ORIGINAL ARTICLE

Design and *In Vitro* Evaluation of Curcumin Dental Films for the Treatment of Periodontitis

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Abstract

Aim: The objective of this research was to design and evaluate dental film containing curcumin for the topical treatment of periodontal diseases. **Materials and Methods:** Curcumin, hydrophobic polyphenolic compounds derived from the rhizomes of *Curcuma longa*, shows wide spectrum of antibacterial, anti-inflammatory, and antioxidant properties activity against a number of periodontal pathogens and hence selected for site-specific delivery in the treatment of periodontitis. Dental films were prepared by solvent-casting technique using polymers such as ethyl cellulose, hydroxypropyl methylcellulose K4M, and Eudragit RL 100 with polyethylene glycol 400 as plasticizer, and prepared films (F1-F7) were evaluated for various physicochemical parameters such as weight variation, surface pH, folding endurance, moisture loss, moisture absorption, drug content, *in vitro* drug release, *in vitro* antibacterial, and stability studies. No chemical interaction between drug and the polymer was seen as confirmed by Fourier transforms infrared spectroscopy studies. **Results and Discussions:** *In vitro* dissolution studies showed an initial burst release to achieve immediate therapeutic level of drug in periodontal pocket, followed by a progressive fall and extended release of the drug with more uniformity for prolonged period of time. Formulation F7 released 98.25% of drug at the end of 168 h was considered as the optimized formulation. Release kinetics of curcumin from film followed the Higuchi diffusion model. Stability studies did not show any significant changes with respect to content and appearance. **Conclusion:** Good physicochemical properties were shown by the films. The study suggests that curcumin dental film is a potential drug delivery device for the topical treatment of periodontal diseases.

Key words: Controlled release, curcumin, *in vitro* release, periodontitis, site-specific delivery

INTRODUCTION

Periodontal disease is one of the world's most prevalent chronic oral diseases affecting more than 50% of Indian community and occurs in all groups, ethnicities, races, genders, and socioeconomic levels.[1,2] Periodontal disease is a localized inflammatory response due to microbial infection of a periodontal pocket arising from the accumulation of plaque. This produces an inflammatory response in adjacent tissues, and these diseases may be broadly classified according to the extent of periodontal tissue involvement. The inflammatory response is confined to gingival in gingivitis but extends to deeper tissues in periodontitis. Progression of periodontitis results in loss of tooth support structure, increase periodontal pocket depth, clinical attachment loss, and destruction of alveolar bone.[3] The role of anaerobic bacteria (such as *Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Campylobacter rectus, Prevotella melaninogenica,* and *Actinobacillus actinomycetemcomitans*) in the etiology of

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periodontal diseases has been well established. The bacteria accumulate in the periodontal pocket that develops between the roots of affected teeth and the soft tissues. Conventional methods for the removal of subgingival bacteria include periodic mechanical debridement of plaque from tooth surfaces and repeated topical or systemic administration of antibacterial agents. Disadvantages associated with conventional method of treatment for periodontal disease are superinfection, low or non-compliance, low gingival crevicular fluid levels of antibiotics, toxic systemic side effects, short duration (gels), and high relative cost.[4] The gingival crevicular fluid provides a leaching medium for the release of a drug from the dosage form and for its distribution throughout the periodontal pocket. These features, together with the fact that the periodontal diseases are localized to the immediate environment of the pocket, make the periodontal pocket a natural site for treatment with local sustained-release drug delivery systems. The duration of action is generally short when antibacterial agents are administered in solution, and frequent application is required to maintain effective concentrations in the periodontal pocket. This makes patient compliance critical to ensure optimal clinical efficacy. Due to the shortcomings associated with the above methods of delivery, attention has been focused on the development of prolonged release intra pocket delivery systems such as dental films. As the average depth of a periodontal pocket is between 6 and 8 mm, the therapeutic drug delivery device, therefore, should be small and not expose beyond gingival margin when inserted in the periodontal pocket. Further, it is necessary that a small dosage of the drug in the device should be highly effective as a therapeutic agent. Ideally, these systems should deliver the antibacterial agent for prolonged periods to the affected pocket(s) at levels in excess of the minimum inhibitory concentration for the causative organisms.[5]

