelength was found to be 278nm. It was concluded that the method was linear and obeyed the Beer's law in the concentration range of 2µg/ml to 20µg/ml at 278nm. The linear regression equation for cefuroxime axetil was y = 0.061x + 0.2747 (r^2 = 0.999). The slope & intercept of standard curve were found to be 0.061 & 0.2747 respected with correlation coefficient r=0.999.

Formulation development of cefuroxime axetil mucoadhesive gel

Process flow chart

The process flow chart for the preparation of Cefuroxime axetil periodontal gel is shown in Figure 9:

Figure 9: Process flow chart for preparation of periodontal gel of cefuroxime Axetil.

Process flow chart	Unit operation	Formulation and Process variables
Sodium alginate/carbopol dissolved at different concentrations in hot water by using mechanical stirrer ↓ Cefuroxime axetil dissolved in PEG 400/200 by using mechanical Stirring ↓ Sodium alginate/carbopol 934p solution and solution of drug mixed by using magnetic stirrer (pH adjusted) ↓ Buccal mucoadhesive gel	Mixing & heating	• Concentration of sodium alginate • Concentration of carbopol 934p • Mixing speed • mixing time Mixing speed and time

Formulation development variables

The variables influencing the formulation development of buccal mucoadhesive gel are presented in Table-7.

Table 7: Formulation and process variables for buccal mucoadhesive gel.

Variables
Formulation variables
• Nature of polymers
• Polymer concentrations
Process variables
• Stirring speed
• Stirring time
• Temperature

From amongst the above listed variables, the nature of polymers/polymer blends and their concentration were optimized to prepare mucoadhesive gel of cefuroxime axetil of desired quality attributes.

Formulation Composition

The composition of cefuroxime axetil gel preparation is presented in Table-8:

Table 8: Formulation design for preparation of periodontal gel of cefuroxime axetil.

Ingredients	F1	F2	F3	F4	F5	F6
Cefuroxime axetil(mg)	375	375	375	375	375	375
Sodium alginate(%)	7	7	9	…..	.....	……
Carbopol 934p(%)	.....	.....	.....	1	1	1.5
PEG 400(ml)	4	…….	4	4	…….	4
PEG 200(ml)	…….	4	.....	……..	4	…….
Distilled water (q.s)	50	50	50	50	50	50

Ingredients	F7	F8	F9	F10	F11	F12
Cefuroxime axetil(mg)	375	375	375	375	375	375
Sodium alginate(%)	9	11	11	…..	.....	……
Carbopol 934p(%)	.....	.....	.....	1.5	2	2
PEG 400(ml)	……	4	…….	……..	4	
PEG 200(ml)	4	…….	4	4	.....	4
Distilled water (q.s)	50	50	50	50	50	50

Significance of ingredients

Carbopol 934P and sodium alginate are used as gelling agents and PEG 400 and PEG 200 are used as solubilising agent.

Method of preparation

Preparation of gel formulations using sodium alginate

Accurately weighed cefuroxime axetil was taken in a beaker and dissolved in PEG 400/ PEG 200(Solution 1).Required quantity of sodium alginate was dissolved in small amount of hot water by using mechanical stirring (Solution 2). Solution 2 was mixed with Solution 1 and volume was adjusted upto 50 ml using distilled water and pH of formulations was adjusted to 6.5-7.5 using NaOH.

Preparation of gel formulations using Carbopol 934p

Accurately weighed Carbopol 934P was dissolved into small amount of water by mechanical stirring (Solution 1). Accurately weighed cefuroxime axetil was dissolved in PEG 400/PEG 200 by using stirrer (Solution 2). Both the solutions 1 and 2 were mixed magnetically and 1-2 drops of triethanolamine was added to it and volume was adjusted upto 50 ml using distilled water and pH of formulations was adjusted to 6.5-7.5 using NaOH.

Evaluation of the developed cefuroxime axetil mucoadhesive gel formulations

pH measurement

The pH of the prepared formulations was measured by dispersing 1gm of gel in 100 ml of water and then pH was noted using a calibrated digital pH meter. The pH of the formulations is shown in Table 9.

Table 9: pH of the cefuroxime axetil periodontal gel formulation.

Formulation Code	pH*	Formulation Code	pH*
F1	6.3±0.06	**F7**	6.3±0.10
F2	6.3±0.10	**F8**	6.4±0.14
F3	6.4±0.14	**F9**	6.3±0.10
F4	6.3±0.10	**F10**	6.2±0.14
F5	6.2±0.14	**F11**	6.3±0.10
F6	6.3±0.06	**F12**	6.4±0.14

*****Data indicate mean±SD of triplicate determinations

Result & Discussion

The pH of the formulations was in the range of 6.3±0.1 to 6.5±0.1. The normal range of oral mucosal pH is reported to be 5.5-7.5. Therefore, the effects of the formulations (F_1-F_{12}) on the pH of oral tissues should be considered. It was notable that the pH values of all the formulations were not strongly acidic or alkaline and thereby not causing any damage to the hard (enamel and dentin) and soft oral tissues. Furthermore, the three buffer systems of the salivary system are able to maintain a non-harmful pH (5.5-7.5) in the oral cavity. Thus, it may be assumed that all the formulations are applicable for oral mucosal treatment.

Determination of drug content and content uniformity

The prepared formulations were analyzed for drug content, by taking 1gm of formulation in 100ml volumetric flask. About 20 ml of simulated saliva fluid pH 6.5 was added to the volumetric flask and shaken well. Further, the volume was made up to the mark with same solvent. From this solution 2ml was transferred to a 10ml volumetric flask the volume was made up to the mark with same solvent. The total cefuroxime axetil content was determined by comparing the U.V. absorbance of the resultant solution at a wave length of 278 nm from the standard curve of cefuroxime axetil in simulated saliva fluid of pH 6.5. The data is reported in Table 10.

