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FABRICATION AND EVALUATION OF CHITOSAN-GELATIN COMPOSITE FILM AS A DRUG CARRIER FOR *IN VITRO* TRANSDERMAL DELIVERY

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Keywords:

FT-IR, differential scanning calorimetry, transdermal drug delivery, chitosan, gelatin, theophylline, swellability

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ABSTRACT: Natural polymer composite films from a mixture of chitosan and gelatin of various compositions were solution casted using acetic acid with and without theophylline. The films were characterized by FT-IR, TG, differential scanning calorimetry, SEM, XRD and swellability in phosphate buffer. SEM micrographs indicated uniform dispersion of the drug in the polymer blend and drug crystals were seen at higher magnification. TG, DSC and FT-IR studies implied polymer-polymer and polymer-drug weak interactions in the casted film. *In vitro* transdermal delivery of drug from theophylline loaded films were evaluated spectrophotometrically in phosphate buffer (pH=5.4) using Franz diffusion cell. The study revealed that at initial stage of release (upto 6h) there was only moderate change on the drug release profiles with increased content of gelatin in the film. But at higher release times (10h) the release rate was enhanced with increased gelatin-chitosan ratio. This was attributed to the improved swellability of the film in the buffer. The drug release followed a non-Fickian mechanism. The experimental observations implied that the gelatin-chitosan composite film may be used as transdermal carrier for systemic delivery of drug via the skin.

INTRODUCTION: Transdermal delivery represents delivering self-contained, discrete dosages forms to the general circulation through the skin, a desirable alternative to oral delivery of drugs and poised to provide a substitute to hypodermic injection too. The application of medications to the skin to ease ailments has been practiced by humankind over thousands of years. This included application of poultices, gels, ointments, creams, and pastes and was primarily intended for a local topical effect.

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Over the last two decades there has been a resurgence of interest on transdermal drug delivery into the systemic circulation because they are non-invasive, inexpensive and can be self-administered with improved patient compliance. Patients more often forget to take their medicine, and even get tired of swallowing pills, especially if the frequency of intake is many in each day.

Moreover, bypassing the gastrointestinal (GI) tract would avoid both the GI irritation that frequently occurs and partial first-pass inactivation by the liver. Unlike oral dosage forms which produce blood level spikes and troughs, transdermal delivery results in steady absorption of drug over hours or days which are usually preferable[1]. The use of adhesive skin patches to deliver drugs systemically is a relatively new phenomenon [2]. Transdermal vaccine delivery could improve

immune responses by targeting delivery to immunogenic Langerhans cells in the skin [1]. Transdermal delivery systems have proved advantageous for delivery of selected drugs, such as estrogens, testosterone, clonidine, nitroglycerin, scopolamine, fentanyl, and nicotine[3, 4].

Transdermal permeation of a drug via the skin involves three steps namely sorption by stratum corneum, penetration of drug through viable epidermis and uptake of the drug by capillary network in the dermal papillary layer. The major problem in this route of delivery may be the skin toxicity of the drug and the barrier nature of the skin. The permeation of drug into skin can be possible only if the drug possesses low molecular weight (<500 D) and intermediate lipophilicity (P) (log P= 1-3) as well as high potency (total daily dose < 10 mg) and only few drugs meet these criteria [4].

Polymers are the backbone of transdermal delivery systems and advances in the field of polymer science have facilitated the design of different transdermal delivery systems with considerable flexibility using natural, synthetic and semisynthetic polymers to control the release of drug through the intact skin [5-8].

Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug gets released through it via diffusion. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product, and inexpensive and its degradation products must be non-toxic or non-antagonistic to the host. The mechanical properties of the polymer should not deteriorate excessively when large amounts of active agent are incorporated into it.

The nontoxic, biocompatible and biodegradable natural polymers such as chitosan and gelatin which meets majority of the aforementioned properties are widely used as carriers in transdermal delivery [9-14]. Chitosan is used in drug delivery, cell delivery systems, orthopaedics, wound healing, ophthalmology, and bone healing as it enhances the function of polymorphonuclear cells, macrophages and fibroblastic proliferation and migration [14-16]. Chitosan exhibits anti-microbial activity against bacteria [17].

It is hypoallergenic with rapid blood clotting and haemostatic properties, and acts as fat attractor by binding to dietary lipids [18-21]. Gelatin, a protein derived from collagen and bones is translucent, colorless, brittle and tasteless, promotes general joint health and stiffness in athletes. It has good film forming property and known for its wound healing properties by preventing fluid loss due to exudation [13, 22-26].

Since both chitosan and gelatin are having wound healing and other good health promoting properties, it is anticipated that the combination of these two polymers as blend may serve as a promising film forming matrix for transdermal delivery of drugs into the skin with improved healthcare.

The present investigation involves the preparation of composite films of chitosan and gelatin loaded with theophylline as model drug and evaluates the *in vitro* transdermal delivery features of drugs using an in-house fabricated Franz-diffusion cell (**Figure 1**).