Dental films are most widely used form of medicated intra-pocket dental drug delivery device. Films are matrix type delivery systems wherein drugs are distributed throughout the polymer films and drug release through the films occur by diffusion and/or matrix dissolution or erosion. Advantages of dental films over conventional dosages form are ease of insertion, minimum pain on insertion, dimension and shape of the film can be controlled to corresponding to the dimension of the pocket, less storage space, show good retention for at least 5 days, less maintenance of machinery, and minimal or no side effects.[6] A numbers of delivery systems have been investigated for use in periodontal disease.[7-18]

Periodontal treatment aims to cure inflamed tissue, reduces the number of pathogenic bacteria, and eliminates the diseased pockets. Recent advances in the field of dentistry have promoted the use of various herbal and natural products for the treatment of various oral diseases and conditions.[19-20] There have been numerous reports of the use of curcumin for the treatment of oral diseases.[21-34] Curcumin, a hydrophobic polyphenolic compounds derived from the rhizomes of *Curcuma longa,* has a wide spectrum of biological and pharmacological activities. The antibacterial, anti-inflammatory, and antioxidant properties of curcumin are desirable assets which might validate its use in the treatment of periodontitis. The present study was aimed to formulate periodontal film containing curcumin with rate controlling polymers which has a prolonged action and shows the antibacterial activity directly at the site of infection without loss of dosage.

MATERIALS AND METHODS

Materials

Curcumin procured from Yarrow Chem Ltd., Mumbai, ethyl cellulose, Eudragit RL 100, hydroxypropyl methylcellulose (HPMC) K4M, and polyethylene glycol 4000 were procured from S.D. Fine Chemicals Pvt., Ltd. Mumbai, India.

Fabrication of dental films by solvent casting method

Periodontal films were prepared by solvent casting technique. Ethyl cellulose, Eudragit RL 100, and HPMC K4M combinations were dissolved alone and also in combination in 10 mL of ethanol using a magnetic stirrer to get different concentrations of polymer solution. Curcumin of required quantity and plasticizer were added to the polymer solution with continuous stirring. After complete mixing, the solution was poured into a clean Petri dish placed on a horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel plugged with cotton. The stem kept at room temperature for 24 h. After complete evaporation of solvent, cast films were obtained, which were then wrapped in an aluminum foil and stored in a desiccator. Table 1 shows the composition of different dental films.

Evaluation of dental films

Thickness uniformity of the films[2]

The thickness of each film (size of 1 cm^2) was measured using screw gauge at different positions of the film, and the average thickness was calculated.

Uniformity of weight of the films[3]

Weight variation test was carried out by weighing 10 patches cut from different places of same formulation, and their individual weights were determined using the digital balance. The mean value was calculated. The standard deviations of weight variation were computed from the mean value.

Surface pH

Periodontal films were left to swell for 1 h on the surface of agar plate, prepared by dissolving 2% (w/v) agar in warmed distilled water under stirring and then pouring the solution into the Petri dish for gelling or to solidify at room

Table 1: Composition of dental film

Ingredients	F1	F2	F3	F4	F5	F6	F7
Curcumin (mg)	100	100	100	100	100	100	100
HPMC K4M (mg)	-	1000	-	250	750	-	-
Ethyl cellulose (mg)	1000	-	-		250	250	750
Eudragit RL 100 (mg)	-	-	1000	750	-	750	250
Ethanol (mL)	10	10	10	10	10	10	10
PEG (mL)	1	1	1	1	1	1	1

HPMC K4M: Hydroxypropyl methylcellulose K4M, PEG: Polyethylene glycol

temperature. The surface pH was measured by means of pH paper on the surface of the swollen film.[2]

Percentage moisture loss[4]

The percentage moisture loss was determined by keeping the periodontal films in desiccators. The moisture content value was calculated by the equation:

$$\% \text{ moisture loss} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

Percentage moisture absorption[14]

The percentage moisture absorption test was carried out to check of known size was weighed and placed in a desiccator containing 100 mL of saturated solution of aluminum chloride, and 79.5% RH was maintained. After 3 days, the inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula:

$$\% \text{ moisture absorption} = \frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100$$

Folding endurance[2]

The folding endurance of the films was determined by repeatedly folding one film at the sample place till it broke or folded up to 200 times, which is considered satisfactory to reveal good film properties. The film was folded number of times at the same place without breaking gave the value of folding endurance.