Table 10: Drug content (%) of prepared cefuroxime axetil gel formulations.

S.No.	Formulation Code	drug content (%)
1	F_1	103.00±0.32
2	F_2	93.54±0.47
3	F_3	97.92±0.58
4	F_4	95.10±0.47
5	F_5	94.22±0.33
6	F_6	82.16±0.29
7	F_7	87.38±0.38
8	F_8	83.16±0.31
9	F_9	88±0.39
10	F_{10}	88.53±0.41
11	F_{11}	85.19±0.35
12	F_{12}	90.36±0.42

Result & discussion

Drug content was found to range between 82.16±0.29 - 103±0.32%. Small values of standard deviation (S.D.) showed that cefuroxime axetil was uniformly distributed in the formulations. This is because of easy and single step preparations i.e. addition of drug to the polymer solution accounted for minimal or no drug loss.

Determination of viscosity

The viscosity of formulations (F_1 to F_{12}) was measured by Brookfield digital viscometer. The measurement was carried out using spindle number S95 at 10, 20, 30, 50 & 100 rpm and temperature was maintained at 25^0C. The data is reported in Table 11.

Table 11: Viscosities of cefuroxime axetil gel formulations at different rpm.

Formulation code	Viscosity in centipoises (cps) at different rpm				
	10	**20**	**30**	**50**	**100**
F_1	26185	20800.2	16138	8443.4	……
F_2	27885	21300.4	17738	9953	……
F_3	38456	32480.8.3	27980	10360	…….
F_4	18500	16340.7.3	15000	8700	3500
F_5	17800	15860.6.7	14600	7600	3060
F_6	27260.7.1	24300.6.3	21850.5.8	12150.4.9	9300.4.5
F_7	33848.8.5	30060.7.9	27668.7.2	16437.6.8	11341.4.3
F_8	44767.7.9	41200.8.1	38327.7.1	26317.6.8	17425.4.1
F_9	42172.8.2	39520.7.3	35420.6.8	30312.8.9	21321.6.8
F_{10}	27351.6.3	23850.6.9	18420.5.7	14459.4.6	12399.4.1
F_{11}	41359.7.9	38600.8.1	32624.7.7	27421.7.1	21436.6.8
F_{12}	40858.6.9	38150.7.8	33514.7.9	27331.6.9	19600.5.3

***** Data indicate mean±SD of triplicate determination

Result & discussion

The viscosity of the gels should be such that it should allow the contents to express from the container and spread on the lesion easily. At the same time, formulations should have appropriate retention characteristics to prevent flowing and being removed. The viscosity values of the prepared gel formulations were in the range of 15860±6.7 - 41200±8.1 cps at 20 rpm (Table-11). Shear thinning phenomenon, an advantageous property of buccal gel, was observed (Fig.10). In this flow the molecule at rest are entangled with the association of the immobilized solvent. Under the influence of shear, the molecules tend to become disentangled and align themselves in the direction of flow. The molecules thus offer less resistance to flow and this together with the release of entrapped water account for the lower viscosity. The effect of type of polymer and its concentration on the viscosity of formulation is shown in Figure 11:

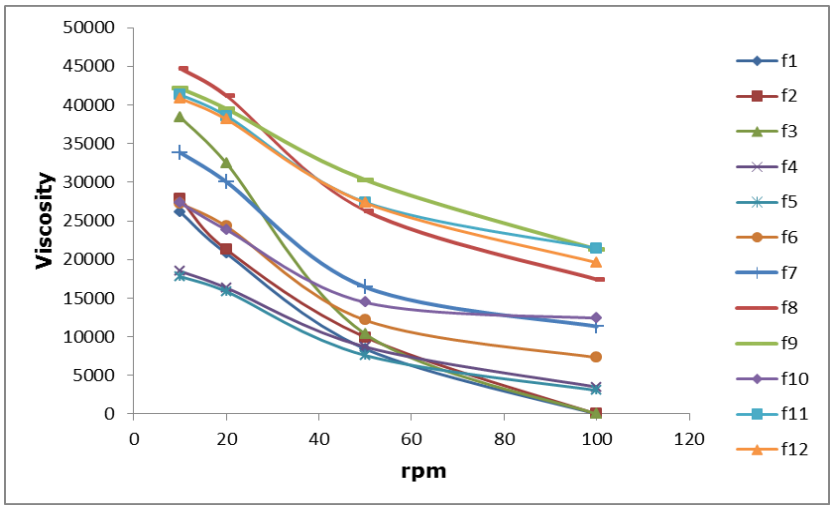


Figure 10: Effect of rpm on viscosity of Cefuroxime axetil periodontal gel.

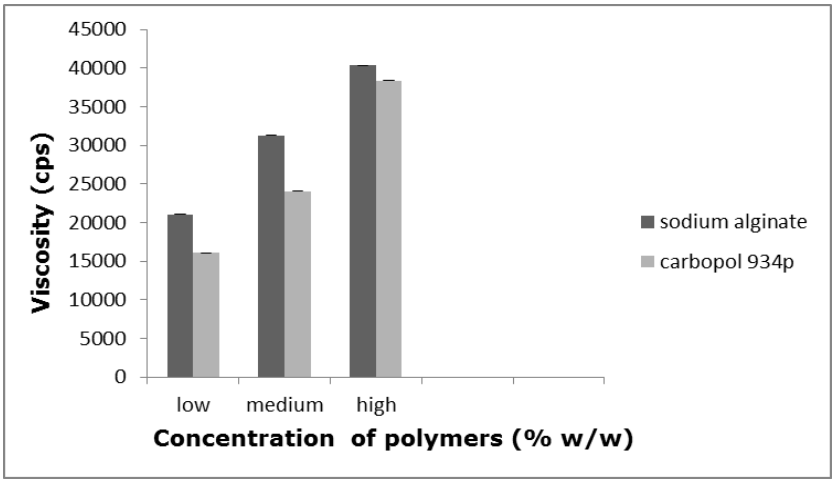


Figure 11: Effect of conc. of polymers on viscosity of Cefuroxime axetil periodontal gel.