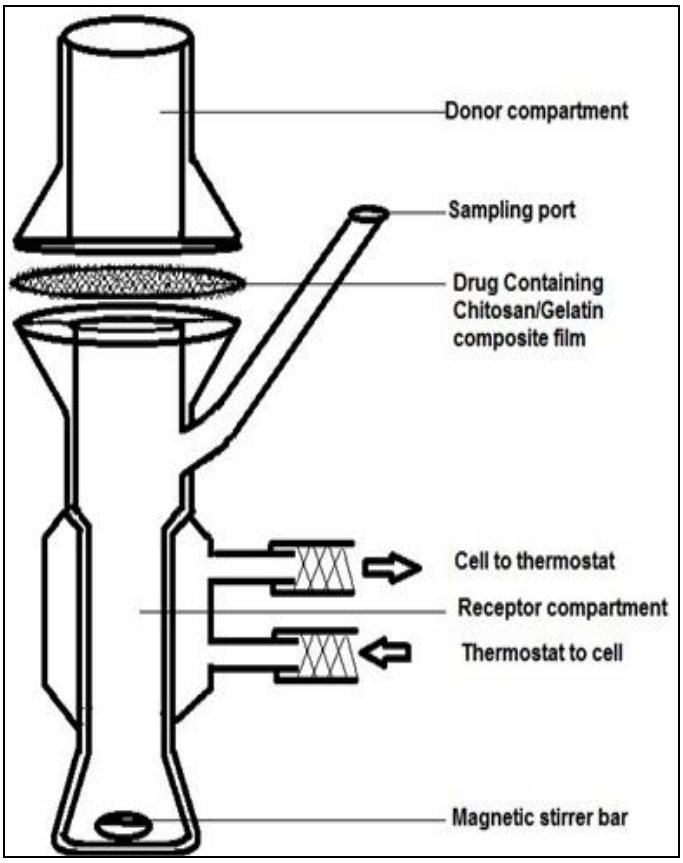


FIGURE 1 : FRANZ DIFFUSION CELL

Material: Chitosan (CTS, high density, 80-85% deacetylated) purchased from Kerala State Co-operative Federation for Fisheries Development Ltd, Cochin was used after purification by reprecipitation from 1% acetic acid solution and drying. Gelatin procured from Sterling Biotech Ltd., Ooty was reprecipated from water using acetone as nonsolvent, dried and used. Glacial acetic acid (99.5 %), methanol (99 %), disodium hydrogen phosphate (97 %), sodium dihydrogen phosphate (98.5 %) (Rankem) and theophylline (THP) anhydrous (Himedia, 99%) were used as received. Phosphate buffer of pH 5.4 was prepared by dissolving the required amount of disodium hydrogen phosphate and monosodium dihydrogen phosphate in distilled water. The chemical structures of chitosan, gelatin and theophylline are shown in **Figure 2**.