Tensile strength of the films[4]

Tensile strength of the films was determined by universal strength testing machine. The sensitivity of the machine is 1 g. It consists of two load cell grips. The lower one is fixed, and upper one is movable. The test film of specific size (4 cm × 1 cm) was fixed between these cell grips, and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms.

Swelling index (SI)[16]

SI of the films was conducted in simulated salivary fluid of pH 6.6. The film sample (1 cm^2) was weighed and placed in a pre-weighed stainless steel wire sieve of approximately 800 µm mesh. The mesh containing the film sample was then submerged into 15 mL of the simulated salivary fluid contained in a porcelain dish. At definite time intervals, the stainless steel mesh was removed, excess moisture removed carefully by wiping with absorbent tissue and reweighed. Increase in weight of the film was determined at each time interval until a constant weight was observed. The degree of swelling was calculated using the formula:

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

Where S.I is the Swelling index, W_t is the weight of film at time t, and W_0 is the weight of the film at time 0.

Drug content uniformity of films[4]

Films (size of 1 cm^2) were dissolved in 10 mL of ethanol in volumetric flasks. The volumetric flask was kept aside till the film is completely dissolved. From this solution, 1 mL solution was pipette out, suitable diluted, and measured the absorbance at 421 nm by ultraviolet (UV)-visible spectroscopy.

In vitro drug release[4]

Since the pH of the gingival fluid lies between 6.5 and 6.8, phosphate buffer pH 6.6 was used as simulated gingival fluid and the film remains immobile in the periodontal pocket, a static dissolution method was adopted for the dissolution studies. Sets of six films of known weight and dimension were placed separately into small sealed vials containing 2 mL of phosphate buffer. The vials were kept at 37°C ± 0.5°C for 24 h; the 1 mL buffer was then drained off and replaced with a fresh 1 mL of buffer. The concentration of the drug was determined using UV-visible double beam spectrophotometer (UV-1700 Shimadzu, Kyoto, Japan), and this procedure was continued for 7 consecutive days.

In vitro antibacterial activity[4]

The films (size of 1 cm^2) were taken for the study; 60 mL of nutrient agar media was prepared and sterilized at 15 lb. pressure for 20 min in an autoclave. Under aseptic condition, 20 mL of nutrient agar media was transferred into sterile Petri plates. After solidification, 0.1 mL of microbial suspension

of known concentration was spread on media and incubated at 37°C for 168 h. Then, the zone of inhibition was measured using "Hi Antibiotic Zone Scale" (PW096, HiMedia Laboratories Pvt., Ltd., Mumbai).

Fourier transforms infrared spectroscopy (FTIR)[35]

FTIR spectral studies were carried out for the pure drug and the excipients to check the compatibility using Shimadzu 8400 S, Tokyo, Japan. The spectrum was recorded in the range of 4000-400/cm. Interaction between the components, if any, was indicated by either producing additional peaks or absence of characteristic peak corresponding to drug and carrier.

Differential scanning calorimetry (DSC) of pure curcumin

DSC was employed to study any potential change in curcumin that the drug may have experienced during its processing into periodontal films. DSC thermogram was obtained using thermal analyzer instruments (DSC- 60, Shimadzu, Japan).

Accelerated stability studies

Optimized formulations were subjected to short-term stability testing. Films wrapped in aluminum foil and kept in a humidity chamber maintained at 40°C ± 2°C/75% ± 5% RH for 3 months as per the International Conference on Harmonization (ICH) guidelines. Changes in the physical appearance, surface pH, folding endurance, and drug content of the stored films were investigated during the period and after 3 months.

