



Research on Novel Formulation of Model Drug Containing Lidocaine Hydrochloride and Doxycycline Hyclate for Periodontal Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Author GSB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SKM and GSB managed the analyses of the study. Author GSB managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

In the present day circumstances, it has been reported that the Dental diseases are a most important physical condition problem in all parts of the globe, general in all age groups, races and genders. The proportion of dental diseases has developed to a great extent in current years. Around 70% of inhabitants suffer from dental problems. The human population is exaggerated by foremost of oral diseases. To treat dental problems such as pain due to dental caries, periodonitis, gingivitis, and other gum infections, painkillers alongside with antibiotics and various dental paints are the generally prescribed drugs by dentists as primary mode of treatment. However the general side effects of most of the painkillers are hyperacidity and gastric annoyance upon oral administration. On the other hand, nearly all antibiotics due to measured onset of action and hepatic "first-pass" consequence fail to construct prompt and extend actions. Furthermore, most of the dental formulations are washed out by saliva inside a few hours of application. To conquer the above-mentioned problems, a soft polymeric mold containing antibiotic and anasthetics drugs and

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having a suitable constancy to stick to the tooth, was developed for continued drug release to endow with improved relief in dental patients. Carbopol 934, Ethyl cellulose, Gum tragacanth, Hydroxy propyl cellulose, and PEG 400 were used to organize the formulation containing Lidocaine hydrochloride and doxycycline hyclate individually and in combination, by addition and solvent evaporation technique. Dissimilar physicochemical characterization studies such as mucoadhesion test and swelling index were conceded out. In vitro drug release studies showed sustained release of Lidocaine hydrochloride and doxycycline hyclate in simulated saliva for 24 h. Additional studies are necessary to succeed with these formulations in humans. Upon accomplishment, this type of dosage form may open up new avenues towards dentistry.

Keywords: Lidocaine hydrochloride; doxycycline hyclate.

1. INTRODUCTION

Periodontal disease is a universal word which encompasses numerous pathological conditions affecting the tooth sustaining structures. Periodontal diseases comprise conditions such as chronic periodontitis, violent periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis. These circumstances are characterized by a obliteration of the periodontal ligament, a resorption of the alveolar bone and the immigration of the functional epithelium alongside the tooth facade [1]. It is a restricted inflammatory rejoinder caused by bacterial infection of a periodontal pocket connected with subgingival plaque [2]. Even though bacteria are the primary cause of periodontal disease, the appearance of microbial pathogenic factors unaccompanied may not be adequate to cause periodontitis. Periodontal pathogens construct injurious by-products and enzymes that break extracellular matrices as well as host cell membranes to generate nutrients for their development. In doing so, they begin scratch directly or indirectly by triggering host-mediated responses that escort to self-injury [3-4]. In the early on phase of the sickness (gingivitis), inflammation is curbed to the gingiva but extends to deeper tissues in periodontitis, foremost to gingival swelling, bleeding and awful breath. In the delayed phase of the disease, the underneath collagen of the periodontium is degenerated, alveolar bone begins to resorb and gingival epithelium migrates alongside the tooth facade forming a 'periodontal pocket'. This periodontal pouch provides perfect conditions for the abundance of microorganisms: primarily Gram negative, facultative anaerobic species. The microflora establishes in periodontitis is complex and poised mainly of Gram negative anaerobic bacteria. The restorative achievement or collapse depends not only on the antimicrobial movement of the chemotherapeutic mediator but as well on the position of infection, carrier system

and path of administration [5-6]. Doxycycline inhibits bacterial protein synthesis by requisite to the 30S ribosomal subunit; it has bacteriostatic movement alongside a board range of Gram positive and Gram-negative bacteria. The drug has been used to delight dental microbial plaques and periodontal diseases as bacterial infection. Lidocaine hydrochloride, an anesthetic mediator, is accessible as dermal formulation, intravenous injection, intravenous infusion, nasal spray, oral gel, and topical gel. Lidocaine has been extensively used as anesthetic agent for dental scaling, root arrangement, sting sensitivity, and early on abrasion healing subsequent nonsurgical periodontal therapy. Now we conjecture that if a squashy mold of gummy materials containing together antibiotic and analgesic drugs is close to an aberrant tooth and drugs release gradually from it at a prearranged rate for a period of 24 h or additional and enter the mark region (here affected tooth and gum), it will assist to conquer the local disease and pain in the exaggerated tooth for a protracted period to give patient fulfillment. The prepared formulation should be such that they can be close and detached by the patient when it is needed. It should be such that it relics attached to the tooth pending it is taken off using a small extra force. Information are available concerning the penetration of Lidocaine hydrochloride [7] and doxycycline Hyclate [8] athwart the gingival mucosa. Since the drugs used can pervade throughout gingival mucosa, the systemic drug incorporation is also probable from the formulations. On the other hand, in the current study, the formulation was proposed for local action of the drugs and no regional or systemic drug fascination has been reported. With the above-mentioned hypothesis, an attempt was complete to develop and evaluate in vitro a polymeric mold with a suitable uniformity, which can be capped on to the exaggerated tooth to discharge the anesthetics as well as antibiotic types of drugs for a expanded epoch of

time for their local act. To arrange the formulation, polymers and resinous materials preferred are biocompatible.

2. MATERIALS AND METHODS

2.1 Materials

Drugs: Lidocaine hydrochloride and doxycycline hyclate.

Polymers: Carbopol 934, Ethyl cellulose, Gum tragacanth, Hydroxy propyl cellulose, PEG 400.

2.2 Development of Formulation

Soft dental molds of matrix-type dosage form were formulated with the combination of polymers such as ethyl cellulose, gum tragacanth, hydroxy propyl cellulose, PEG 400. A paste was formed by homogenous mixing of drugs and polymers in ethanol (95%). This was then poured in cap-like ethanol-proof plastic molds and thereafter solvent was evaporated at $37 \pm 0.5^\circ\text{C}$, for 2h. Thus the formulations with the desired stickiness and consistency were achieved. The formulations had impermeable cover from all the sides other than the side intended to place on the affected tooth once the formulations were prepared; they were taken out from the molds. The bottom sides of the formulation were attached to small cutouts of thick adhesive tape and the formulations were then coated in a laboratory scale coating pan by film coating method. Essentially 5% ethanolic solution of ethyl cellulose was sprayed with pneumatic spraying pressure of 300 KPa at 40°C with a rotating speed of 8rpm. A negative pressure of 5Pa was maintained in the pan. During preheating and drying the rotation was maintained at 3 rpm for 5 min. They were after that reserved at room temperature meant for 24 h. Presence of organic solvent was also analyzed and a negligible amount ($< 0.25\%$) of ethanol was detected.