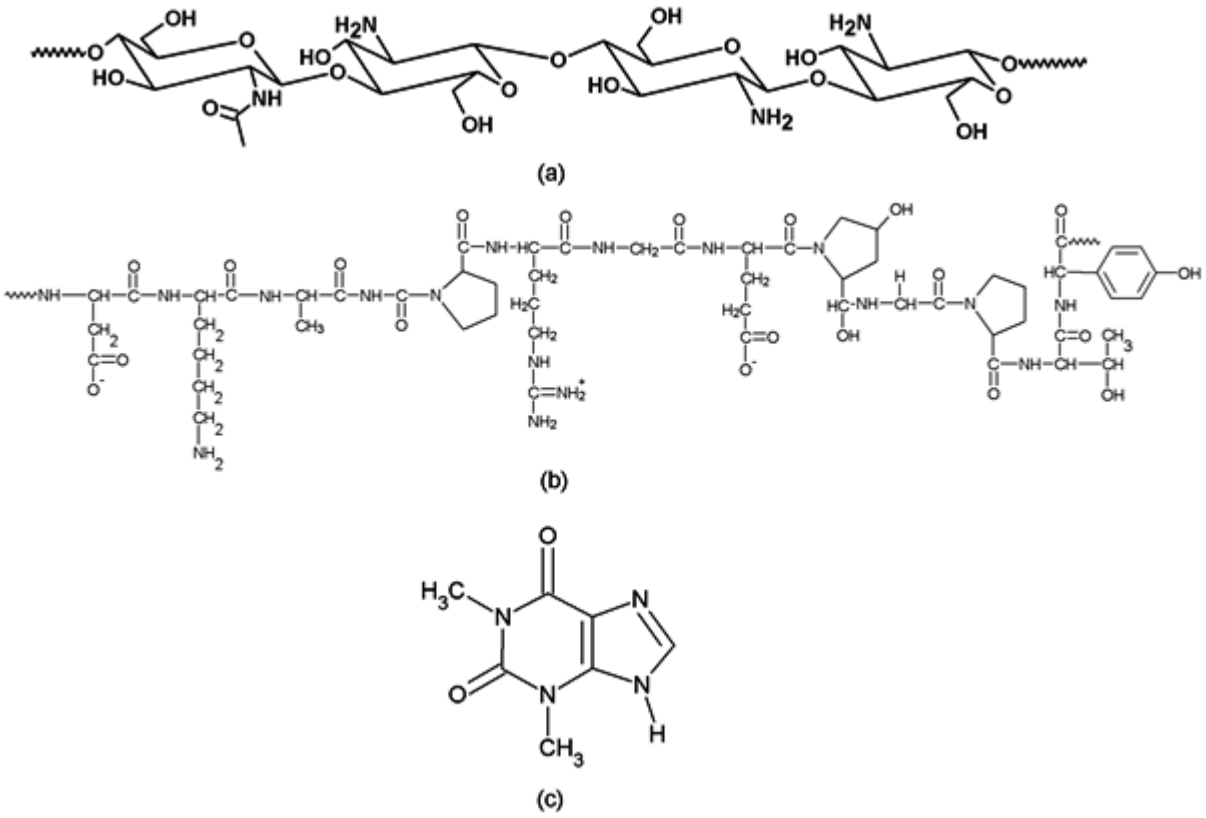


FIGURE 2: CHEMICAL STRUCTURES OF CHITOSAN (A), GELATIN (B) AND THEOPHYLLINE (C)

Gelatin-chitosan composite film: Chitosan and gelatin of total weight 2 g was taken in seven different weight ratios (1:1, 1:2, 1:3, 1:7, 1:15, 1:0, 0:1) and dissolved in 30 ml of 2% acetic acid with and without drug, stirred and sonicated to get homogenous solutions. The solutions were poured separately into identical petridishes (dia10cm) and allowed to evaporate at 40°C. The films were peeled out using methanol as non-solvent. The obtained polymer films were designated as CG1-1, CG1-2, CG1-3, CG1-7, CG1-15, CG1-0 and CG 0-1 and as CGT1-1, CGT 1-2, CGT1-3, CGT1-7, CGT1-15, CGT1-0 and CGT0-1 without and with drug respectively. The thicknesses of the composite films were measured by taking the average of nine thickness measurements on nine different points of film using a screw gauge.

The film thickness and the cross-sectional area of the film employed were 0.36 mm and 4.5 cm^2 respectively.

Swellability: The swelling studies was performed in 25 ml of phosphate buffer solution (p H= 5.4) by immersing polymer films of cross-sectional area 4.5 cm^2 and allowing to swell at 37 °C. The weight of the swollen polymer films at predetermined time intervals were calculated after wiping the polymer films with a tissue paper. The percentage swelling was calculated using the equation

$$\% \text{ of swelling} = ((W_s - W_d) / W_d)) \times 100$$

Where W_s and W_d are the weights (g) of the swollen and dry polymer films respectively.

The swelling characteristics of the polymer films were analyzed by comparing percentage swelling Vs time (min) plots.

Scanning Electron Microscopy (SEM): SEM micrographs of polymer and drug-loaded polymer films for different magnifications were recorded using ZEISS EVO Series SEM model EVO 50 after deposition of gold on the film by sputtering.

Fourier Transform -Infrared (FT-IR) Spectroscopy: FT-IR spectra of dried polymer, drug-loaded polymer films and the drug were recorded on KBr pellet for the spectral width 400 to 4000 cm^{-1} using Shimadzu FT-IR-8400S at a resolution of 2 cm^{-1} by accumulating 48 scans.

Thermogravimetry (TG): TG / DTG studies were performed on TGA Q500 V20.10 Build 36 equipment for the temperatures ranging from ambient to 800°C using a sample size of 1.5–3.5 mg at a heating rate of 10°C/min, under nitrogen atmosphere.

Differential Scanning Calorimetry (DSC): DSC thermograms of the dry polymer and drug-loaded polymer films and the drug were recorded on Perkin Elmer Pyris 6DSC model in nitrogen atmosphere at a heating rate of 10°C per minute.

X-Ray Diffractometer (XRD): The X-Ray diffractograms of the dry polymer and drug-loaded polymer films were recorded using Shimadzu XRD-6000 diffractometer with CuK_{α} radiation operated at the voltage and current values of 40 kV and 30 mA for the 2θ values in the range of 5-45° at a scan rate of 10° per minute.