RESULTS AND DISCUSSIONS

The physicochemical properties of curcumin periodontal films are presented in Tables 2a and b.

Thickness uniformity of the films

The thickness of each film was measured at 10 different points, and the average thickness with S.D was calculated. The data of films thickness indicate that there was no much difference in the thickness among the formulations. Thickness of film was found in the range of 0.39 ± 0.0069-0.42 ± 0041 mm (n = 6), and the results are given in Table 2a.

Uniformity of weight of the films

Drug loaded films (1 cm × 1 cm) were tested for uniformity of weight, and the results are given in Table 2a. Films of all the patches were found to be uniform weight, ranging from 10.13 ± 0.112 to 11.12 ± 0.462. This can be attributed to proper mixing of drug and polymers.

Table 2a: Physicochemical evaluation data of curcumin dental film

Periodontal film code	Mean±SD (n=6)			
	Thickness (mm)	Weight uniformity (mg)	Percentage moisture loss	Percentage moisture absorption
F1	0.42±0.0041	10.13±0.112	6.88±0.0552	8.97±0.0498
F2	0.40±0.0082	11.12±0.462	13.85±0.550	10.22±0.0213
F3	0.41±0.0013	11.07±0.275	10.88±0.031	10.97±0.0018
F4	0.39±0.0069	10.94±0.128	9.86±0.0597	11.87±0.0621
F5	0.40±0.0013	10.82±0.100	10.30±0.042	12.35±0.0420
F6	0.42±0.0011	10.19±0.210	12.23±0.064	12.62±0.0530
F7	0.40±0.0024	10.73±0.022	9.22±0.0361	13.99±0.650

SD: Standard deviation

Table 2b: Physicochemical evaluation data of curcumin dental film

Periodontal film code	Folding endurance (n=6)	Surface pH	Tensile strength (kg) (n=6)	Swelling index	Drug content (n=6)
F1	89±1.21	6.6	2.26±0.025	15.6	88.96±0.0321
F2	95±3.23	7	2.46±0.059	14.9	91.95±0.0042
F3	102±7.32	6.5	2.62±0.090	14.7	92.43±0.0210
F4	118±2.21	6.6	3.12±0.094	15.2	94.46±0.0312
F5	124±9.21	6.8	2.79±0.070	14.8	95.21±0.0219
F6	115±7.11	6.9	3.05±0.032	15.5	96.17±0.0162
F7	125±3.03	6.7	2.68±0.082	15.3	98.22±0.0165

Surface pH

Surface pH of all the formulations was found to be in between 6.5 and 7, and hence, no periodontal pocket irritation is expected.

Percentage moisture loss

Moisture loss studies were conducted on all the formulations and reported in Table 2a. For all the formulations, the percentage moisture loss varied between 6.88 ± 0.0552 and 13.85 ± 0.550. Formulation F2 showed maximum amount of moisture loss due to more concentration of HPMC K4M undergoing moisture loss in dry condition, and formulation F1 showed minimum percentage moisture loss because of hydrophobic ethyl cellulose.

Percentage moisture absorption

For all the formulations, the percentage moisture loss varied between 8.97 ± 0.0498 and 12.62 ± 0.0530, and the results are given in Table 2a. Formulation F7 showed highest percentage moisture absorption.

Folding endurance value

Folding endurance of the films was >100 times indicated that the formulation have good film properties, folding endurance of the films was >100 times indicated that the formulation have good film properties except film F1 (89±1.21).

Tensile strength of the films

The order of tensile strength of the films is F4 > F6 > F5 > F7 > F3 > F2 > F1. This revealed that formulation prepared with HPMC K4M and Eudragit RL 100 exhibited higher tensile strength, whereas formulation with only ethyl cellulose showed lower tensile strength.

Swelling index

All the prepared formulations (F1-F7) of curcumin dental film were evaluated for SI. The SI was found maximum for formulation F1 (15.6) and minimum for formulation F5 (14.8).

