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Research Article

FORMULATION AND CHARACTERIZATION OF PERIODONTAL FILMS CONTAINING AZITHROMYCIN AND SERRATIOPEPTIDASE

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ABSTRACT

Objective: The objective of the present work was to formulate and evaluate periodontal film, which could be capable of delivering therapeutic concentration of azithromycin and serratiopeptidase for a prolonged period of time and could be easily placed into the periodontal pocket.

Methods: The films were prepared by solvent casting method using combinations of ethyl cellulose, hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose 50 cps, eudragit L-100, and Chitosan in different ratios using dibutyl phthalate as plasticizer. The periodontal films were evaluated for weight variation, thickness, percentage moisture absorption, percentage moisture loss, folding endurance, percentage swelling index, percentage elongation, and *in vitro* percentage cumulative drug-enzyme release profile.

Results: Formulation F12 was found to be a good periodontal film. Hence, it was considered as an optimized formulation. *In vitro* drug-enzyme release rate studies using keshary-chien diffusion cell showed maximum drug release in F12 formulation (95.92% for azithromycin and 94.20% for serratiopeptidase at the end of 24 h) compared to other formulations.

Conclusion: The optimized formulation F12 showed the best drug-enzyme release profile among the others for the preparation of periodontal film. There is a scope for the further study and development of the azithromycin and serratiopeptidase periodontal films.

Keywords: Periodontal films, Azithromycin and serratiopeptidase, Solvent casting method, keshary-chien diffusion cell.

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INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in the gastrointestinal tract and first-pass metabolism. The oral cavity provides a diverse environment for colonization by a wide variety of microorganisms [1]. Periodontal disease is a general term encompassing several pathological conditions such as gingivitis and periodontitis. Periodontitis is a local infection with primary bacterial etiology in the gingival crevices, which affects the structural organs surrounding the teeth such as periodontal ligament, connective tissue, and bone. The warm and moist pocket environment fasters the growth of Gram-negative, anaerobic bacteria that proliferate in the subgingival space. The aim of dental health care is to control the population of microorganisms. Slowing or arresting of the oro-dental infections can be achieved by controlling bacterial plaque [2]. Gingival and periodontal disease has affected the humankind for decades and in now looked on as a principle health problem. About 35% of adults are affected by periodontitis, of these 13% adults over 30 years of age have a moderate or severe form of periodontitis and 22% have a mild form of the disease [3]. Periodontitis is a complex multifactorial disease mainly caused due to Gram-negative microbes and host response to their colonization leading to the destruction of periodontal apparatus. Henceforth, periodontal pocket acts as a source of continuous localized infection which acts as a niche of various potential periodontal pathogens including *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Peptostreptococcus micros, Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, Eubacterium* spp., *Treponema denticola, Selenomonas* spp., beta-hemolytic streptococci, a variety of enteric rods, and Pseudomonas, enterococci, *Staphylococci,* and possibly yeasts.[4] Azithromycin is a first and most important member of new class of antibiotics known as azalides, used for aerobes and anaerobes found in periodontal pocket. Azithromycin is commonly used for a wide variety of mild-to-moderate bacterial infections caused by susceptible strains of the designated microorganisms in the specific conditions: *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus Agal,* etc [5]. Serratiopeptidase is an enzyme produced by entering bacterium *Serratia* sp. E-15, has the potential of developing a therapeutically efficacious system for treatment of periodontal inflammatory anaerobic infections, is a non-steroidal anti-inflammatory drug reduces swelling, and offers a powerful treatment for pain and inflammation. Studies have shown that this enzyme can actually team up with antibiotics and deliver increased concentrations of antibiotics to the site of the infection [6]. To overcome the disadvantages of systemic chemotherapy with antibiotics, recent technical advancements have led to the development of new drug delivery systems that provide controlled therapeutic activity by targeting the delivery of a drug to a particular site. If a particular drug is targeted to a desired site, it minimizes the distribution of the drug to other body organs. Controlled drug delivery systems offer numerous advantages compared with conventional dosage forms [7].

METHODS

Materials

Azithromycin and serratiopeptidase used in the formulation and development study were provided by the college. The laboratory reagents and chemicals used in the formulation and development study were supplied by the manufacturer in the college.