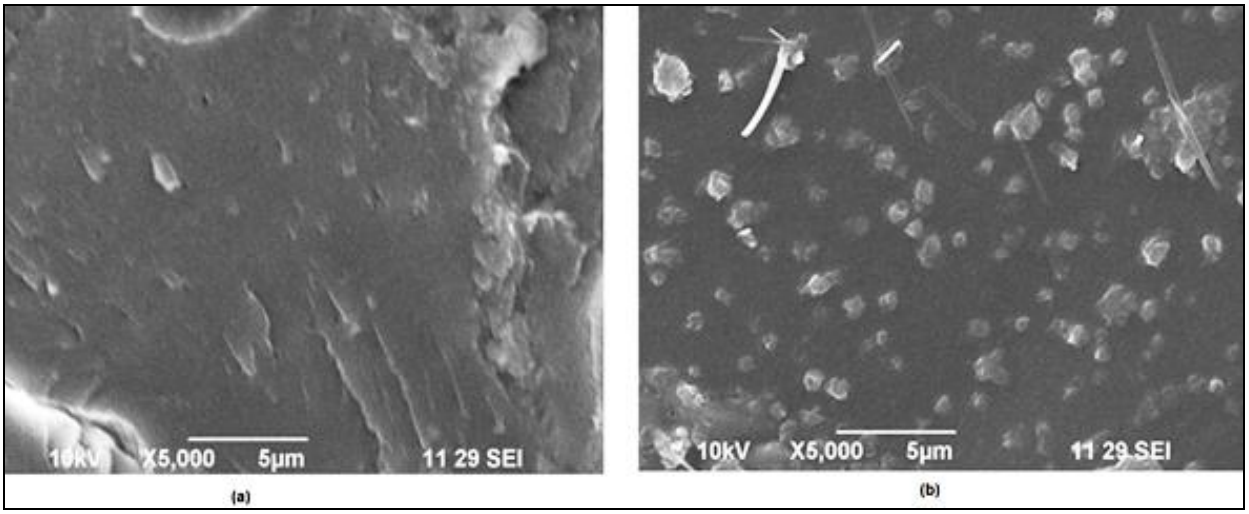
UV-Visible Spectrophotometer: UV spectra of pure drug and the drug released from the polymer film during drug release studies were recorded for the spectral width 200-400 nm on Perkin Elmer Lamda 35 UV–VIS Spectrophotometer (UVWINLAB software).

***In-vitro* drug release by Franz- diffusion cell:** An in-house fabricated Franz-diffusion cell of receptor capacity 26 ml was used for *in-vitro* transdermal drug release studies at 37°C. The cell was filled with 26ml of phosphate buffer and thermostated at 37°C. The drug-loaded polymer films of cross-sectional area of 4.5 cm^2 were sandwiched between the flat ground joints of donor and receptor compartments (Figure1) such that the film will be in contact with the buffer. Since the drug was loaded into the polymer film by solution casting, donor compartment was filled with 5 ml of phosphate buffer (pH=5.4). The amount of theophylline released into the buffer solution, was estimated UV spectrophotometrically by pipetting out 200 µl of sample from the sampling port and measuring its absorbance[27] at 272 nm at regular intervals of time. The pipetted volume was compensated by adding another 200µl of buffer during each sampling.

RESULTS AND DISCUSSION

Characterization of polymer films:

Surface feature of film by SEM analysis: The external morphology of the polymer films was analyzed using SEM. A representative SEM micrograph for the composite film CGT1-1 is shown in **Figure 3**.



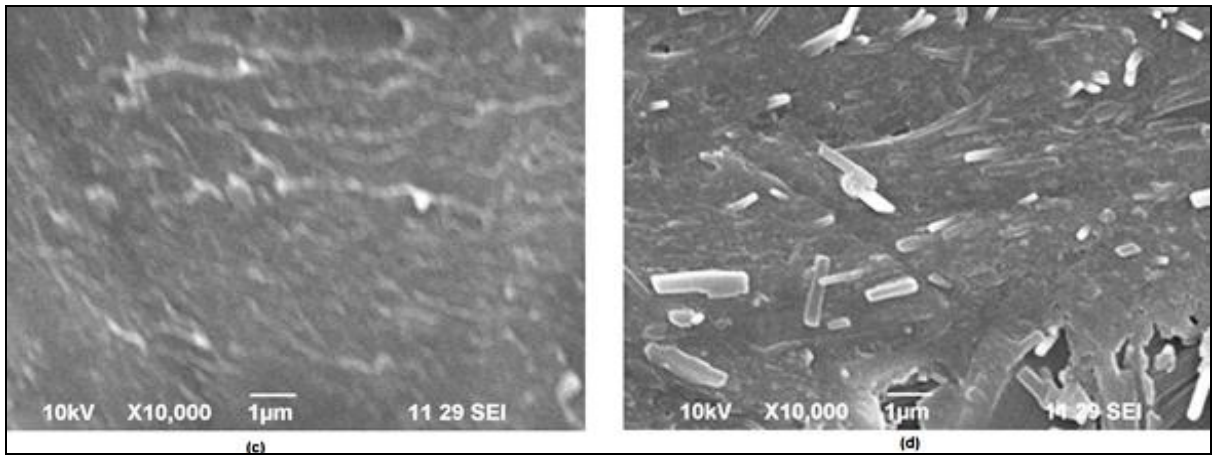


FIGURE 3: SEM MICROGRAPHS OF CG1-1(A & C) AND CGT1-1(B & D) AT DIFFERENT MAGNIFICATIONS

Analysis of micrograph revealed homogeneous nature of the composite film which is in accordance with the literature report [28] and uniform dispersion of the loaded drug throughout the entire film without any agglomeration. Dispersed drug (Theophylline) crystals were clearly seen at higher magnifications (Figure 3 (d)).

FT-IR studies: The FT-IR spectra of the chitosan-gelatin composite films CG1-1, CG1-3, CGT1-1, CGT1-3 and the drug THP displayed in **Figure 4**.