Drug content uniformity

The results of content uniformity indicated that the drug was uniformly dispersed. The percentage drug content in various formulations ranged from 88.96 to 98.22% given in Table 2b.

In vitro release studies

In vitro release studies performed using phosphate buffer pH 6.6 showed an initial burst release [Figure 1], which is expected to kill most of the periodontal organisms, followed by controlled release, sufficient to inhibit the growth of the microorganisms. Periodontal film made of ethyl cellulose and Eudragit RL 100 (F7) is better than others because the extent of release was maintained for about 7 days. All the formulations showed initial burst release and controlled release in later phases, as shown in Figure 1. The percentage drug release from film F1, F2, F3, F4, F5, F6, and F7 was found to be 79.2, 83.63, 85.84, 88.82, 90.9, 82.89, and 98.25% of drug was released at the end of 7th day, respectively. *In vitro* release studies showed that the drug release was more sustained in case of film F7 followed by F5 > F4 > F3 > F2 > F6 > F1. The regression values of films F1-F7 are higher with first order, and therefore, the release kinetics followed first order from all films. The release kinetics of the optimized formulation (F7) was shown in Figure 2.

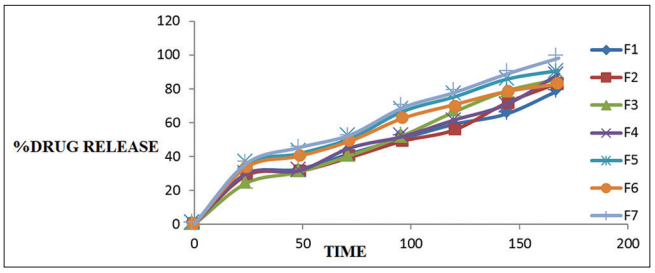

Figure 1: *In vitro* cumulative percentage drug release plots of F1-F7

Hixson Crowell cube root law and Higuchi's models were applied to test the release mechanism. The R^2 values are higher for Higuchi's model compared to Hixson Crowell cube root law for all the films [Table 3]. Hence, curcumin release from all the films followed diffusion rate controlled mechanism.

In vitro antibacterial activity

In vitro antibacterial activity was performed as mentioned in methodology on *Staphylococcus aureus*. The zone of inhibition of the prepared formulations was found to be effectively high in F7 film after 168 h. The results of antibacterial activity were shown in Table 4. The study indicates that the formulated polymeric films containing curcumin retained their antibacterial activity. Among all the formulated polymeric films, the film F7 having a high zone of inhibition compare to other films.

FTIR

FTIR spectra of curcumin alone and its combination with polymers are shown in Figures 3 and 4. FTIR spectra of the pure curcumin showed characteristic bands at 3857.70/cm due to C-OH, 1510.44/cm due to C=O, and 955.62/cm due to C=C functional groups. FTIR spectra of drug-polymer mixture showed characteristic bands at 3825.00/cm due to C-OH,