2.3 Drug-Excipient Interaction Study Using FTIR Spectroscopy

Drug-excipient communication, one of the very essential parameter, is premeditated previous to expansion of the formulations. Lidocaine hydrochloride and doxycycline hyclate individually; mixture of them; individual drug/drug mixture with polymeric combination and polymeric combination alone was mixed separately with IR grade KBr in the ratio 1:100

and subsequent pellets were organized by applying 5.5 metric ton of force in a hydraulic press. Polymers were Carbopol 934, Ethyl cellulose, Gum tragacanth, Hydroxy propyl cellulose, PEG 400. The pellets were scan more than a wave number range of 4000 to 400 cm^{-1} in Magna IR 750 Series II (Nicolet, USA) FTIR spectroscope.

2.4 Mucoadhesion Test

To determine the mucoadhesive strength of the experimental formulations, each formulation to be tested was attached to a natural tooth fixed in plaster of paris base in a tooth model. A little physical balance having two rounded pans (diameter, 2 cm) hang from a rod which was impartial with a fulcrum on a stand was used as a customized mucoadhesion test assembly [9-10] Lower end of a circular pan was attached to the formulation, which had not been coated with EC and had been attached to the tooth model described earlier. The above formulation was made wet before attaching to the tooth model with $200\ \mu\text{l}$ of simulated saliva (pH- 6.8, viscosity 0.740 cp at $37 \pm 0.5^\circ\text{C}$) which was 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. Instantaneously subsequent to the accessory weights were positioned on the other pan. Placing of weights was continued till the pan was separated.

2.5 Swelling Index

The formulation were weighed (W_0) and permissible to engorge on a Petridis in imitation saliva, pH 6.8 at $37 \pm 0.5^\circ\text{C}$. At predetermined time intervals (0.25, 0.5, 1h), samples were taken out and excess saliva was removed with filter paper. Then the weight (wet weight) of the formulation was taken and recorded. When the weight became constant (W_t), the weight taken was used for calculating the swelling index (S.I). Swelling index was calculated in terms of water uptake as described earlier [11] and presented as percentage of water uptake. (Table 1A, 1B, 1C).

$$S.I = \frac{(W_t - W_0) \times 100}{W_0}$$

2.6 Scanning Electron Microscopy (SEM)

The morphological characteristics of above formulation (before and after drug release study) were studied using scanning electron microscope (JSM-6700F, JEOL, Tokyo, Japan). Experimental

samples were cut and mounted onto stubs and then platinum was sputtered under vacuum. They were visualized at an acceleration voltage of 5 KV (Results are shown in Figs. 5,6).

2.7 In-vitro Drug Release Study

Drug release study is to know the release pattern of drug from a formulation, the rate and duration of drug release [12]. Drug release study of Lidocaine hydrochloride/ doxycycline hyclate / Lidocaine hydrochloride – doxycycline hyclate formulations was carried out in a modified USP apparatus IV. This is a flow-through apparatus and the drug release occurs from only one side of the formulation, which remains open towards the reservoir containing simulated saliva, pH-6.8 as a dissolution media at $37 \pm 0.5^\circ\text{C}$ [13], with a flushing rate of 0.65 ml/min since this was

reported to be the mean flow rate of saliva [14]. doxycycline hyclate and Lidocaine hydrochloride were assayed spectrophotometrically at 273 nm and 263 nm, respectively, using Cary 50 UV-VIS spectrophotometer (Varian, Palo Alto, USA). Since the absorbance wavelength of doxycycline hyclate and Lidocaine are comparable, using simultaneous determination equation method [15] the overlain spectra of both the drugs were determined.

The λ max of doxycycline hyclate and Lidocaine hydrochloride are 273 nm and 263 nm, respectively. Both the drugs obeyed linearity at the concentration of 10-100 micro g/ml and the correlation coefficient (R²) was less than 1 in both the cases (for Lidocaine hydrochloride it was 0.9975 and for doxycycline hydrate it was 0.9994). The calculated molar absorptivities

Table 1A. Swelling index Drug + Polymer (D+P)

Time	S.I.	W0	Wn
11:33 PM		0.404 mg	
12:03 PM	22.524	0.404 mg	0.495 W1
12:33 PM	33.168	0.404 mg	0.538 W2
01:33 PM	39.851	0.404 mg	0.565 W3
02:33 PM	56.93	0.404 mg	0.645 W4
03:33 PM	59.653	0.404 mg	0.657 W5
04:33 PM	69.554	0.404 mg	0.685 W6
05:33 PM	71.028	0.404 mg	0.692 W7

Table 1B. Swelling index Anesthetic + Polymer (A+P)

Time	S.I.	W0	Wn
11:33 PM		0.679 mg	
12:03 PM	29.896	0.679 mg	0.882 W1
12:33 PM	37.555	0.679 mg	0.934 W2
01:33 PM	43.74	0.679 mg	0.976 W3
02:33 PM	57.584	0.679mg	1.076 W4
03:33 PM	64.359	0.679 mg	1.116 W5
04:33 PM	69.661	0.679 mg	1.152 W6
05:33 PM	70.25	0.679 mg	1.156 W7

Table 1C. Swelling index Drug + Anesthetic +Polymer (D+A+P)

Time	S.I.	W0	Wn
11:33 PM		0.428 mg	
12:03 PM	40.654	0.428 mg	0.602 W1
12:33 PM	73.598	0.428 mg	0.743W2
01:33 PM	116.941	0.428 mg	0.925 W3
02:33 PM	159.112	0.428 mg	1.109 W4
03:33 PM	188.551	0.428 mg	1.235 W5
04:33 PM	229.205	0.428 mg	1.409 W6
05:33 PM	243.457	0.428 mg	1.470 W7

(E 1%, 1 cm) of Lidocaine hydrochloride were 270.8 M⁻¹ cm⁻¹ and 433.28 M⁻¹cm⁻¹ at 273 and 263 nm, respectively and for Amoxicillin the standards were 1048.62 M⁻¹cm⁻¹ and 796.95 M⁻¹ cm⁻¹ at 273 with 263 nm, correspondingly. The values of recovery of 1:1 mixture of Lidocaine hydrochloride and doxycycline hydrate from a binary mixture were 99.68% and 99.76%, respectively.

2.7.1 Antimicrobial activity of drug

Media used for Bacterial growth – NAM (Nutrient Agar Media)

Bacterial strain – *Staphylococcus aureus*

3. RESULTS AND DISCUSSION

3.1 Development of Formulation

The present study was intended to develop a cylindrical soft solid dental mold containing doxycycline hyclate and Lidocaine hydrochloride so that the drugs might release from the formulation for a prolonged period and provide local action upon its application on an affected tooth. Subsequent to a showing with numerous combinations of different polymers and evaluating the dissimilar physico-chemical parameters and *in vitro* drug release, the most excellent polymeric composition achieved has been reported in this research work. The formulation being reported here was formulated with Carbopol 934, Ethyl cellulose, Gum tragacanth, Hydroxy propyl cellulose, PEG 400 at a ratio of 1:1:0.5:0.5 containing doxycycline hyclate / Lidocaine hydrochloride/ doxycycline hyclate Lidocaine hydrochloride. The drug-polymer ratio by weight was taken 1:10 for each of the formulations, containing doxycycline

hyclate and Lidocaine hydrochloride, respectively. For the formulations containing both the drugs, doxycycline hydrate: Lidocaine hydrochloride: polymer mixture was in the ratio of 0.5: 0.5:10. Drug-excipient communication is a most significant pre-formulation study to extend a new formulation. Among the various methodologies available to understand the drug excipient interaction, common approaches are FTIR spectroscopy, DSC, IR spectra etc [16].