Methods

Periodontal films were prepared by solvent casting technique. The formulations were designed as shown in the Table 1. Glass molds were used for casting the films. Ethylcellulose, hydroxypropyl

Table 1: It shows formulae used for the development of periodontal films

Ingredients	Film code														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Azithromycin (mg)	340	340	340	340	340	340	340	340	340	340	340	340	340	340	340
Serratiopeptidase (mg)	09	09	09	09	09	09	09	09	09	09	09	09	09	09	09
Ethyl cellulose (mg)	1200	1150	1100	1000	900	1100	1000	900	_	450	900	900	450	450	_
HPMC K4M (mg)	150	200	250	350	450	_	_	_	450	_	_	_	_	_	_
HPMC 50cps (mg)	_	_	_	_	_	250	350	450	_	_	_	_	_	_	450
EudragitL100 (mg)	_	_	_	_	_	_	_	_	900	900	450	450	450	450	450
Chitosan (mg)	_	_	_	_	_	_	_	_	450	450	900	450	900	450	450
Chloroform (ml)	10	10	10	10	10	10	10	10	15	15	15	15	15	15	15
Ethanol (ml)	10	10	10	10	10	10	10	10	15	15	15	15	15	15	15
DBP (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3

HPMC: Hydroxypropyl methylcellulose, DBP: Diastolic blood pressure

methylcellulose, eudragit L100, and chitosan were used in different ratios [8]. They were dissolved in chloroform and ethanol mixture with dibutyl phthalate as a plasticizer in a beaker using a magnetic stirrer to get different concentrations of polymeric solutions [9]. Required quantity of azithromycin and serratiopeptidase was taken in spatula and dissolved in a sufficient amount of water. Mercury was poured carefully in the form of the layer into the labeled clean glass molds wrapped in an aluminum foil. After complete mixing, the solution was poured into these molds, placed on a horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel plugged with cotton in the stem at room temperature for 24 h [10]. The prepared films were packed immediately in individual airtight aluminum seal packs and stored at 25°C until used [11].

Characterization of films

Formulated periodontal films were subjected to the preliminary evaluation tests. Films with any imperfections, entrapped air, or differing in thickness, weight, or content uniformity were excluded from further studies. Physicochemical properties such as thickness, weight uniformity, and percentage moisture loss, folding endurance, surface pH, swelling index, and drug content uniformity of the prepared periodontal films were determined.

Thickness uniformity

The thickness of each periodontal film was measured using the screw gauge at different 6 positions of the film, and the average was calculated.

Estimation of percentage moisture loss

6 films of different concentrations of size (7×4 mm) were weighed accurately, and then, they were kept in desiccators for 3 consecutive days and then reweighed. The percentage moisture loss was calculated by the formula [12].

Moisture loss=(initial weight – final weight/initial weight)×100

Uniformity of weight

Periodontal film pieces (size of 7×4 mm) were taken from different areas of film. The weight variation of each film was calculated [13].

***In vitro* drug release studies**

Since the pH of gingival fluid lies between 6.5 and 6.8, phosphate buffer pH 6.6 was used as the simulated gingival fluid. The *in vitro* drug release was performed using a keshary–Chien (K-C) diffusion cell. Phosphate buffer pH 6.6 was used as a receptor solution as a dissolution medium. The volume of diffusion cell was 10 ml. The prepared periodontal film (7×4 mm) was firmly pressed onto the center of the semipermeable membrane, and then, the membrane was mounted in the donor compartment. The donor compartment was then placed in a position such that the surface of membrane just touches the receptor fluid surface. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was continuously stirred at 100 rpm using magnetic beads and the temperature was maintained at 37±1°C. The diffusion was carried out for 24 h and 1 ml of the receptor fluid was withdrawn at predetermined time interval and replaced immediately with the same volume of fresh dissolution media to maintain sink conditions. The samples were analyzed for drug release at 216 nm and 226 nm using ultraviolet (UV) visible spectrophotometer after suitable dilution with diffusion media [14].