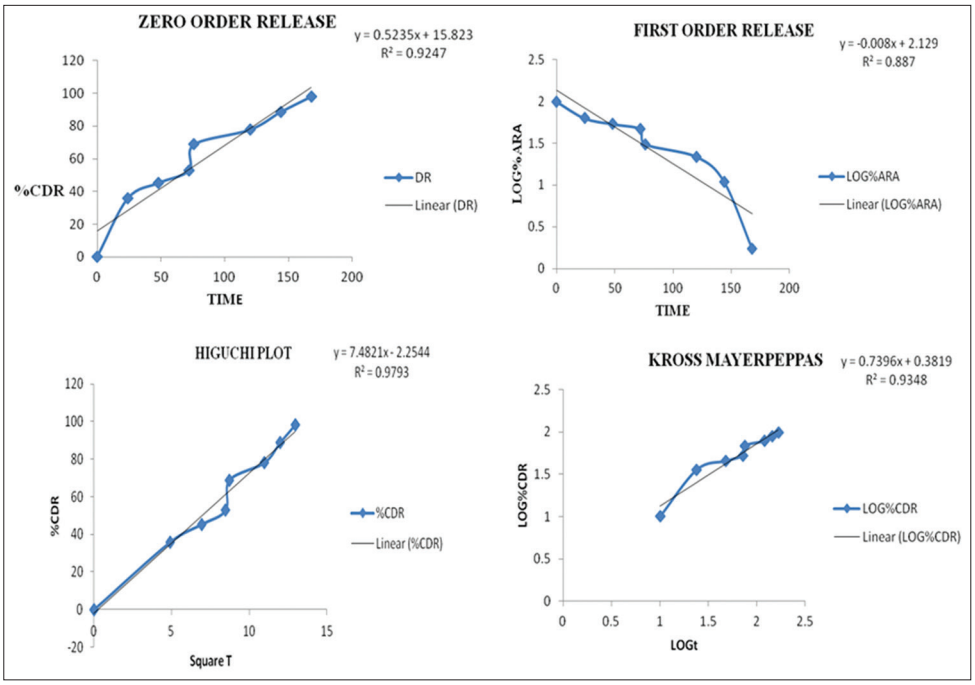

Figure 2: *In vitro* release of curcumin from film F7

Table 3: Kinetic values obtained from different plots of formulation F1-F7

Periodontal film code	Correlation coefficient			
	Zero order	First order	Higuchi model	Korsmeyer-Peppas model
F1	0.948	0.945	0.970	0.948
F2	0.958	0.904	0.945	0.949
F3	0.984	0.947	0.954	0.981
F4	0.958	0.828	0.979	0.856
F5	0.942	0.965	0.976	0.933
F6	0.927	0.988	0.981	0.934
F7	0.924	0.887	0.979	0.934

Table 4: In vitro antibacterial activity of curcumin films F7

Periodontal film code	Zone of inhibition (mm) at 168 h
F1	16.16
F2	17.10
F3	18.99
F4	19.24
F5	20.55
F6	22.04
F7	30.50

1557.94/cm due to C=O, and 961.50/cm due to C=C functional groups, indicating the chemical stability of curcumin in the chosen polymeric mixture shown in Table 5. This also indicates that curcumin is not involved in any chemical reactions with the polymer used. Further, the interference was also verified using UV spectrophotometric method.

DSC of pure curcumin

DSC was employed to study any potential change in curcumin that the drug may have experienced during its processing into periodontal films. Thermal analysis of the pure drug was done to see the melting point of drug. DSC curve of curcumin showed a sharp endothermic peak at 176.9°C corresponding to its melting points. The thermogram of curcumin is shown in Figure 5.

Accelerated stability studies

Optimized formulation was subjected to short-term stability testing. Films wrapped in aluminum foil and kept in a humidity chamber maintained at 40°C ± 2°C and 75 ± 5%

Table 5: FTIR data of drug and polymer

Drug/drug+polymer	C-OH stretch (cm^{-1})	C=O stretch (cm^{-1})	C=C stretch (cm^{-1})
Curcumin (pure drug)	3857.70	1510.44	955.62
Drug+ethyl cellulose+Eudragit	3825.00	1557.94	961.50

FTIR: Fourier transforms infrared spectroscopy

Table 6: Data of stability studies of the formulation F7

Time (days)	Physical appearance	Folding endurance	Surface pH	Percentage drug content mean±SD
0	No changes	150-165	6-7	98.22±0.187
10	No changes	145-160	6-7	98.05±0.128
20	No changes	140-155	6-7	97.99±0.153
30	Slight changes	135-150	6-7	96.26±0.213