The viscosity data was analysed using ANOVA and a significant ($p<0.05$) difference was observed in the viscosity. It may be concluded that types of polymer and its concentration affect the viscosity of the formulations. The apparent viscosity values were used as a measure of gel consistency. These values appeared to be markedly different; revealing variability in net work structure. F_9 formulation prepared using high concentration of sodium alginate showed highest viscosity values indicating higher consistency which may be due to its cross-linked structure, reflectingthis rheological behavior.

Extrudability

The gel formulations were filled in clean, lacquered aluminum collapsible tubes with a nasal tip of 5 mm opening extrudability was then determined by measuring the amount of gel extruded through the tip when a constant load of 1 Kg. was placed on the tube. Extruded gel was collected and weighed. The percentage of gel extrude was calculated by the following formula and results are mentioned in Table 12.

%extruded gel=weight of extruded gel from tube×100/weight of gel fill in tube

Table 12: Extrudability of cefuroxime axetil gel formulations.

Formulation code	% Extrudability*	Formulation code	% Extrudability*
F_1	4.62±0.67	**F_7**	4.16±0.51
F_2	5.31±0.56	**F_8**	2.6±0.45
F_3	3.88±0.85	**F_9**	2.9±0.46
F_4	6.74±0.42	**F_{10}**	4.66±0.51
F_5	7.75±0.41	**F_{11}**	2.56±0.39
F_6	4.37±0.59	**F_{12}**	3.18±0.48

***Data indicate mean±SD (n=3)

Result & Discussion

The packing of gels have gained a considerable importance in delivery of desired quantity of gel from jar or extrusion of gel from collapsible tubes. In the present study extrudability of gel formulations was determined based upon the quantity of % gel extruded from tube on application of certain load. More the quantity of gel extruded, better the extrudability. The order of increasing % extrudability of formulations were $F_{11}>F_8>F_9>F_{12}>F_3>F_7>F_6>F_1>F_{10}>F_2>F_4>F_5$ respectively. The effect of types of polymer and its concentration on extrudability is shown in Figure 12. The graph is plotted based on a preliminary data using mean±SD of effect observed at the levels studied.

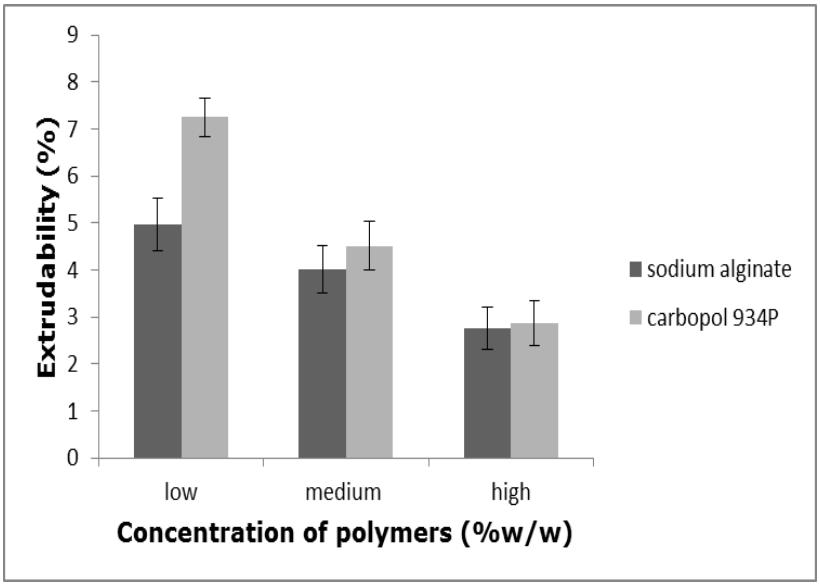


Figure 12: Effect of conc. Of polymers on extrudability of Cefuroxime axetilperiodontal gel.

There was significant ($p<0.05$) difference in extrudability values (ANOVA one way). It may be concluded that polymer types and concentration affect the extrudability of the formulations. It is to be noted that though Carbopol has been used in a concentration Of 1%,1.5%,2%, it affords significantly better extrudability than sodium alginate used in concentration Of 7%,9% and 11%.

Spreadability

Spreadability of formulations was determined using modified apparatus consisting of wooden block which was provided with a pulley at one end. A rectangular ground glass plate was fixed on this block. An excess of gel (about 2gm) under study was placed on this ground plate. The gel was then sandwiched between this plate and another plate having the dimension of the fixed ground plate and provided with hook. A 1 Kg. weight was placed on the top of the two plates for 5 min. to expel air and to provide a uniform film of gel between the plates was then subjected to a pull of 150 gm., with the help of a string attached to the hook and the time (in sec.) required by the top plate to cover a distance of 5 cm is noted. The Spreadability was calculated by the following formula and results are mentioned in Table 13.

$$S = m \times l / t$$

Here, S – Spreading coefficient, m – weighed tied to upper slide, l – distance traveled by top plate, t – Time required to travel top plate 5 cm.

Table-13: Spreadability of cefuroxime axetil gel formulation.