Drug content uniformity

The prepared film formulations were analyzed for drug content by taking film (size of 7×4 mm) from each batch and individually dissolved in 5 ml of pH 6.6 phosphate buffer in a beaker. The dispersion was kept in the dark place for overnight. The dispersion was filtered. 0.1 ml of the filtered solution was diluted to 10 ml with pH 6.6 phosphate buffer in a 10 ml volumetric flask. Drug concentrations were determined by taking three readings, using a UV visible spectrophotometer at 216 NM and 226nm [15]

Tensile strength

The tensile strength was determined by the apparatus designed. A small film (7×4 mm) was cut on a glass plate with a sharp blade. The instrument was designed such that it had a horizontal wooden platform with fixed scale and attachments for two clips that hold periodontal film under test. Of the two clips, one was fixed and another was movable. Weights were hanged to one end of the pulley and the other end of the pulley was attached to movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. To determine elongation and tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. Percentage elongation and tensile strength were calculated using the following formulae [16,17].

Swelling index

Swelling index of the drug-loaded films was determined by placing the film (area 7×4 mm) in the Petridis containing about 10.0 ml of phosphate buffer pH 6.6, and before placing the film in the Petridis, its initial weight was calculated and increase in weight due to swelling was determined by weighing the film at predetermined time interval [18].

Folding endurance

The folding endurance value for all periodontal films was >200; it indicates that all formulations had ideal periodontal film properties [19].

Surface pH

Surface pH of all the formulations was determined. All the formulations were found to have a pH between 6 and 7. This reveals that the prepared periodontal films would not alter the pH of the gingival fluid in the periodontal pocket and therefore may not cause any irritation [20,21].

RESULTS

To confirm the identity, purity, and stability of drugs for formulation and to establish a drug profile, preformulation studies were undertaken. Identification of azithromycin and serratiopeptidase was performed by UV visible spectroscopic method. The maximum absorption of

azithromycin and serratiopeptidase was found at 216 nm and 229 nm, respectively. The standard curves of azithromycin and serratiopeptidase were prepared in pH 6.6 phosphate buffer.

Thickness of the films

The thickness of each film was measured at 6 different points and the average thickness with a standard deviation was calculated. The data on periodontal films thickness indicated that there was no much difference in the thickness within the formulations. The order of the thickness of the periodontal films is F12 <F11<F9<F10<F13<F15<F14<F8<F7<F2<F4<F5<F3<F6<F1.

Tensile strength

The order of tensile strength of the periodontal films is F12<F14<F13<F15<F11<F10<F9<F8<F7<F6<F5<F4<F3<F2<F1. The tensile strength is shown in Table 2.

Drug content uniformity

The percentage drug content in various formulations ranged from 84.38% to 96.20% of azithromycin and 84.73% to 94.50% of serratiopeptidase is given in Table 3. It was observed from the drug content data that there was no significant difference in the uniformity of the drug content. However, when compared with the theoretical drug content, the estimated drug content was slightly less in both drugs. It may be due to the drug loss during fabrication of the periodontal films.

Table 2: Tensile strength of loaded and unloaded periodontal films

Film code Unloaded films	Tensile strength (Kg/mm^2)	
	Loaded films	
F1	2.366±0.162	2.706±0.032
F2	2.254±0.015	2.420±0.04
F3	2.204±0.098	2.381±0.077
F4	2.105±0.121	2.211±0.042
F5	1.724±0.026	2.154±0.044
F6	1.24±0.0184	1.998±0.056
F7	1.50±0.062	1.93±0.043
F8	1.39±0.021	1.92±0.051
F9	1.54±0.023	1.87±0.034
F10	1.67±0.041	1.81±0.028
F11	1.45±0.050	1.56±0.032
F12	1.01±0.31	1.15±0.0201
F13	1.11±0.025	1.31±0.035
F14	1.05±0.056	1.27±0.024
F15	1.09±0.032	1.44±0.041

*Each reading is at least three determinations

Weight uniformity test

Drug loaded films (7×4 mm) were tested for uniformity of weight, and the results of weight uniformity are given in Table 3. Lesser standard deviation values indicated that the films were uniform in weight. Weight variation ranged from 10.40±0.11 to 11.15±0.116 mg. The order of the weight of periodontal films is F14<F15<F12<F13<F11<F10<F9<F6<F7<F8<F5<F4<F3<F2<F1.

Percentage moisture absorption

Percentage moisture absorption was found to be ranged from 8.10±0.04 to 15.20±0.02. The percentage moisture absorption is shown in Table 3.