3.2 FTIR Study

FTIR spectroscopy shows the interaction between the molecules at the level of functional groups [17]. Here drug-excipient interaction was studied using FTIR-spectroscopy. Fig. (1A-1G) show the IR spectra of a mixture of polymers- Carbopol 934, Ethyl cellulose, Gum tragacanth, Hydroxy propyl cellulose, PEG 400 in a ratio of 1:1:0.5:0.5, respectively; a mixture of Lidocaine hydrochloride with those polymeric combinations; and a mixture of doxycycline hyclate with those polymers at the mentioned ratio, respectively.

3.3 Swelling Index Study

The swelling outcomes were articulated in terms of proportion water uptake at 37°C. Fig. (2A, 2B) shows the swelling behavior of Formulation. The water uptake by the prepared formulation can be ranked as follows: doxycycline hyclate formulation < doxycycline hyclate -Lidocaine hydrochloride formulation < Lidocaine hydrochloride formulation. The results show that the percentage water uptake of the prepared formulations ranged from 331% to 414%. The highest percentage of hydration was obtained for Lidocaine

Zone of Inhibition:

Table 2A. Blank (Zone diameter mm)

Placebo	50 (µl)
1	0
2	0
3	0
Mean±SD	0±0

Table 2B. Standard 1 (Zone diameter mm)

Doxycycline	100ug/ml
1	34.00
2	36.00
3	30.70
Mean ± SD	33.566±2.676

Table 2C. Standard 2 (Zone diameter mm)

Lidocaine	100 ug/ml
1	29.00
2	32.40
3	28.60
Mean \pm SD	30.00 \pm 2.088

Hydrochloride formulation. The decreased swelling ability of doxycycline hyclate formulation may be because of less water affinity of V than Lidocaine hydrochloride. Weight loss of 3.5%-3.6% was observed in 7 h after immersion in simulated saliva. That may be due to the loss of drugs from the formulation. The average mucoadhesive strengths (measured in g) were found to be 60.5, 56.25, 58.75 and 59.8 g for the formulation without drug, with Lidocaine hydrochloride, with doxycycline hyclate and with both the drugs, respectively. In case of the mucoadhesive polymers desired strength was reported to be about 30 g [18]. More strength seems to be required for attaching the formulation to a tooth. Our findings show that the values were almost double. Nevertheless, in our study, mucoadhesive potency was established to be excellent enough to remain the formulations attached to the tooth and over again, the tackiness was such that it was simple to take out the formulation from the tooth with a slight attempt. Release of Lidocaine hydrochloride and doxycycline hyclate from the prepared formulations was considered in simulated saliva (pH-6.8). The release of doxycycline hyclate and Lidocaine hydrochloride from the formulation containing Lidocaine hydrochloride alone and doxycycline hyclate alone, respectively.

3.4 *In-vitro* Drug Release Study

The release of doxycycline hydrate and Lidocaine hydrochloride from above formulation containing both the drugs together. Lidocaine hydrochloride release from the formulations showed to follow apparent zero order kinetics at the beginning, because of the faster diffusion of the drugs from the surface, drug release provided a first-order kinetic pattern. However, with the length of time the release pattern gradually tended to be concentration independent zero order type of release. Swelling of the polymers with the duration might vary the tortuosity of the polymeric network pathways which gradually shifted the drug release pattern from first order to zero order kinetics [19]. Likewise, doxycycline hyclate release was found

to obey apparent zero order kinetics, too. At the beginning, the drug release obeyed first-order kinetics which gradually changed towards zero-order kinetics. Interestingly cumulative amounts of release of Lidocaine hydrochloride were found to be much higher in values than those of doxycycline hyclate. This could be because of the higher aqueous solubility of Lidocaine hydrochloride as compared to doxycycline hyclate. (Fig. 3A, 3B).

In the current day circumstances, it has been reported that the Dental diseases are a foremost health predicament in all parts of the globe, ordinary in all age groups, races and genders. The proportion of dental diseases has developed to a large amount in current years. Approximately 70% of inhabitants suffer from dental evils. The inhabitants is affected by most important of oral diseases like periodontal infections, dental caries; it has been pragmatic that deprived oral hygiene augmented risk of cardiovascular diseases in patients anguish from periodontitis also deprived maternal oral hygiene showed babies with low birth mass. According to estimates by Government of India-World Health Organization joint programme, regarding 50% of school kids are anguish from Dental caries and more than 90% of adults are having periodontal diseases. As well, the extensive array of surroundings renders the mouth a microbial ecstasy; contribution preferred accommodation on the cheek, back of the tongue and in the humid, oxygen underprivileged region connecting the tooth facade and the contiguous periodontal tissues. A substantial number of products are now suggested for use in the oral cavity. The towering prevalence of caries and periodontal disease is general particularly in the children and mature correspondingly. A number of products have been accessible for the management of dental disorders except small effort has been ended on the continued release drug delivery products to the oral-dental cavity. In due course, it is believed to generate an extent for receiving novel reports on newer formulation previously recognized beneath medication for dental diseases.