Formulation code	Spreadability coefficient* gm. cm/sec	Formulation code	Spreadability coefficient* gm. cm/sec
F_1	26.5±3.94	F_7	20.6±3.10
F_2	23.3±3.52	F_8	17.3±2.90
F_3	15.5±2.60	F_9	15.4±2.16
F_4	22.0±3.51	F_{10}	18.56±3.12
F_5	25.4±7.46	F_{11}	13.25±2.80
F_6	16.19±3.01	F_{12}	13.83±2.85

***Data indicate mean±SD of triplicate determinations.

Result & discussion

Spreadability is a term expressed to denote the extent of area to which the gel readily spreads on applications to the affected parts. The therapeutic efficiency of a formulation also depends upon its spreading coefficient, higher the spreading coefficient values better the spreadability. The spreadability coefficient values of the prepared gel formulations were in the range of 15.5±2.60 - 26.5±3.94 gm.cm. sec^{-1} (Table-13). The effect of type of polymers and its conc. On the spreadibility of formulation is shown in Figure 13:

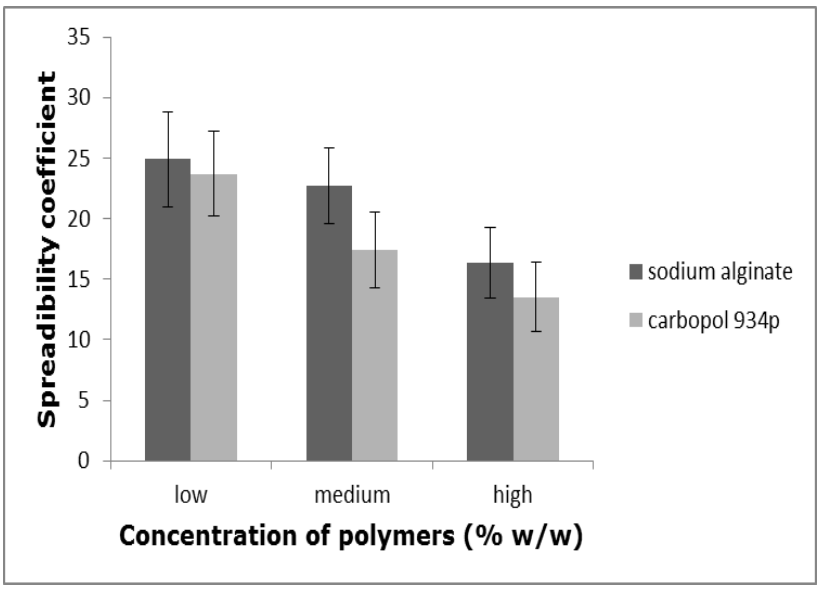


Figure 13: Effect of conc. of polymers on spreadibilty of Cefuroxime axetilperiodontal gel.

No significant ($p<0.05$) difference in the spreadibility coefficient was foundbut the formulation prepared using 2% carbopol & 11% sodium alginate. However there was a significant ($p<0.05$) difference in spreadibility of gel formulation prepared using 7% & 11% sodium alginate.

***In vitro* mucoadhesive studies**

In vitro mucoadhesive studies were carried out using goat buccal mucosa and modified two-armed balance. The plastic jar on one side of the balance was counter balanced by using suitable weight on the other side. At the counter balanced pan's bottom goat mucosa was attached by using double sided adhesive tape. At the same side of the balance base, a piece of goat mucosa having same surface area was fixed. A fixed quantity (1 gm) of gel was applied to mucosa. Preload of 100 gm. for 5 min. was applied for gel adhesion between mucosa and then removed. In the plastic jar water was added 1drop/sec. till the mucosa and gel detached. Quantity of water was determined. Force of adhesion was expressed as the detachment stress in dyne/cm^2, and was determined from the minimal weight required to detach the tissue from the surface of each formulation using the following equation and results are mentioned in Table 14.

Detachment force (Dyne/cm^2) = weight of water collect in jar (gm) x 980/Area of tissue exposed

Table-14: Mucoadhesive strength of cefuroxime axetil gel formulations.

Formulation code	Detachment force* (dyne/cm^2)	Formulation code	Detachment force* (dyne/cm^2)
F_1	5880±9.5	**F_7**	6315±10.13
F_2	5880± 9.5	**F_8**	6829±10.25
F_3	8820±9.9	**F_9**	6637±10.22
F_4	5390±8.9	**F_{10}**	7293±11.97
F_5	6860±11.0	**F_{11}**	7643±11.90
F_6	7482±11.95	**F_{12}**	7519±11.70

***Data indicate mean±SD of triplicate determinations

RESULT AND DISCUSSION

The mucoadhesive properties of prepared gel formulations were examined by evaluation of the detachment force required to overcome the adhesive bond between each formulation and the buccal mucosa. The polymers employed in these formulations have been described as bioadhesive and, therefore, it would be anticipated that the formulation would display good mucoadhesive properties. It also was noted that factors such as the molecular weight of polymer, the type and degree of cross-linking agent, molecular architecture and the polymer amount in the gel influenced the mucoadhesive performance. The detachment force values of the prepared gel formulations were in the range of 5880±9.50 - 8820±9.90 dyne.cm^{-2} respectively (Table-14).

The effect of types of polymer and concentration on the mucoadhesive strength of formulation is shown in Figure 14. There was significant difference in mucoadhesive property among the gel formulations.

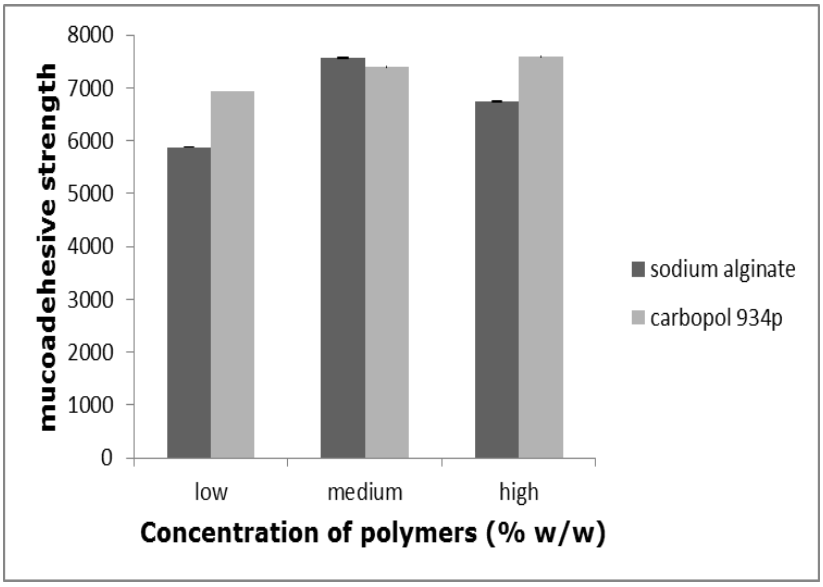


Figure 14: Effect of concentration of polymers on mucoadhesion strength of cefuroxime axetil periodontal gel.