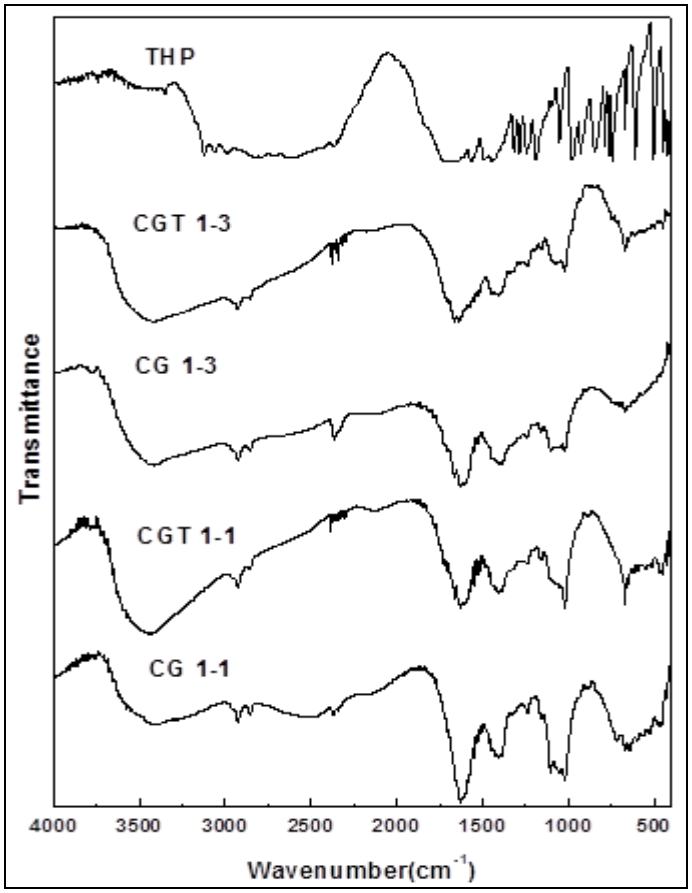


FIGURE 4: FT-IR SPECTRA OF CG 1-1, CG 1-3, CGT1-1, CGT 1-3 AND THP IN KBR MATRIX

FT-IR spectra of chitosan-gelatin composite film depicted the characteristic absorption peaks [31, 32] of chitosan and gelatin (3200-3450 cm^{-1} (O-H & N-H stretching), 1030-1100 cm^{-1}(C-O-C stretching), 1640 cm^{-1}(C=O stretching), 1530-1580 cm^{-1} (amide II).

The absorptions at 2,920-2950(CH_2) and 2,850-2870 cm^{-1} (CH_3) are attributed to C–H stretching vibrations of methylene in chitosan and alkyl pendant groups in gelatin. The absorption peaks observed at 1,700–1,600 and 1,560–1,500 cm^{-1} are attributed to C=O stretching of amide I and amide II of type B in gelatin [29, 30].

The absorptions around 1,200 and 3,450 cm-1 (N–H stretching) (Figure 4) are typical for the amide III and amide A vibrational modes, respectively. C=O, N–H, and C–N bond stretchings and H–N–C bending are usually appear in the amide I, A, II, and III regions, respectively. The absorptions in the range 1,550–1,500 cm-1 (Figure 4) are due to N–H bending motions.

As the gelatin content increased a change in the C=O stretching frequency and shift in the band of absorption frequencies around 3500 cm^{-1} was observed and this may be attributed to the intermolecular interaction between chitosan and gelatin chains by H-bonding, polyelectrolyte complex formation [32] etc.

TGA/DTG: The weight loss around 100^{o}C is attributed to the presence of traces of moisture because the onset degradation temperatures of chitosan, gelatin and THP were around 275, 380 and 250°C respectively (**Figure 5**).