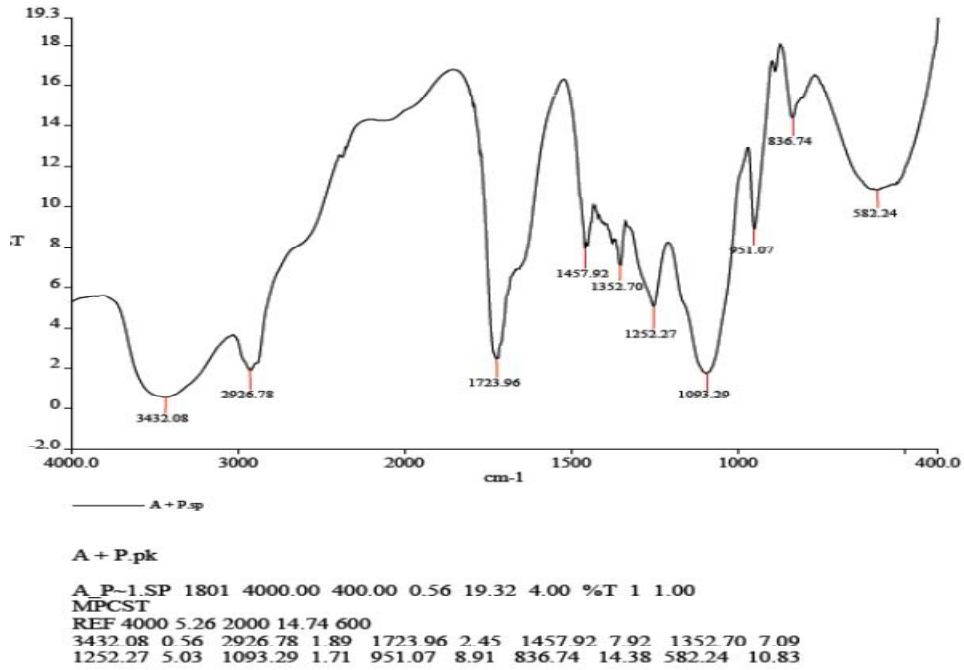


Fig. 1(A). FTIR spectra of A+P

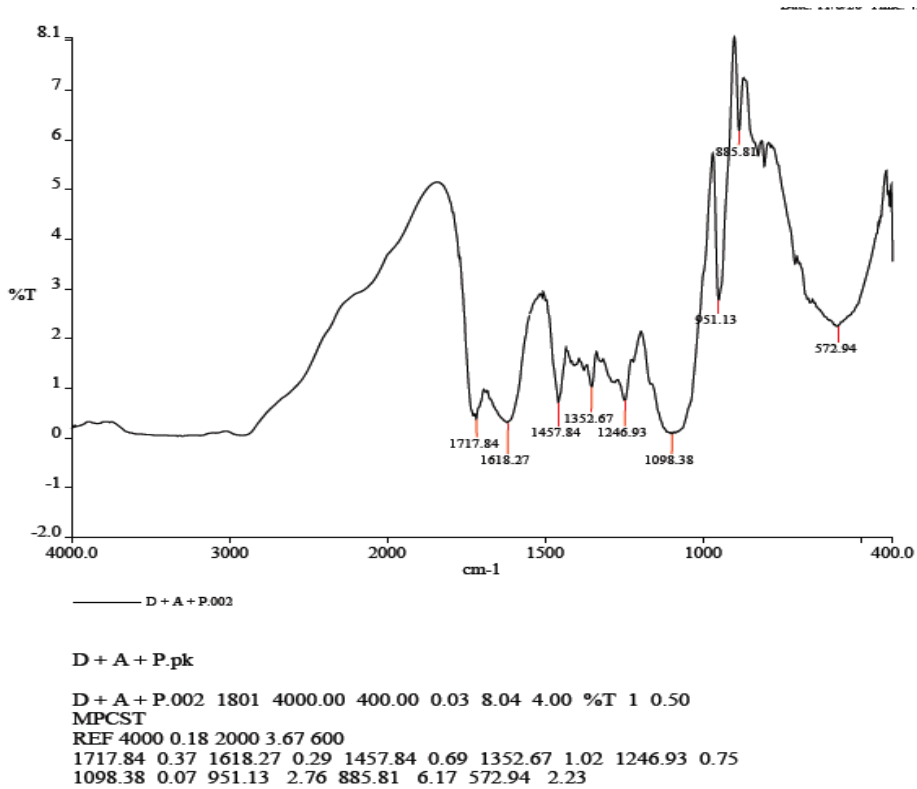


Fig. 1(B). FTIR spectra of D+A+P

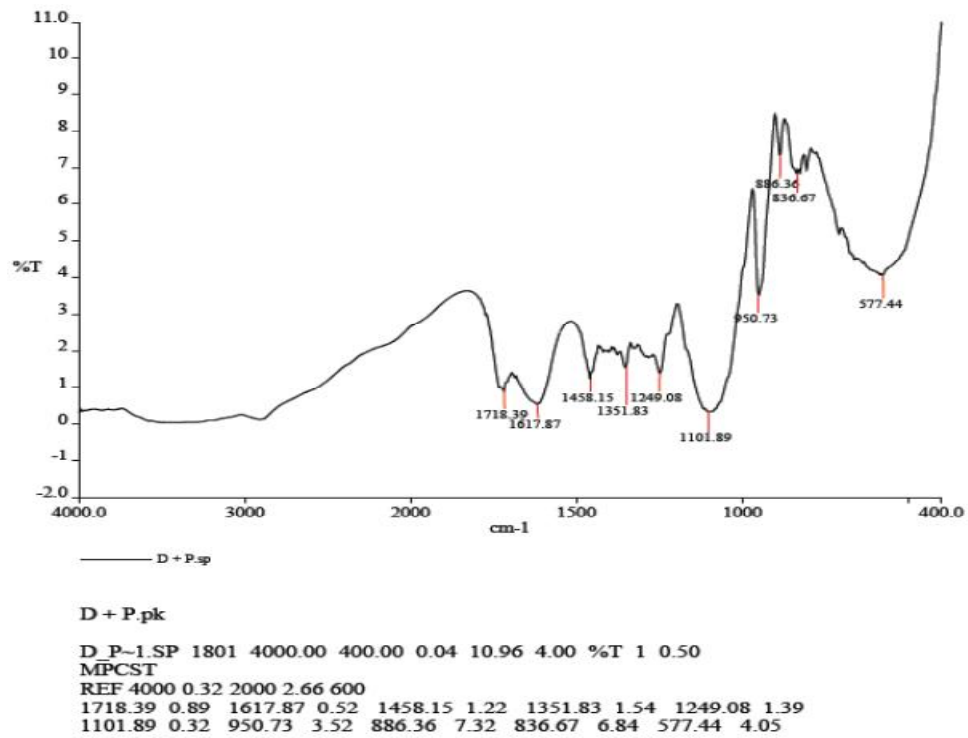


Fig.1(C). FTIR spectra of D+P

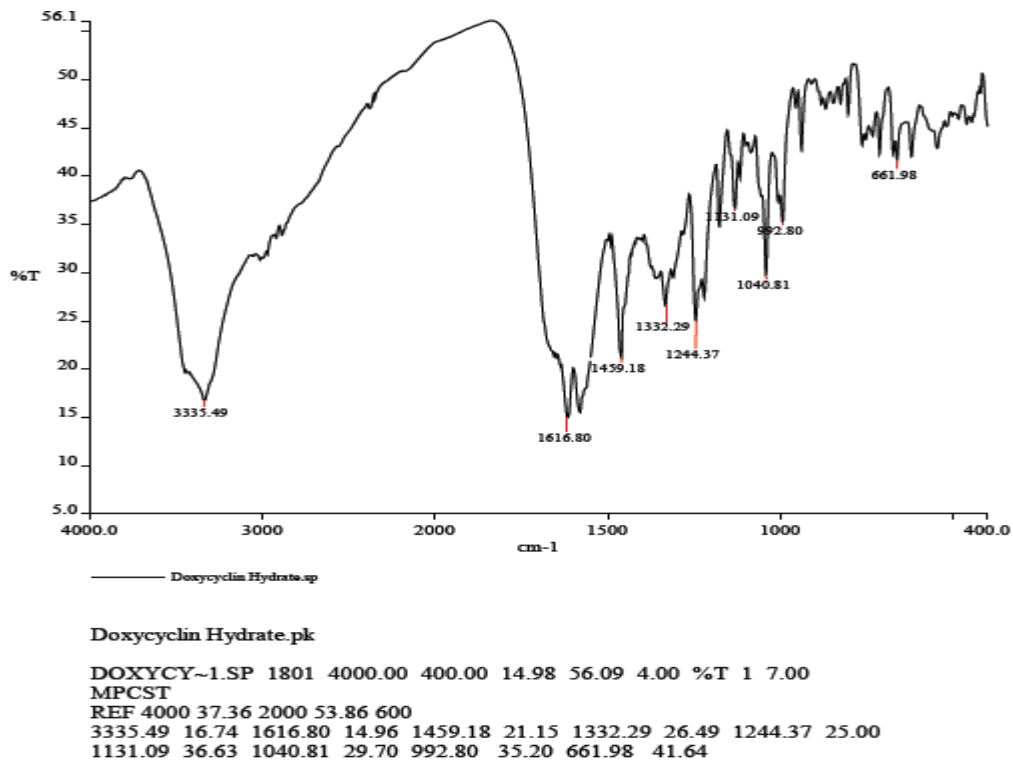
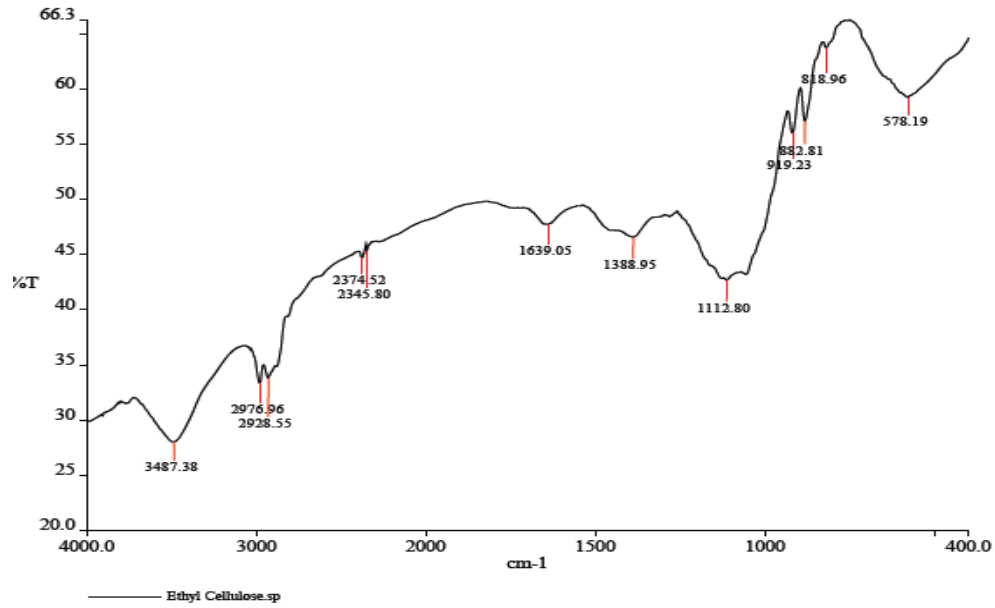
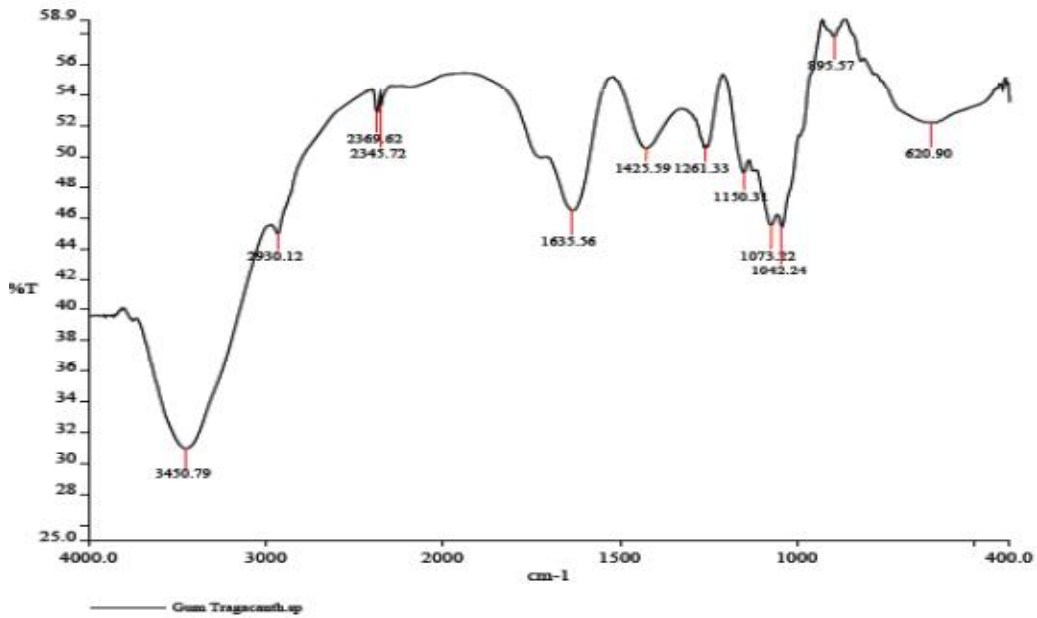