***In vitro* release study**

The dialysis membrane (Hi media) pore size 2.4 nm, MWCO 12000-14000 was utilized for diffusion studies. Prior to the diffusionstudies, the dialy sismembranewassoakedovernight in simulated saliva fluid pH 6.5. The hydrated membrane was used for diffusion study**.** Dialysis membrane was placed between donor and receptor compartments. In the receptor compartment of Franz diffusion cell simulated saliva fluid pH 6.5 was filled and 1 gm gel was applied to the membrane through donor compartment. The release study was performed at 37±2^{0}C to different time intervals for 4 hrs. 1ml of recipient fluid was withdrawn at time intervals as shown in Table 15 & 16 and replaced with equal volume of fresh simulated saliva fluid pH 6.5. Samples were analyzed spectrophotometerically at 278 nm and *in vitro* cefuroxime axetil release profile of different formulations is shown in Figure 16 & 17 and is across egg & dialysis membrane respectively. Considering constant zero order drug release in 4 hrs, a theoretical reference (T.R) profile was computed which is also shown in Figure 16.

Table 15: *In vitro* release of cefuroxime axetil from the prepared periodontal gels across egg membrane.

Cumulative drug release (%)	Time (min.) → / Formulation ↓	15	30	60	120	180	240	f_2
	F1	3.25± 0.20	6.3±0 .15	12.7± 0.50	25.51 ±0.45	34.11 ±0.15	45.16 ±0.32	81.72
	F2	4.95± 0.01	7.65± 0.34	14.9± 0.23	28.81 ±0.54	37.12 ±0.67	46.13 ±0.43	84.10
	F3	2.99± 0.12	4.65± 0.43	0.65± 0.13	22.65 ±0.26	30.11 ±0.62	40.12 ±0.51	66.06
	F4	1.82± 0.35	3.25± 0.91	8.53± 0.17	23.34 ±0.43	31.33 ±0.24	39.12 ±0.73	63.74
	F5	3.13± 0.35	6.37± 0.91	1.17± 0.17	21.16 ±0.43	32.31 ±0.24	40.31 ±0.73	67.33
	F6	1.85± 0.35	2.55± 0.52	7.78± 0.72	16.83 ±0.80	22.15 ±0.81	33.51 ±0.87	71.77
	F7	3.75± 0.31	5.39± 0.39	10.83 ±0.50	25.63 ±0.59	32.07 ±0.60	43.89 ±0.70	67.90
	F8	2.18± 0.33	3.19± 0.16	7.13± 0.27	17.98 ±0.50	27.51 ±0.56	34.63 ±0.69	70.88
	F9	2.53± 0.15	3.31± 0.62	8.89± 0.35	17.05 ±0.65	29.67 ±0.60	38.19 ±0.70	70.90
	F10	2.09± 0.14	2.63± 0.20	8.10± 0.25	18.19 ±0.30	23.51 ±0.71	36.89 ±0.82	71.03
	F11	0.85± 0.55	1.39± 0.23	6.05± 0.30	13.10 ±0.60	18.27 ±0.60	25.33 ±0.86	74.26
	F12	1.17± 0.27	1.93± 0.37	6.35± 0.57	13.70 ±0.62	19.00 ±0.83	27.45 ±0.84	74.64
	Theoretical profile	3.15	6.25	12.51	25.31	37.49	50.00	

* Data indicate mean±SD (n=3)

** T.R. = Theoretical reference profile; considering zero order release

Table-16: *In vitro* release of cefuroxime axetil from the prepared periodontal gels across dialysis membrane

Cumulative drug release (%)	Time (min.) → / Formulation ↓	15	30	60	120	180	240	f_2
	F1	2.98±0.20	5.11±0.15	11.15±0.50	23.34±0.45	31.35±0.15	43.13±0.32	71.64
	F2	3.16±0.01	6.13±0.34	12.95±0.23	25.13±0.54	34.95±0.67	44.12±0.43	78.67
	F3	2.14±0.12	4.03±0.43	10.05±0.13	21.55±0.26	34.95±0.67	44.12±0.43	61.16
	F4	1.42±0.35	3.02±0.91	8.16±0.17	22.34±0.43	30.33±0.24	37.56±0.73	61.08
	F5	2.99±0.35	5.37±0.91	10.75±0.17	21.01±0.43	31.39±0.24	38.33±0.73	63.69
	F6	0.91±0.34	2.09±0.51	4.57±0.71	11.47±0.79	25.15±0.98	32.64±0.90	73.30
	F7	2.95±0.31	5.06±0.38	12.39±0.49	24.51±0.58	32.89±0.59	40.54±0.69	67.83
	F8	1.89±0.32	3.84±0.15	7.42±0.26	16.72±0.49	23.97±0.55	31.93±0.68	71.49
	F9	2.57±0.14	4.89±0.61	8.36±0.34	19.85±0.64	27.21±0.59	35.91±0.69	69.99
	F10	1.17±0.13	2.9±0.19	6.77±0.29	13.39±0.70	28.27±0.81	34.91±0.89	71.76
	F11	0.42±0.14	1.53±0.21	3.65±0.29	10.92±0.59	19.37±0.59	23.47±0.85	75.33
	F12	0.67±0.15	2.13±0.26	4.15±0.39	11.25±0.59	20.13±0.61	25.19±0.82	74.62
	Theoretical profile	3.15	6.25	12.51	25.31	37.49	50.00	

* Data indicate mean±SD (n=3)

** T.R. = Theoretical reference profile; considering zero order release

Result & discussion

The release of cefuroxime axetil from the prepared gel formulation as at 4th hour in the descending order F2<F1<F12<F11<F6<F10<F9<F8<F7<F5<F3<F4

Formulation release profiles were compared to theoretical reference profile by calculating similarity factor f_2; the values of f_2 were less than 50. It indicates formulations were not equivalence to theoretical reference profile (Appendix Table 2). The effect of type of polymers and their concentration on *in-vitro* cefuroxime axetil release at 4th hr from mucoadhesive gel formulations is shown in Figure 15 & 16.