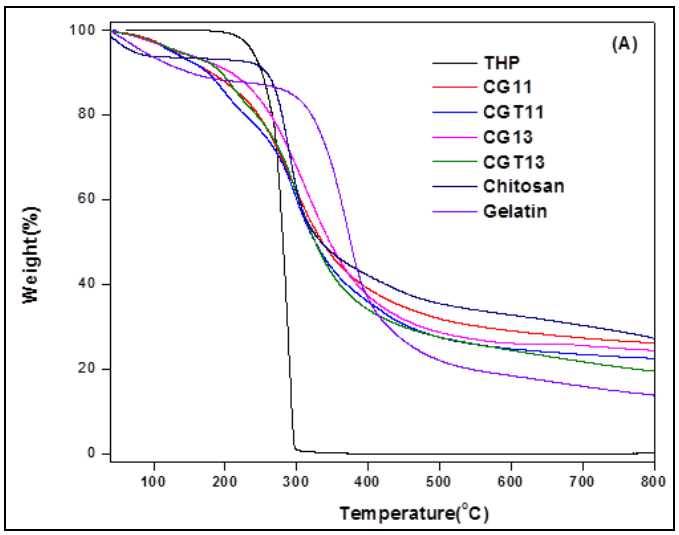


FIGURE 5A: TG THERMOGRAMS OF CHITOSAN, GELATIN, CG 1-1, CG 1-3, CGT 1-1, CGT 1-3 AND THP

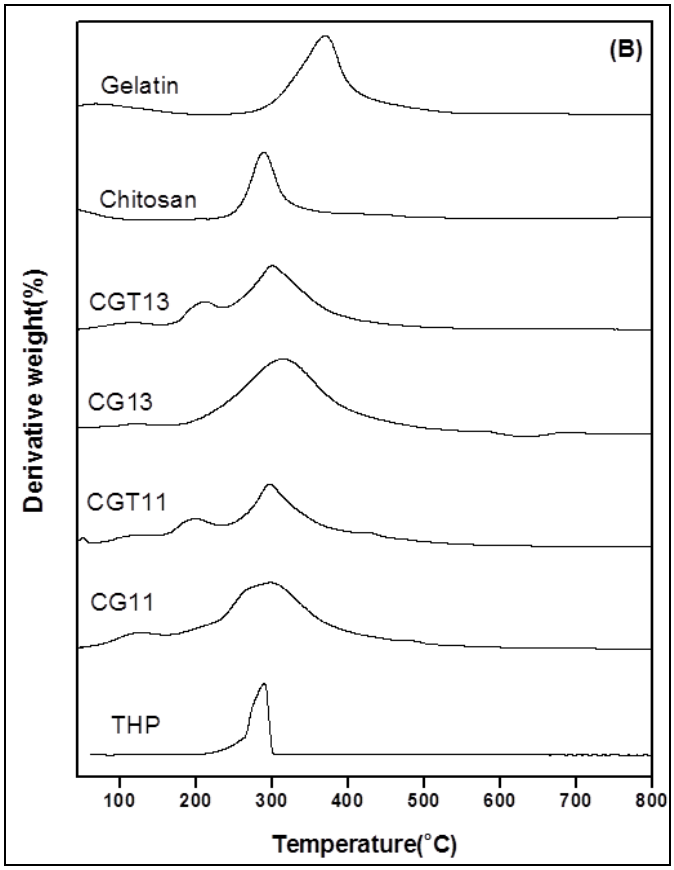


FIGURE 5B: DERIVATIVE THERMOGRAMS (DTG) OF CHITOSAN, GELATIN, CG 1-1, CG 1-3, CGT 1-1, CGT 1-3 AND THP

TG/DTG trace of the drug indicated that drug started degrading before the melting temperature [30]. Comparison of TG/DTG thermograms (**Figures 5A & 5B**) indicated that in drug loaded films the onset temperature for degradation of drugs starts earlier to the degradation of virgin drug. This may be due to the drug-matrix weak interaction.

DSC analysis: DSC thermograms of the polymer films CG 1-1, CG 1-3, CGT 1-1, CGT 1-3 and the drug THP are shown in the **Figure 6**.

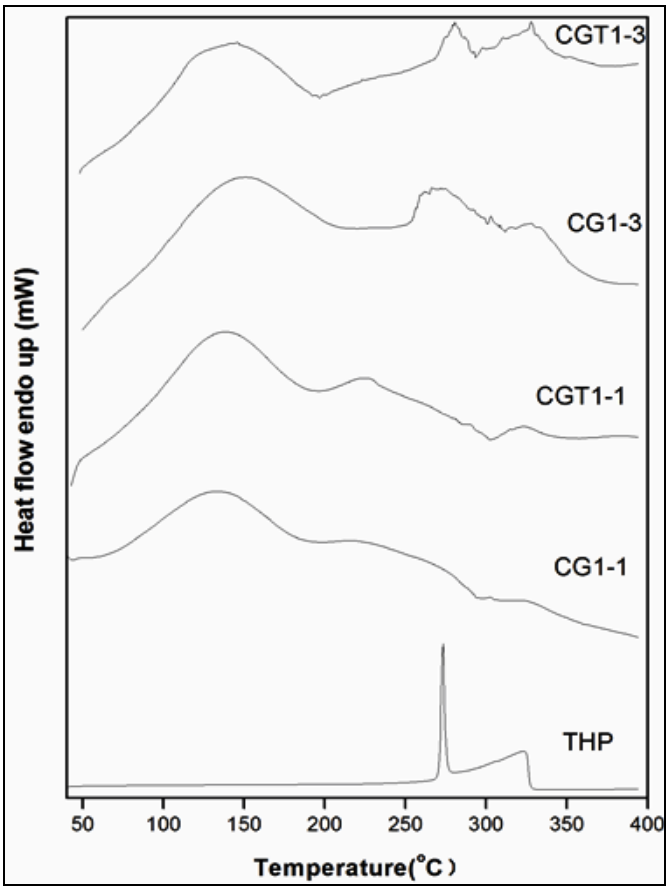


FIGURE 6: DSC THERMOGRAMS OF CG 1-1, CG 1-3, CGT 1-1, CGT 1-3 AND THP

The endotherms observed below 150°C in these DSC traces are attributed to the evaporative loss of residual moisture from the samples. The transition between 150-220°C may be more likely due to the glass transition [31, 32]. The drug THP melts at 272°C with decomposition [30]. The transition above 250°C was attributed to the decomposition of matrix [31]. Since chitosan degrades [31] around 275°C, the melting endotherm of theophylline in the drug loaded composite film was masked by the backbone degradation of chitosan. The less pronounced transition temperatures observed between 150 to 220°C were more likely attributed to the glass transitions because gelatin, chitosan and THP degrades beyond this temperature range. The variation in glass transition temperatures may be due to the differences in film composition and presence or absence of drugs in the film. The shift in glass transitions indicated [32] intermolecular interactions between chitosan and gelatin chains and polymer matrix-drug (THP) interactions.