Fig. 1(D). FTIR spectra of doxycycline hyclate



Ethyl Cellulose.pk

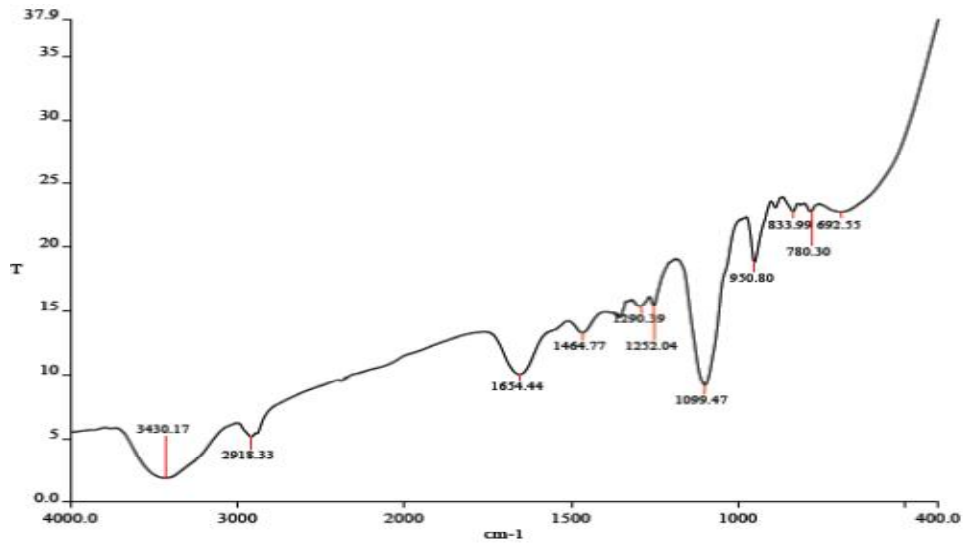
ETHYLC~1.SP 1801 4000.00 400.00 28.00 66.28 4.00 %T 1 0.50
MPCST
REF 4000 29.86 2000 48.09 600
3487.38 28.00 2976.96 33.32 2928.55 33.79 2374.52 44.69 2345.80 45.29
1639.05 47.72 1388.95 46.57 1112.80 42.67 919.23 55.99 882.81 57.09