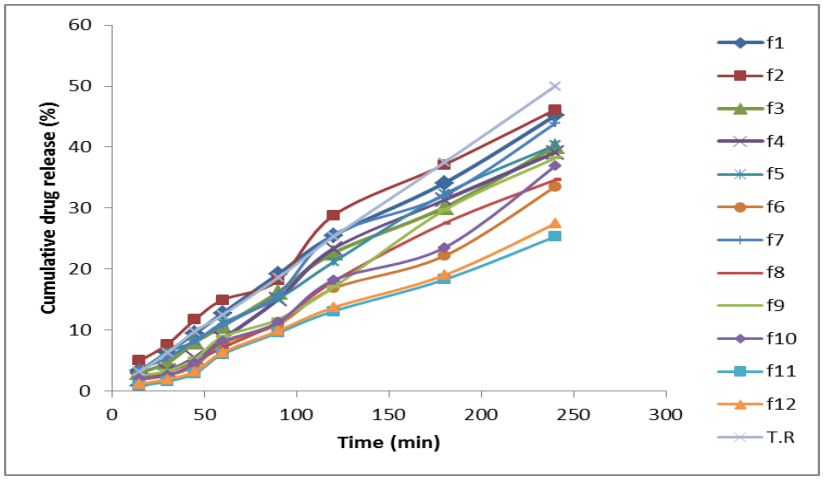


Figure 15: *In-vitro* cumulative release of cefuroxime axetil across eggmembrane from the preparedperiodontal gel formulation.

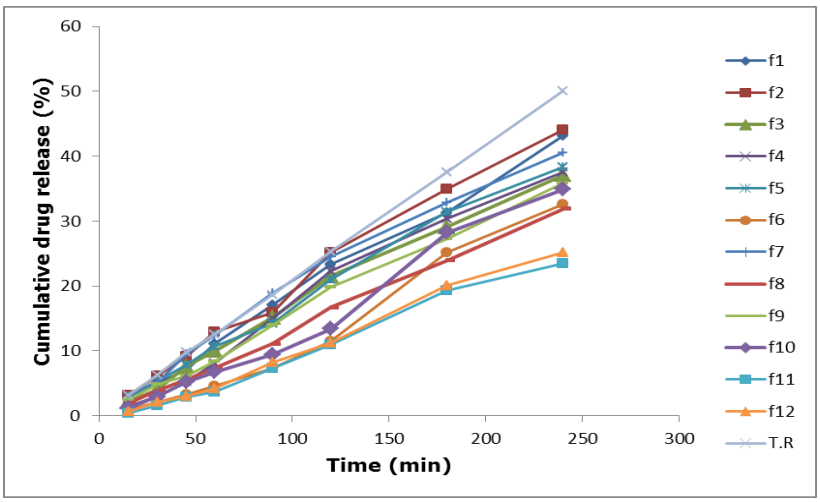


Figure 16: *In-vitro* cumulative release of Cefuroxime axetil across dialysis membrane from the preparedperiodontal gel formulation.

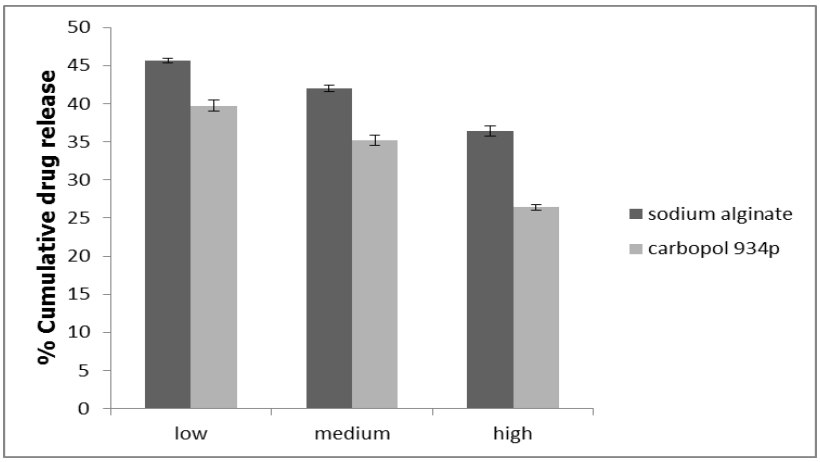


Figure 17: Effect of type and concentration of polymers *in vitro* cefuroxime axetil release at 4th hr from periodontal gel formulations.