XRD analysis: The X-ray diffraction patterns of the polymer films CG 1-1, CG 1-3, CG 1-0, CGT 1-1, CGT 1-3 and CGT 1-0 are shown in the **Figure 7**.

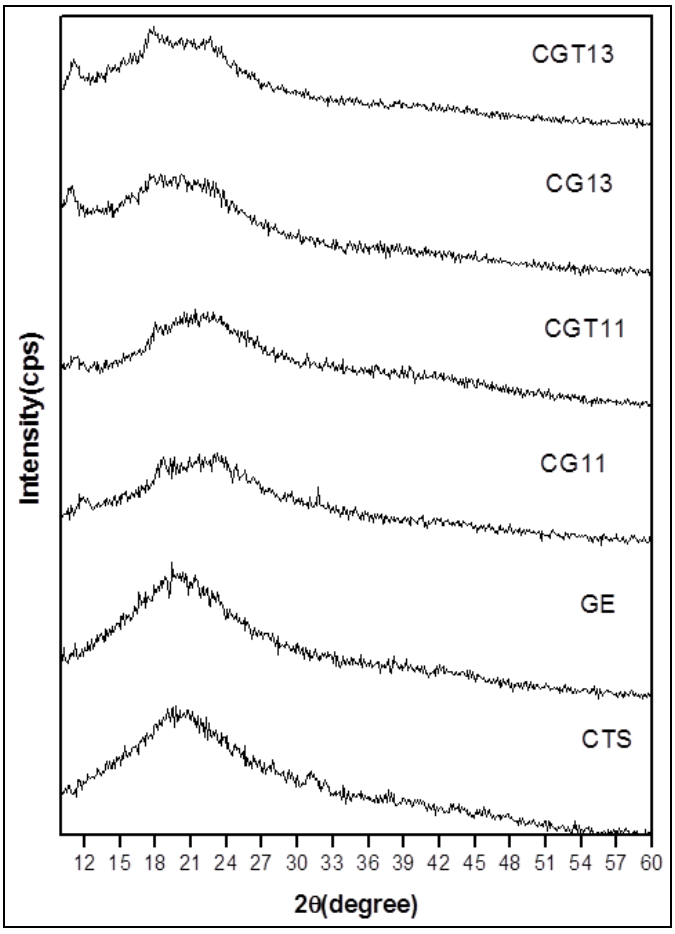


FIGURE 7: XRDS OF THE POLYMER FILMS CG 1-0, CG 1-1, CG 1-3, CGT 1-0, CGT 1-1 AND CGT 1-3

The composite films show weak diffraction peaks in the range 11-24^{o} characteristics of chitosan and gelatin [30, 33] and implying predominant amorphous character of composite films like prestine polymers. In the composite films with and without drugs the diffraction peaks are broadened indicating weak interactions between chitosan-gelatin and matrix-drug.

Analysis of the diffractogram revealed that in a composite film containing equal amount of chitosan and gelatin, further addition of gelatin decreased the amorphous character of the film. Loading of theophylline to the film increased its amorphous nature. The variation of amorphous character of the film with composition and in presence of drug may be attributed to intermolecular interactions [32] between chitosan-gelatin polymer chains and polymer- drug.

Swelling studies: Knowledge on the swelling features of the films is very important to design a desirable drug carrier. Hence, swelling studies were performed for the polymer films CG1-1, CG1-2, CG1-3, CG1-7, CG1-15, CG 1-0 and CG0-1 and the results are displayed in **Figure 8**.

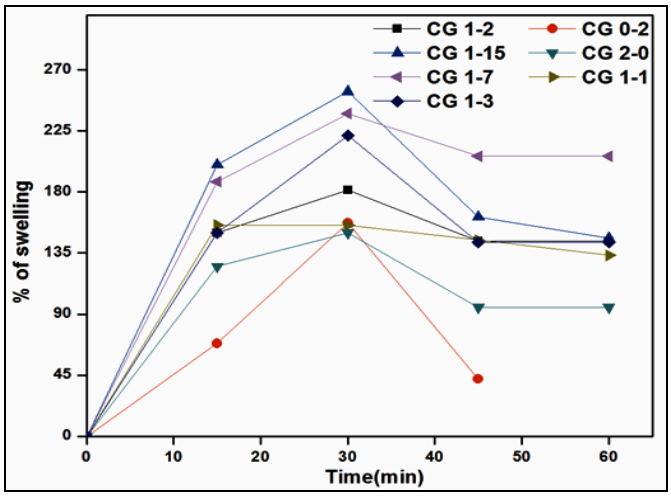


FIGURE 8: SWELLING PROFILES FOR POLYMER FILMS

The percentage of swelling was found to be a function of film composition and the percentage swellings at 30 min for the films CG1-0 and CG-1-15 were found to be 254 and 150 respectively. It was observed that increased amount of gelatin in the polymer films enhanced the swellability for the initial 30 minutes. After thirty minutes a decrease in swellability was observed due to dissolution of gelatin in the buffer.