Gum Tragacanth.pk

GUMTRA~1.SP 1801 4000.00 400.00 30.95 58.92 4.00 %T 1 0.50
MPCST
REF 4000 39.61 2000 55.31 600
3450.79 30.95 2930.12 44.97 2369.62 52.85 2345.72 53.29 1635.56 46.46
1425.59 50.53 1261.33 50.57 1150.31 48.95 1073.22 45.54 1042.24 45.39

Fig. 1(E). FTIR spectra of Gum tragacanth

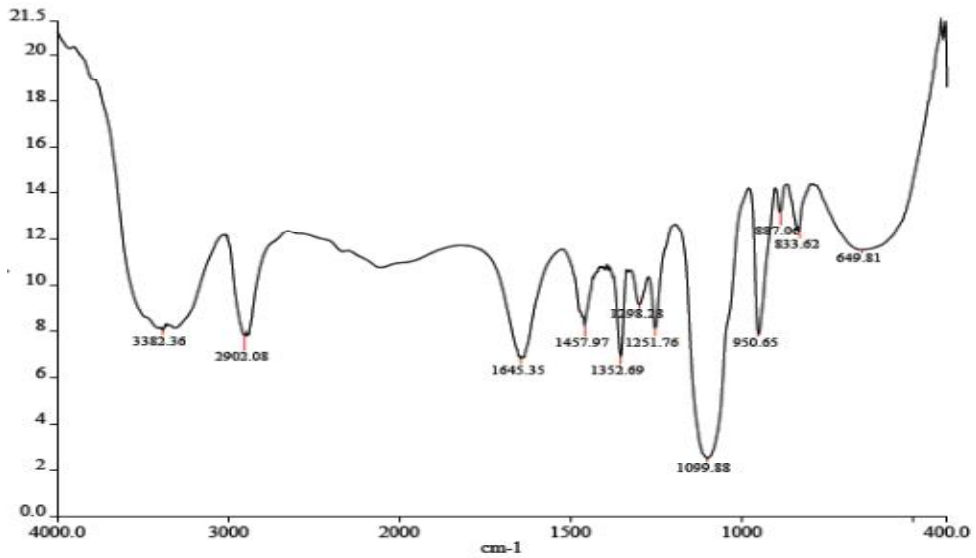


Lidocaine.001

Lidocaine.pk

Lidocaine.001 1801 4000.00 400.00 1.88 37.91 4.00 %T 1 0.50
 MPCST
 REF 4000 5.49 2000 11.49 600
 3430.17 1.88 2918.33 5.11 1654.44 10.00 1464.77 13.30 1290.39 15.38
 1252.04 15.45 1099.47 9.14 950.80 18.81 833.99 22.83 780.30 22.84

Fig.1(F). FTIR spectra of lidocaine



PEG 400.sp

PEG 400.pk

PEG400-3.SP 1801 4000.00 400.00 2.49 21.45 4.00 %T 1 1.00
 MPCST
 REF 4000 20.99 2000 10.94 600
 3382.36 8.03 2902.08 7.79 1645.35 6.81 1457.97 8.21 1352.69 6.92
 1298.28 9.16 1251.76 8.10 1099.88 2.49 950.65 7.85 887.06 13.14