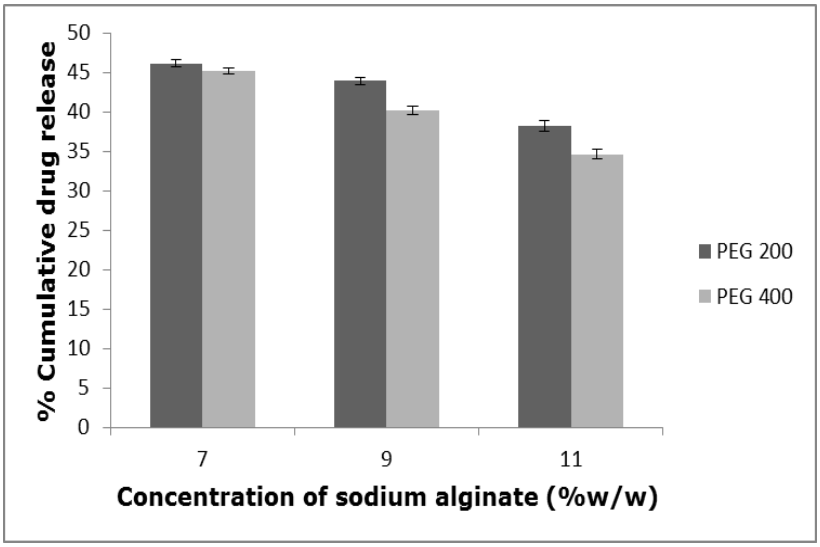


Figure 18: Effect of PEG 200 and PEG 400 on concentration of sodium alginate on *in vitro* cefuroxime axetil release at 4th hr from periodontal gel formulations.

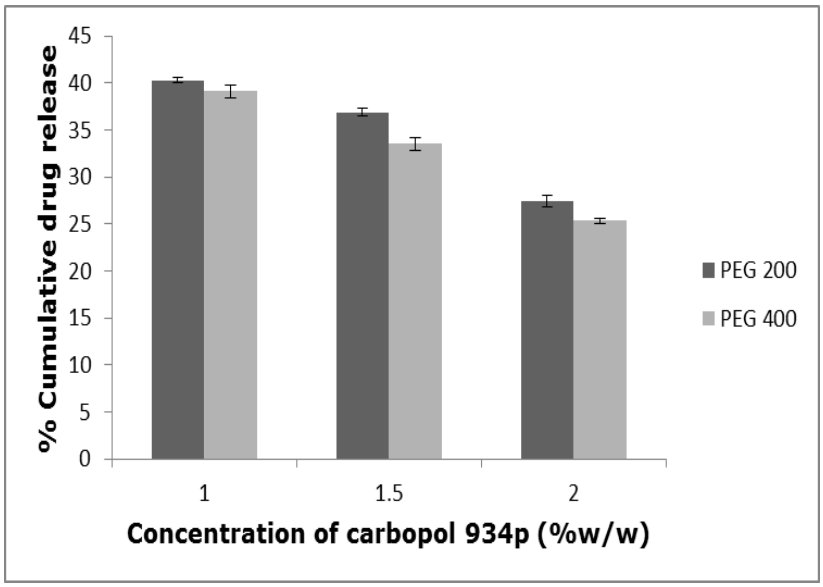


Figure 19: Effect of PEG 200 and PEG 400 on concentration of carbopol 934p on *in vitro* cefuroxime axetil release at 4th hr from periodontal gel formulation.

Model fitting for release kinetics

Drug release from gel was studied and fit in to various models e.g. zero order, first order, Higuchi, Hixon-crowell and Korsmeyer-Peppas model. For each of the models the dependent parameters i.e. cumulative percentage drug released v/s time, log %drug released v/s time, percentage drug released v/s square root of time and cube root %drug unreleased v/s time and fraction release v/s time (Appendix Table 3) were used to calculated correlation coefficient and suggest a model that best fits the release kinetics is shown in Table 17 & 18.

Table 17: Release kinetics across egg membrane of prepared cefuroxime axetil periodontal gel.

Code	Zero order	First order	Hixson Crowell	Higuchi	Korsmeyer-Peppas			Best fit model
	r	r	R	R	r	K	n	
F_1	**0.975**	0.919	0.992	0.961	0.412	0.878	0.973	Zero order
F_2	**0.997**	0.936	0.989	0.964	0.490	0.831	0.994	Zero order
F_3	**0.997**	0.928	0.989	0.964	0.196	0.974	0.996	Zero order
F_4	**0.990**	0.969	0.914	0.993	0.077	0.307	0.986	Zero order
F_5	**0.976**	0.918	0.991	0.962	0.413	0.876	0.740	Zero order
F_6	**0.995**	0.934	0.970	0.958	0.994	0.001	1.289	Zero order
F_7	**0.995**	0.944	0.972	0.959	0.995	0.000	0.993	Zero order
F_8	**0.996**	0.948	0.977	0.954	0.988	0.001	1.105	Zero order
F_9	**0.996**	0.953	0.982	0.954	0.992	0.001	1.119	Zero order
F_{10}	**0.992**	0.939	0.974	0.952	0.974	0.000	1.15	Zero order
F_{11}	**0.996**	0.901	0.952	0.969	0.994	0.001	0.017	Zero order
F_{12}	**0.997**	0.918	0.962	0.964	0.973	0.001	1.324	Zero order

Table 18: Release kinetics across dialysis membrane of prepared cefuroxime axetil periodontal gel.

Code	Zero order	First order	Hixson Crowell	Higuchi	Korsmeyer-Peppas			Best fit Model
	r	r	R	R	r	K	n	
F_1	**0.997**	0.932	0.986	0.967	0.184	0.994	0.996	Zero order
F_2	**0.996**	0.923	0.987	0.965	0.238	0.958	0.997	Zero order
F_3	**0.996**	0.904	0.993	0.952	0.126	1.055	0.995	Zero order
F_4	**0.998**	0.931	0.986	0.966	0.183	0.993	0.993	Zero order
F_5	**0.997**	0.932	0.985	0.965	0.182	0.994	0.996	Zero order
F_6	0.987	0.952	0.988	0.950	**0.992**	0.001	1.316	Korsmeyer-Peppas
F_7	0.992	0.901	0.945	**0.996**	0.991	0.001	1.072	Higuchi
F_8	**0.999**	0.934	0.973	0.983	0.998	0.000	1.215	Zero order
F_9	0.997	0.939	0.971	0.985	**0.998**	0.001	1.055	Korsmeyer-Peppas
F_{10}	0.989	0.931	0.976	0.961	**0.993**	0.001	1.298	Korsmeyer-Peppas
F_{11}	0.994	0.899	0.964	0.975	**0.996**	6E-05	1.536	Korsmeyer-Peppas
F_{12}	**0.996**	0.917	0.971	0.974	0.995	0.001	1.340	Zero order

Result & discussion

Zero order model fits best for drug release from all formulations. Drug release from all formulations indicating that the output rate is constant and drug release was not dependent on drug concentration.