Swelling index

Swelling index of all films was calculated and it was in the range of 10.51±0.04–28.24±0.04. A formulation containing ethyl cellulose and hydroxypropyl methylcellulose K4M shows maximum swelling property than the other films. As the concentration of polymer increased, swelling index also increased. Swelling is very essential before the drug is released from the dosage form. The swelling index is shown in Table 3.

Percentage elongation

Percentage elongation was found to be ranged from 6.47±0.004 to 14.5±0.04. The swelling index was reported in Table 3.

Percentage moisture loss

The percentage moisture loss was found to be in the range of 7.88±0.05–15.02±0.05. Moisture loss studies were conducted on all the formulations and reported in Table 3.

Surface pH

Surface pH of all the formulations was determined as described in the methodology chapter. All the formulations were found to have a pH between 6 and 7. This reveals that the prepared films would not alter the pH of the gingival fluid in the periodontal pocket and therefore may not cause any irritation.

Table 3: Various physicochemical properties of periodontal films

Film code parameters	F1	F2	F3	F4	F5	F6	F7	F8
Weight Variation (mg)*	11.15±0.116	11.12±0.046	11.08±0.276	11.05±0.38	11.01±0.21	10.92±0.24	10.95±0.10	10.96±0.128
Thickness (mm)*	0.44±0.004	0.40±0.009	0.42±0.0016	0.041±0.0070	0.41±0.0014	0.43±0.012	0.39±0.002	0.37±0.0291
% Moisture Absorption*	8.10±0.04	8.94±0.03	9.63±0.01	8.16±0.04	11.35±0.02	12.92±0.04	13.01±0.01	15.20±0.024
% Moisture Loss*	7.88±0.05	9.24±0.037	10.99±0.06	8.96±0.03	11.31±0.042	19.95±0.06	20.51±0.05	28.24±0.043
Folding endurance	161	165	168	181	197	174	185	201
% Swelling index*	18.32±0.06	19.18±0.04	20.26±0.05	20.51±0.04	22.52±0.06	16.57±0.03	16.13±0.02	19.57±0.052
% Elongation*	6.47±0.04	8.71±0.01	10.56±0.02	11.71±0.04	12.85±0.01	12.63±0.06	12.90±0.05	14.90±0.021
Film code parameters	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	
Weight Variation (mg)*	10.90±0.31	10.87±0.21	10.85±0.0211	10.73±0.240	10.84±0.10	10.40±0.10	10.61±0.20	
Thickness (mm)*	0.30±0.001	0.31±0.002	0.29±0.008	0.25±0.002	0.31±0.008	0.35±0.029	0.32±0.005	
% Moisture Absorption*	14.50±0.03	14.9±0.03	15.01±0.02	15.9±0.03	13.9±0.04	13.64±0.02	13.51±0.05	
% Moisture Loss*	23.05±0.02	10.51±0.04	11.05±0.02	20.24±0.04	15.52±0.06	14.56±0.01	11.21±0.05	
Folding endurance	249	251	270	190	235	221	205	
% Swelling index*	23.22±0.01	29.04±0.03	29.22±0.05	31.04±0.01	28.75±0.04	23.54±0.03	22.79±0.04	
% Elongation*	13.99±0.06	14.2±0.01	14.5±0.04	15.02±0.05	13.60±0.05	13.41±0.03	13.28±0.04	

Folding endurance
The folding endurance value for all films was >200; it indicates that all formulations had ideal periodontal film properties.

***In vitro* percentage cumulative drug-enzyme release profile formulation F12**
The formulation F12 was found to be a good periodontal film. Hence, it was considered as an optimized formulation. *In vitro* drug-enzyme release rate studies using K-C diffusion cell showed maximum drug release in F12 formulation (95.92% for azithromycin and 94.20% for serratiopeptidase at the end of 24 h) compared to other formulations as shown in Fig. 1 and kinetic data of *in vitro* release of periodontal film formulation F12 as shown in Table 4 and Figs. 1-5.