SD: Standard deviation

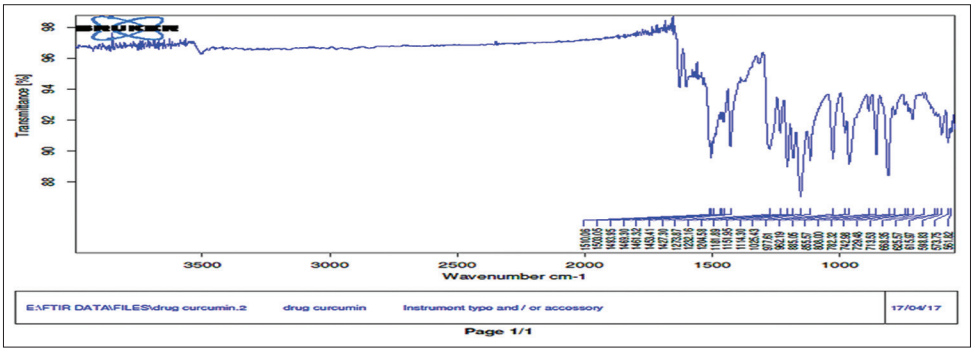

Figure 3: Infrared spectrum of pure curcumin

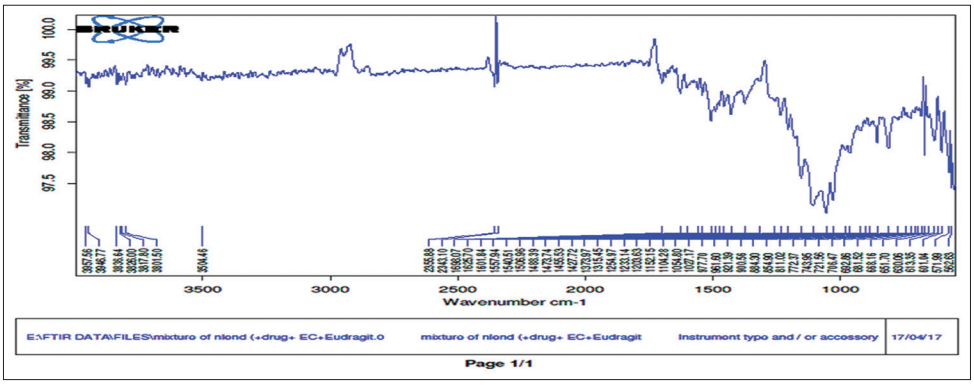

Figure 4: Infrared spectrum of optimized formulation (F7)

RH for 3 months as per the ICH guidelines. Changes in the physical appearance, surface pH, folding endurance, drug content, and *in vitro* drug release of the stored films were investigated during the period and after 3 months. The folding endurance and drug content of the formulation were found to be decreasing and are reported in Table 6. The data presented was the mean of three determinations.

Optimization of films

Out of the seven formulations, the formulation (F7) containing ethyl cellulose and Eudragit RL 100 showed complete and controlled release with 98.25% at the end of 168 h. All physicochemical parameters are satisfactory, and it shows good reproducible results.

CONCLUSION

Local delivery of curcumin in the form of site-specific periodontal films has opened up a new arena for the management of periodontal diseases. Efficacy of such delivery systems is dependent on the sustain release of the drug from the device and its penetration into the base of the

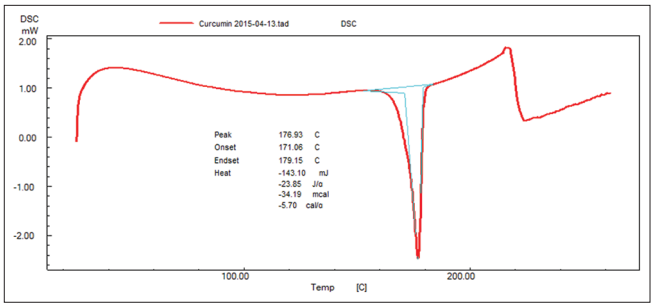

Figure 5: Differential scanning calorimetry of pure curcumin

periodontal pocket and adjacent connective tissue. In the study, curcumin dental films were successfully prepared by solvent casting technique using polymer ethyl cellulose, Eudragit RL 100, and HPMC K4M. The films were smooth, homogenous, non-sticky, and flexible. These films were able to sustain the release of drug for about 1 week and showed good antimicrobial activity against test microorganism studied. Stability studies show that the drug remained intact and stable in the periodontal films during storage. Overall studies indicated that site-specific periodontal films having a lower dose of drug, and sustained effects are a better alternative to systemic therapy in the treatment of periodontal diseases.

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