CONCLUSION

In the present dissertation work, aim was to prepare periodontal gel of cefuroxime axetil using Carbopol 934P, and sodium alginate as gelling agents and PEG 200 & PEG 400 as solvents for cefuroxime axetil. All the 12 formulations have been evaluated. The results of evaluations are presented in Table 19.

Table-19: Results of evaluation of prepared mucoadhesive gels of Cefuroxime axetil.

Parameters		Desiredspecifications	Formulation code					
			Sodium alginate (%w/w)			Carbopol 934p (%w/w)		
			F1 (7%)	F2 (7%)	F3 (9%)	F4 (2%)	F5 (1%)	F6 (1%)
pH		6.2-6.8	6.3 ± 0.06	6.3 ± 0.10	6.4 ± 0.14	6.3 ±0.10	6.2 ± 0.14	6.3 ± 0.06
Drug content (%)		100 115%	103±0.32	93.54±0.47	97.92±0.58	95.1 ± 0.47	94.22±0.33	82.16±0.29
Viscosity (cps) at 20 rpm		15000-25000 cps	20800 7	21300 7	32480 8	16340 7	15860 6	24300 6.3
Extrudability (%)		Morethan 6	4.62± 0.67	5.31 ± 0.56	3.88 ± 0.85	6.74±0.42	**7.75 ± 0.41**	4.37±0.59
Spreadability coefficient ($gm.cm.sec^{-1}$)		More than 20	26.5±3.94	23.3 ± 3.52	15.5 ± 2.60	25.4 ± 7.46	**22±3.51**	16.19±3.1
Detachment force ($dyne.cm^{-2}$)		More than 6000	5880	5880	8820	5390	**6860**	7482±11.95
Drug release at 4^{th} hr (%)	EM	Q_{240}=50%±5%	45.16±0.32	46.13±0.51	40.12±0.46	39.12±0.31	40.31±0.43	33.51 ± 0.87
	DM		43.13±0.32	44.12±0.43	37.13±0.51	37.56±0.73	38.33±0.73	32.64 ± 0.90
Similarity factor, (f2)	EM		81.72	84.10	66.06	63.74	**67.33**	71.77
	DM		71.64	78.67	61.16	61.08	**63.69**	73.30
Best fit model			Zero order	Zero order	Zero order	Zero order	Zero order	Zero order

Parameters		Desiredspecifications	Formulation code					
			Sodium alginate (%w/w)		Carbopol 934p (%w/w)			
			F7 (9%)	F8 (11%)	F9 (11%)	F10 (1.5%)	F11 (2%)	F12 (2%)
pH		6.2-6.8	6.3± 0.10	6.4± 0.14	6.3± 0.10	6.2±0.14	6.3±0.10	6.4±0.14
Drug content (%)		100 15%	87.38± 0.38	83.16± 0.31	88± 0.39	88.53± 0.41	85.19± 0.35	90.36± 0.42
Viscosity(cps) at 20 rpm		15000-25000 cps	30060 7.9	41200 8.1	39520 7.3	23850 6.9	38600 8.1	38150 7.8
Extrudability (%)		Morethan 6	4.16± 0.51	2.6± 0.45	2.9± 0.46	4.66± 0.51	2.56± 0.39	3.18± 0.48
Spreadability coefficient (gm.cm.sec^{1})		More than 20	20.6± 3.10	17.3± 2.90	15.4± 2.16	18.56± 3.12	13.25± 2.80	13.83± 2.85
Detachment Force (dyne.cm^{-2})		More than 6000	6315± 10.13	6829± 10.25	6637± 10.22	7293± 11.97	7643± 11.90	7519± 11.70
Drug release At 4th hr (%)	EM	Q_{240}=50%±5%	43.89± 0.70	34.63± 0.69	38.19± 0.70	36.89± 0.90	25.33± 0.86	27.45± 0.84
	DM		40.54± 0.69	31.93± 0.68	35.91± 0.69	34.91± 0.89	23.47± 0.85	25.19± 0.82
Similarity factor, (f2)	EM		67.90	70.88	70.90	71.03	74.26	74.64
	DM		67.83	71.49	69.99	71.76	75.33	74.62
Best fit model			Zero order	Zero order	Zero order	Zero order	Zero order	Zero order

*Based on pharmacopoeial limits/a market product/prior art

Table 20: The effect of concentration of Sodium alginate and Carbopol 934P on the evaluated parameters.

Variable (polymer)	Viscosity (cps)	Extrudabili-ty (%)	Spreadability Coefficient (gm.cm. Sec-^{1})	Detachme-nt force (dyne.cm$^{-2)}$	Drug release
Conc of Carbopol On increasing from 1 % to 2 %	Increased Significantly	Decreased significantly	Decreased significantly	Increased significantly	Decreased significantly
Conc of sodium alginate on increasing from 7% to 11%	Increased Significantly	Decreased significantly	Decreased significantly	Increased significantly	Decreased significantly

Influence of PEG 200 and PEG 400 on release

It was noted that the formulation containing PEG 200, the release of cefuroxime axetil from the gelwas found to be more as compared to PEG 400.

So all the 12 formulations batch, F5 Formulation was found to be the best satisfactory formulation based on desired specifications of- extrudability, spreadibility, detachment force, drug release and similarity factor.

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