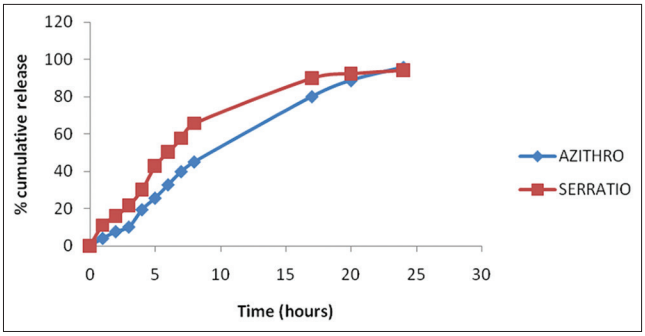

Fig. 1: Percentage cumulative drug-enzyme release profile formulation F12

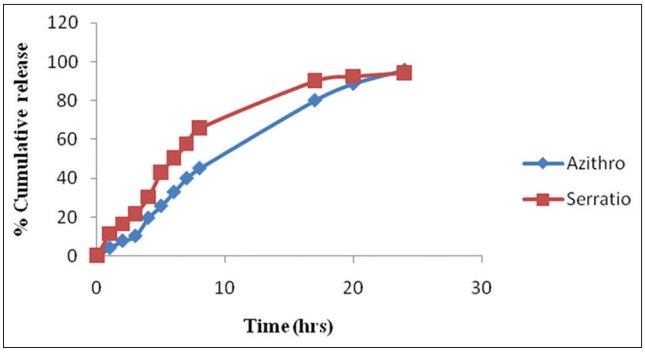

Fig. 2: Zero-order kinetic of F12

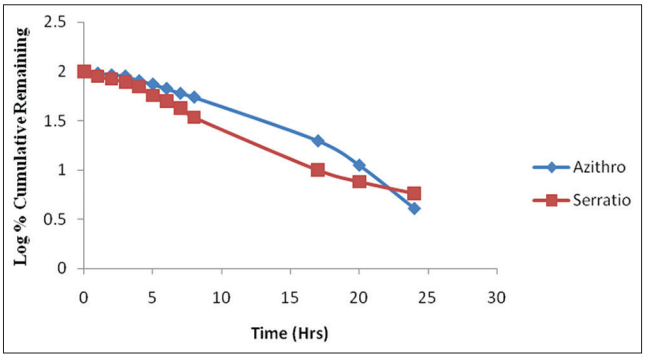

Fig. 3: First-order kinetic of F12

DISCUSSION

The azithromycin and serratiopeptidase formulated had a better release profile. This is the first time that an attempt was made to formulate a delivery system containing drug and enzyme. Fifteen formulations were formulated by a solvent casting method using combinations of EC, hydroxypropyl methylcellulose (HPMC) K4M, HPMC 50 cps, eudragit L-100, and Chitosan in different ratios using dibutyl phthalate as plasticizer. Both polymer combinations used for fabrication of periodontal films showed good film-forming properties. All fabricated films were thin, elastic, and transparent except for formulation F1-F4 which was light yellowish-brown in appearance. Partition coefficient (log P) value of azithromycin is 1.47 in an n-butanol and phosphate buffer pH 6.6 systems. It indicates the lipophilic character of azithromycin and may possess high permeability in periodontal pockets. The folding endurance value for ethyl cellulose:eudragit L 100:chitosan films was > 230, HPMC 50 cps:eudragit L 100:Chitosan was > 200, ethyl cellulose:HPMC 50 cps was 170–210, and ethyl cellulose:HPMC K4M films was >160. It indicates that all formulations had ideal film properties. The film thickness data indicate that there were no much difference in the thickness within the formulations. Thickness of the films ranged from 0.25±0.002 to 0.44±0.004 mm.

The percentage drug content in various formulations ranged from 84.38% to 96.20% for azithromycin and 86.81% to 94.50% for serratiopeptidase. *In vitro* studies of drug-enzyme were carried out in pH 6.6 phosphate buffer, which showed that there was an abrupt release initially and thereafter the release of drug-enzyme was found to be controlled. Overall, formulation F12 was found to be a good periodontal film. Hence, it was considered as an optimized formulation. *In vitro* drug-enzyme release rate studies using K-C diffusion cell showed maximum drug release in F12 formulation (95.92% for azithromycin and 94.20% for serratiopeptidase at the end of 24 h) compared to other formulations. Formulation F12 containing EC:eudragit:chitosan (2:1:1) exhibited higher tensile strength as compared to other formulations, whereas percentage elongation was observed reverse. The release kinetics indicated zero-order release of azithromycin and first-order release for serratiopeptidase. Higuchi plot for the formulation F12 revealed that the predominant mechanism of drug release is diffusion. However, from Pappas's plot, the "n" value for F12 was found to be around 0.5 and 1, thus indicating non-Fickian diffusion, which indicates that drug release mechanism involves chain relaxation mechanism.