Fig.1(G). FTIR spectra of PEG 400

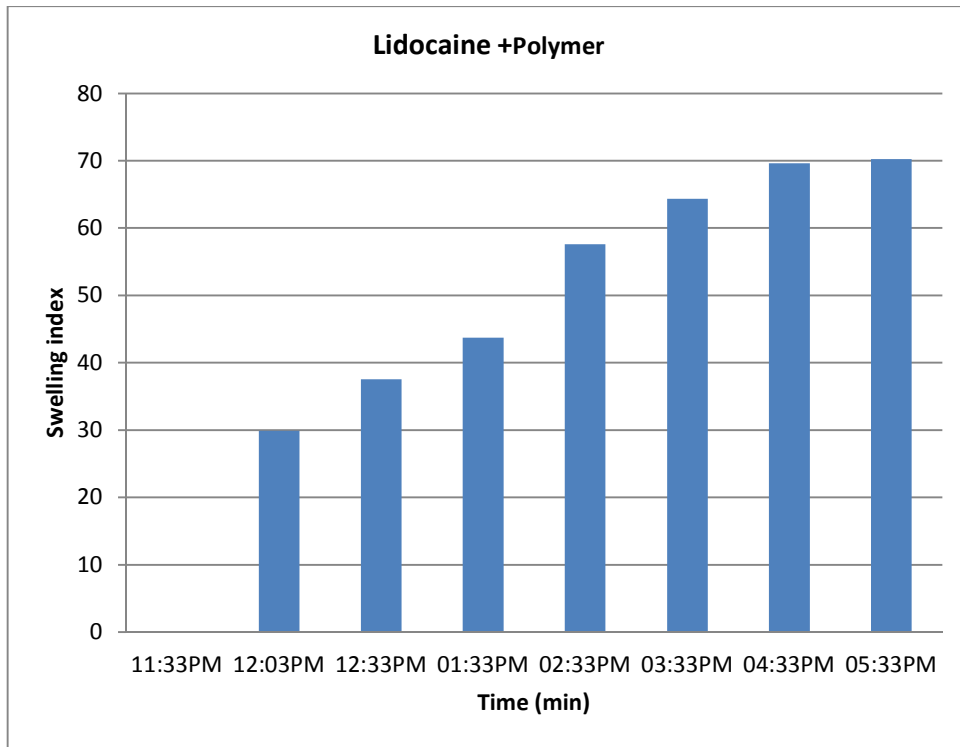


Fig. 2A. Swelling index of L+P

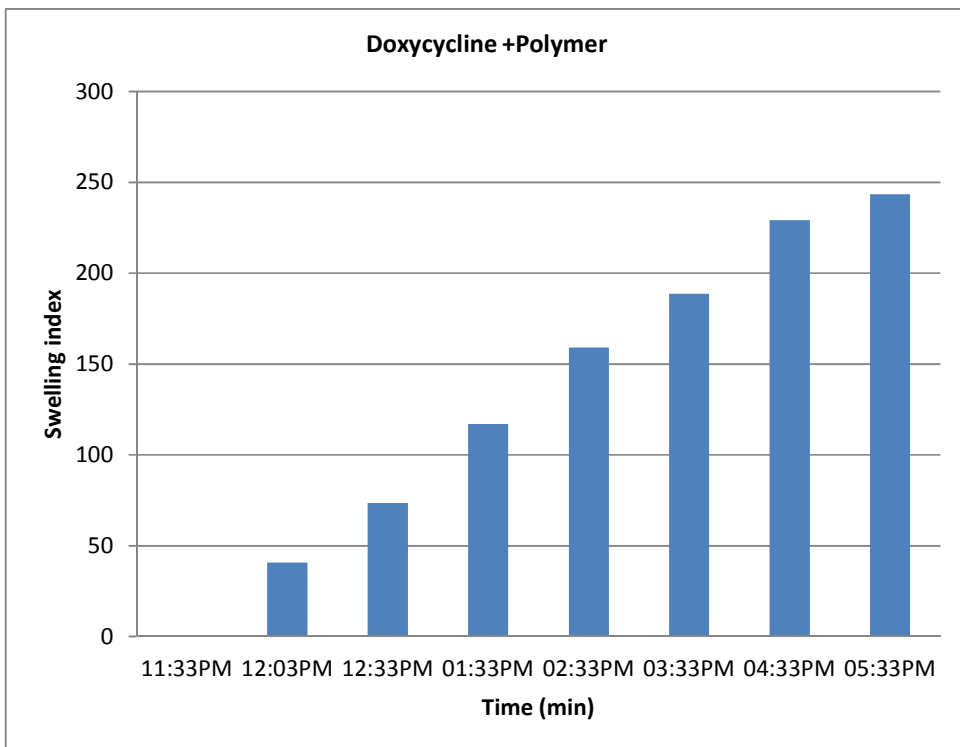


Fig. 2B. Swelling index of D+P

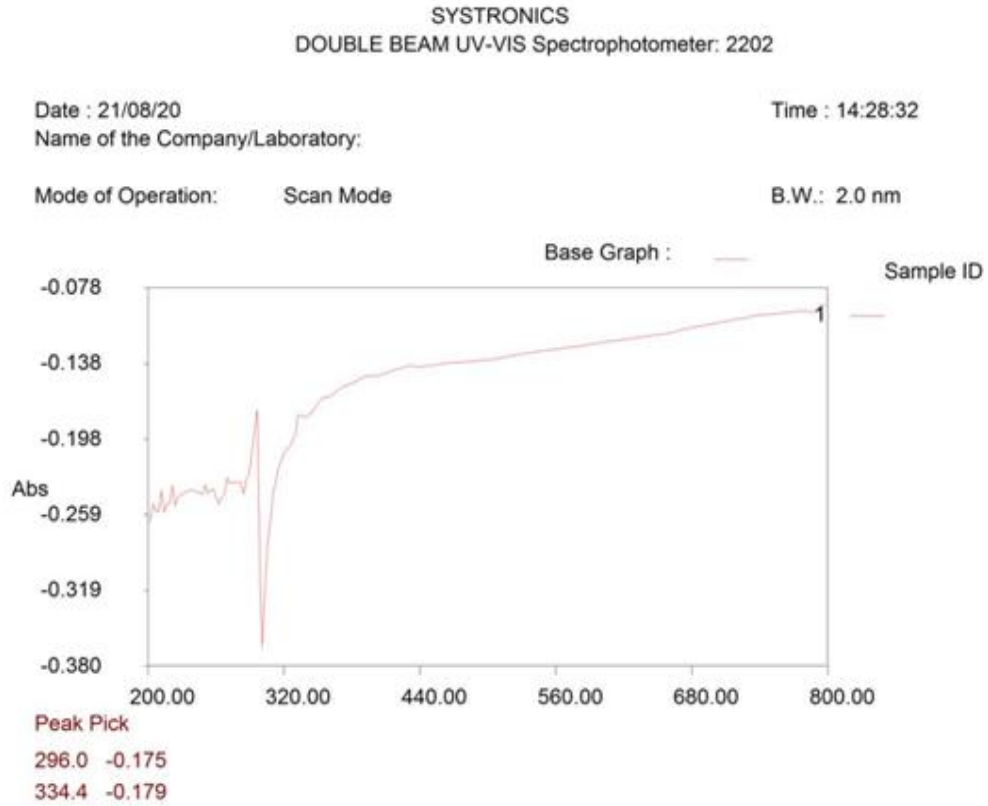


Fig. 3A. λ Max of lidocaine HCL

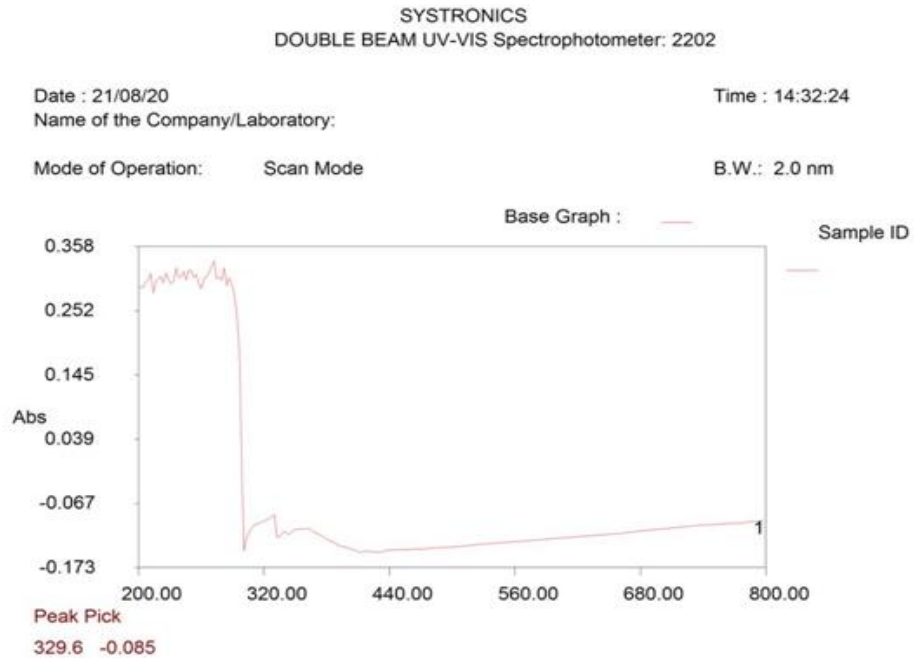


Fig. 3B. λ Max of doxycycline hyclate

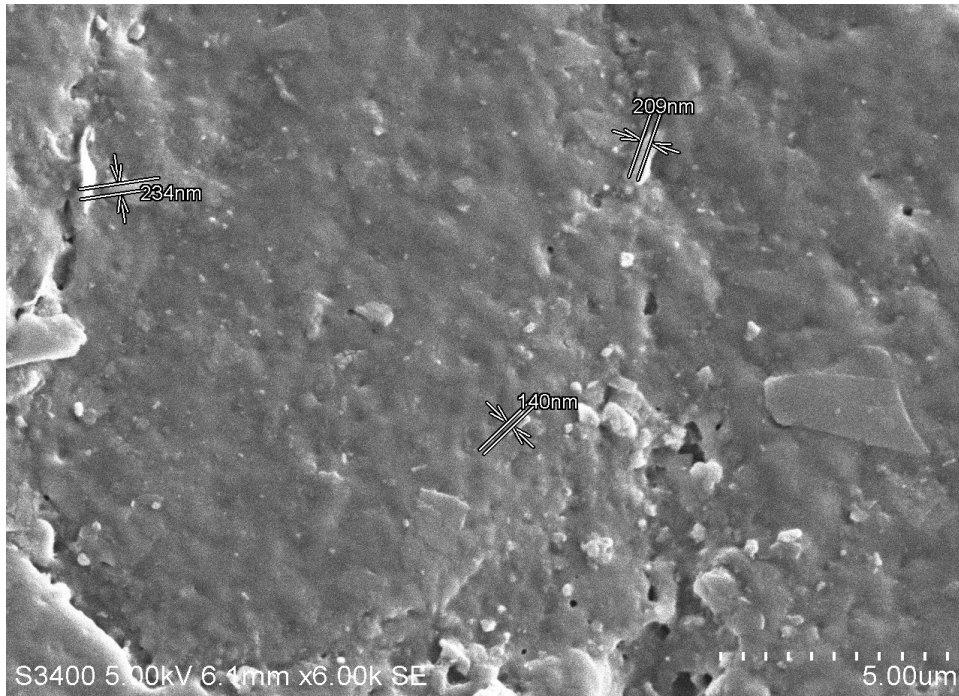


Fig. 4. Scanning electron microscopy (Anesthesia + Polymer)

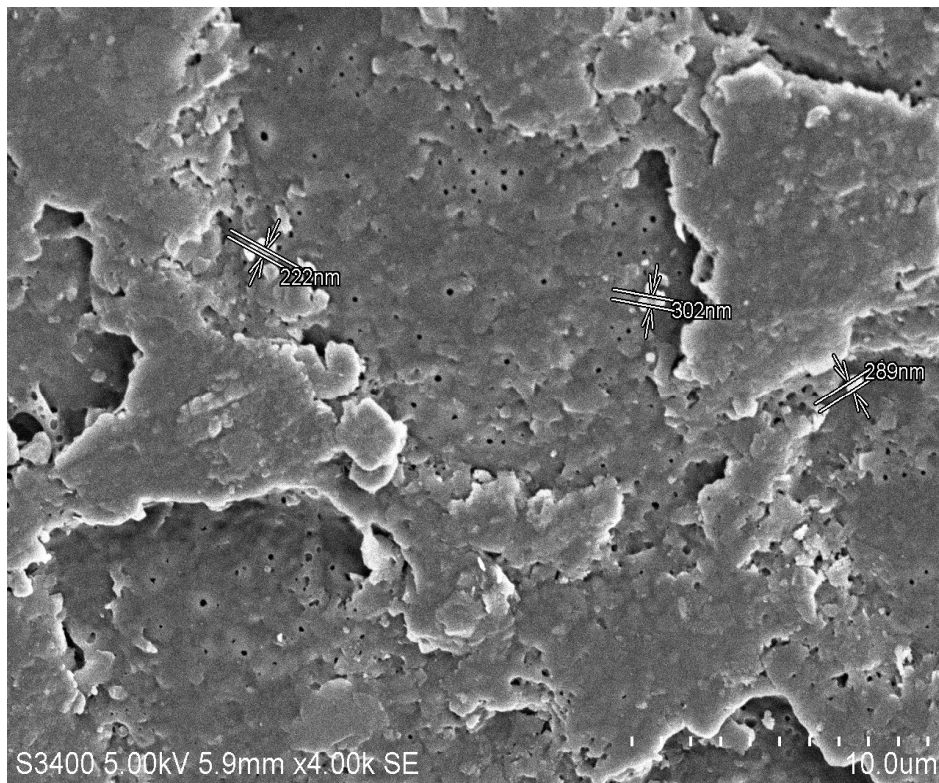


Fig. 5. Scanning electron microscopy (Drug + Anesthesia + Polymer)

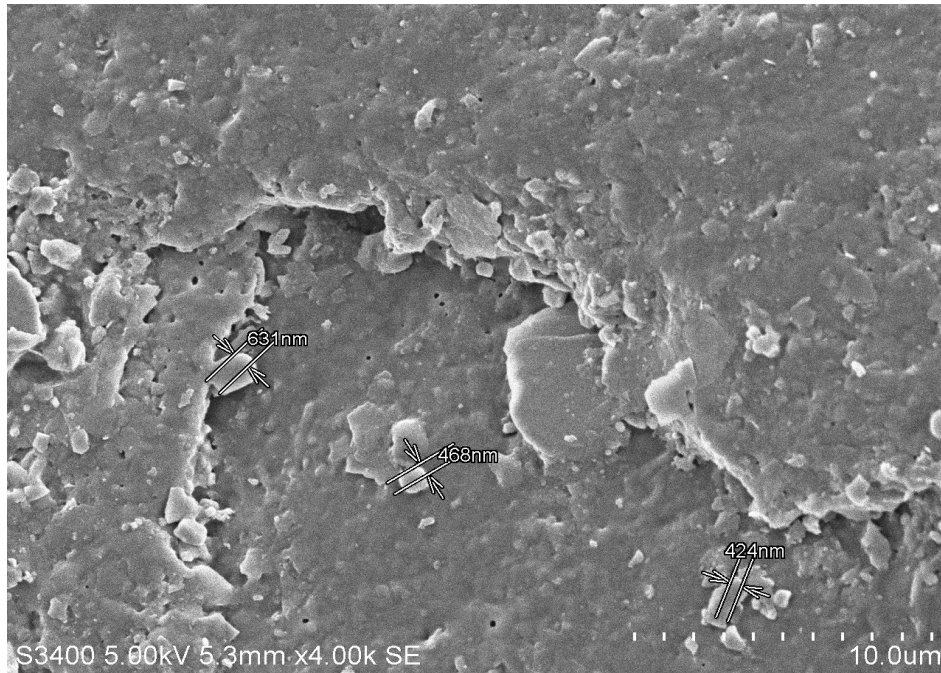


Fig. 6. Scanning electron microscopy (Drug + Polymer)

Nevertheless, the learning gives a methodical scientific come up to to the newer formulation for periodontal disarray, so considerably needed the order of the day this may also accomplish an development of formulation which can act alongside periodontal disorders (ailments).

4. CONCLUSION

The above formulation is a novel form of delivering drugs for a extended interlude by applying it on an exaggerated tooth for local action. The formulation may provide more patient compliance over the conventional dosage forms, since it is an easy and sustaining solution for dental patients against intolerable pain and patient can apply it by himself or herself without anybody's assistance to get a quick relief.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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