***In-vitro* drug release studies:** The *in-vitro* transdermal drug release profiles of theophylline for the polymer films CGT1-1, CGT1-2, CGT1-3, CGT1-7, CGT 1-15 and CGT 1-0 are displayed in **Figure 9**.

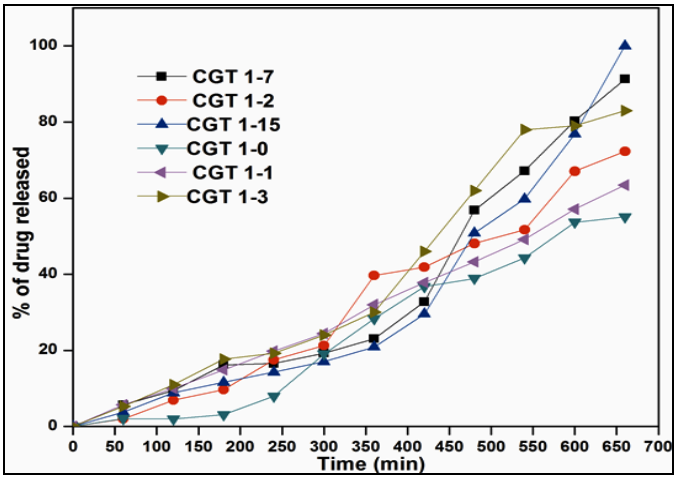


FIGURE 9: DRUG RELEASE PROFILES FROM DRUG LOADED POLYMER FILMS

Analysis of the profiles indicated that the initial drug release rate was more for composite film compared to that in chitosan. For the initial release rate upto 6 hrs there is no general correlation between gelatin content and release rate for the composite films. But at later stage of release (ie., after 10 hrs) the release rate increased with increased gelatin content in the film due to dissolution of the film. This was also substantiated by the increase in release time with gelatin content in the film for the 60% release of the loaded drug (**Table 1**).

TABLE 1: POWER LAW EXPONENT VALUES ('N') FROM KORSEMEYER-PAPPAS PLOT

Polymer film	Amount of drug (mg) in 4.5 sq.cm film	Time (min) taken for 60% of drug release	n
CGT1-1	3.5	1044	1.32778
CGT1-2	2.983	1008	0.32843
CGT1-3	2.89	936	1.03574
CGT1-7	3.68	900	0.99735
CGT1-15	3.5	396	1.13345
CGT1-0	2.75	1080	1.69036

The quantity of drug released for CGT 1-15 and CGT 1-0 at 660 min measured in terms of absorbance values of theophylline at 272 nm were 0.33425 and 0.04707 respectively. Since gelatin dissolved in the buffer, monitoring of drug release for different time intervals was difficult after 10 hrs. For low percentages of gelatin in the film there was not much difference in the release kinetics. When the ratio of gelatin and chitosan is greater than 2, there was a significant increase in theophylline release rate. This may be attributed to the enhanced drug-buffer interaction in presence of buffer due to enhanced swellability.

Drug release mechanism: The mechanism of drug release from the drug-loaded polymer films can be determined by Korsemeyer - Peppas empirical equation [34, 35].

$$M_t / M_\infty = kt^n$$

Where M_t - amount of drug released at time 't', M_∞ -amount of drug released at equilibrium and M_t/M_∞ - fractional release of drug at time 't'. The power law exponent 'n' was determined from the slope of the plot log (M_t/M_∞) Vs log t constructed using the drug release profiles and its values are given in Table 1. The mechanism of release can be predicted from the 'n' values.

For example, if n=0.5, the mechanism is Fickian. If n=1, it is non-Fickian transport (case II transport). Other value of n indicates anomalous transport kinetics, i. e. a combined mechanism of diffusion and case II transport. Analysis of n values in Table 1 indicated that the mechanism of theophylline release from polymer films was anomalous.

CONCLUSION: Theophylline loaded chitosan-gelatin composite films of various compositions with uniform distribution of loaded drug were fabricated and the *in vitro* release features of theophylline were evaluated in Franz –diffusion cell for transdermal delivery applications. Only marginal differences in release rates were seen for the initial release time upto 6 h for the composite films of various compositions.

However, at later stages (after 10 h) the release rate was enhanced with increased content of gelatin in the film which was attributed to enhanced swellability of the film in the buffer. This demonstrated that sustained transdermal delivery of drug may be achieved by fine tuning the composition of the composite polymer film. The transdermal drug release mechanism was observed to be non-Fickian (i.e anomalous). Due to the non-toxicity, biodegradability, biocompatibility and bioadhesive and other inherent health benefits [9-23] of chitosan and gelatin, the study underscores that chitosan-gelatin composite film may be a promising carrier for transdermal drug delivery applications.

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