CONCLUSION

In the present study, an attempt was made to formulate and evaluate periodontal film, which could be capable of delivering therapeutic concentration of azithromycin and serratiopeptidase for a prolonged period of time and could be easily placed into the periodontal pocket.

The percentage drug content in various formulations ranged from 84.38% to 96.20% for azithromycin and 86.81% to 94.50% for serratiopeptidase. It was observed from the data that there were no significant differences in the uniformity of the drug content. However, when compared with the theoretical drug content, the estimated drug content was slightly less indicating drug loss during the fabrication of the films.

Table 4: Kinetic data of *in vitro* release of periodontal films formulation F12

Film Code	Zero Oder (R^2)		First Order (R^2)		Higuchi (R^2)		Korsmeyers–Peppas			
					(n)		(R^2)			
	Azithro	Serratio	Azithro	Serratio	Azithro	Serratio	Azithro	Serratio	Azithro	Serratio
F12	0.975	0.879	0.963	0.991	0.946	0.957	1.004	0.729	0.975	0.953

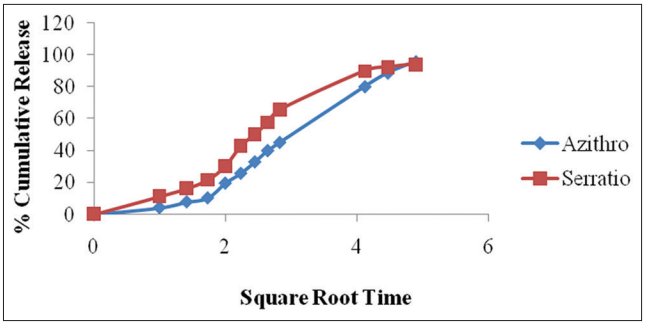

Fig. 4: Higuchi model kinetic of F12

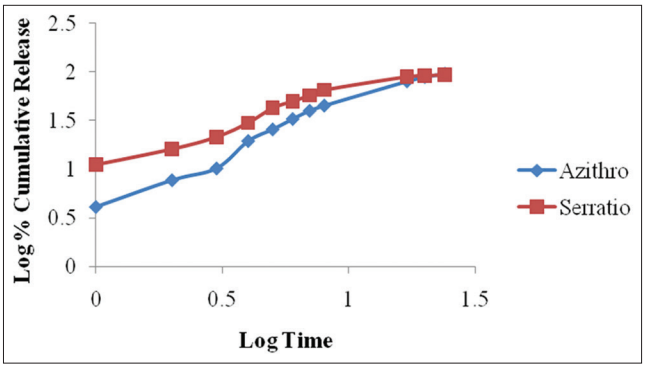

Fig. 5: Korsemeyers–Peppas Model Kinetic of F12

Overall, formulation F12 was found to be a good periodontal film. Hence, it was considered as an optimized formulation. *In vitro* drug-enzyme release rate studies using K-C diffusion cell showed maximum drug release in F12 formulation (95.92% for azithromycin and 94.20% for serratiopeptidase at the end of 24 h) compared to other formulations. Formulation F12 containing EC:eudragit:chitosan (2:1:1) exhibited higher tensile strength as compared to other formulations, whereas percentage elongation was observed reverse. Higuchi plot for the formulation F12 revealed that the predominant mechanism of drug release is diffusion. However, from Pappas's plot, the "n" value for F12 was found to be around 0.5 and 1 indicating non-Fickian diffusion, which indicates that drug release mechanism involves chain relaxation mechanism.

CONFLICTS OF INTERESTS

None

AUTHORS CONTRIBUTION

Soniya Rani designed the study, developed the methodology, collected the data and performed the analysis of the results.
Nardev singh contributed in writing the manuscript.

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