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PREPARATION OF *TERMINALIA CHEBULA* LOADED CELLULOSE/CHITOSAN COMPOSITE FILMS AND THE EVALUATION OF DRUG RELEASE AND ANTIMICROBIAL CHARACTERISTICS

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Key words:

Antimicrobial studies; Cellulose Acetate; Chitosan; Composite Film; Diabetic Wound Healing; *Terminalia Chebula*

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ABSTRACT: Diabetic foot ulcer (DFU) is one of the major problems encountered by nearly 15 % of diabetic patients. Combinations of different antibiotics are used to treat the infection which makes the microorganism multi drug resistant. Among various types of drug delivery system, transdermal drug delivery is preferred in treating DFU because it delivers the drug directly to the wound site, which increases the rate of healing. *Terminalia chebula* (King of medicine) is known to possess wound healing ability and high antimicrobial activity against almost all bacteria isolated from DFU. In this scenario, we have fabricated different combinations of drug loaded composite films of cellulose acetate and chitosan. The formulated films were characterized using UV-visible and FT-IR spectrophotometer. Physicochemical characterization of the films was done with respect to drug uniformity, moisture uptake, folding endurance, drug release and antimicrobial studies. The antimicrobial activity of the films was evaluated for *E.coli* and *B.subtilis* and observed a good control of the growth of microorganism. The results suggest that the cellulose based films are well suited for DFU.

INTRODUCTION: Diabetes mellitus is a group of metabolic disorder characterized by high blood glucose, as a result of insufficient insulin production, action of insulin or a combination effect of both [1]. The prevalence of diabetes has increased tremendously worldwide, and nearly 365 million people were affected diabetes in 2013.

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Every year the number seems to increasing drastically and expected to increase to 592 million by 2035 (http://www.idf.org/diabetesatlas). There are many complications like diabetic retinopathy, coronary artery disease, impaired wound healing associated with diabetes. Among them impaired wound healing of diabetic patients is the major complication [2, 3].

Nearly 15 % of all diabetics will develop a foot ulcer in their life time and the mortality rate associated with that ulcer is more than twice as deadly as breast cancer. In diabetic wounds, decreased levels of nitric oxide, growth factors and increased level of reactive oxygen species

proliferates the wound. The other problems associated with diabetic wound healing are delayed collagen synthesis and accelerated degradation of newly synthesized collagen, impaired epithelialization and reduced angiogenesis [4]. Various efforts are being carried out to find the effective drug release membrane for the treatment of DFU. The selection of polymer and drug are important to meet the required properties for this treatment. Various bio-polymers such as chitosan, gelatin, cellulose derivates and hyaluronic acid with drugs are employed for curing the DFU. Among these polymers, chitosan and cellulose have received great potential for drug delivery applications due their physico-chemical and biological characteristics.

Chitosan, α(1–4)-linked 2-amino-2-deoxy-D-glucopyranose, is derived from chitin, second most abundant natural polysaccharides and is the major component of the exoskeleton of crustaceans [5]. Chitosan is hydrophilic, non-toxic, biocompatible and biodegradable polymer. It has a unique antimicrobial activity and inhibits the growth of wide variety of fungi, yeasts, and bacteria [6]. The positively charged chitosan and the negatively charged cell membrane interact to disrupt the cell wall of the microorganism [7]. Chitosan can be cross linked into matrix using chemical cross-linking agents such as glutaraldehyde and genipin, but they are highly toxic.

Cellulose is a naturally occurring polymer and widely used in the biopharmaceutical industry because of its abundant availability, biodegradability and compatibility with biological systems [8]. It is mechanically stable, durable and well suited for transdermal drug delivery [9]. The drug release rate is relatively constant in cellulose acetate films. It is not affected by concentration gradient but the thickness and permeability of polymeric membrane plays a vital role in transdermal drug delivery applications [10].

Terminalia chebula, (*T.chebula*) King of medicine, has high potent to cure various diseases like diabetes, indigestion etc [11]. Diabetic wounds have low levels of free radical scavengers, i.e. both enzymatic and non-enzymatic antioxidants. The oxidative stress is responsible for induction of diabetic complications [12]. Antioxidants accelerate wound healing and avoid the proliferation of the wound by reducing the reactive oxygen species. So, proper antioxidant activities are required for wound healing [13]. Antioxidants enhance the biological actions of NO by stabilizing NO by protecting it against ROS and other radicals [14]. The tannins are the active component of *T.chebula*; a potent antioxidant known to posses wound healing activity and was known to heal diabetic wounds on external application in diabetes induced rats [15]. In this context, we aim to establish a new drug loaded cellulose/chitosan composite film to treat the DFU and the infections associated with it. The present work combines the advantages of the drugs and the biocompatibility and bio-processing nature of the polymers resulting in desired drug delivery characteristics.

MATERIALS AND METHODOLOGY:

Materials: Cellulose acetate was purchased from Otto Chemia (viscosity of 75-125 cP). Chitosan (Pharmaceutical Grade) was purchased from Otto Chemia. Curcumin was procured from Himedia chemicals. *T. chebula* was purchased from the local market of Coimbatore. Acetic acid, acetone and dimethyl sulfoxide (DMSO) were purchased from Thomas Baker suppliers. Luria media was purchased from Sigma Aldrich.

Preparation of *T. chebula* extract:

T. chebula seeds were washed with distilled water, dried and powdered. The extract were prepared by mixing 5 g of powder with 100 mL of distilled water and stirred continuously at 80 ºC. The solution was filtered using Whatmann filter paper. The filtrate was evaporated at 80 ºC and the residue was grounded and weighed [16].

The dried extract was grounded and weighed.
Weight of the extract = 1.334 g
Weight of the drug powder = 5 g

$$\text{Percentage of recovery} = \frac{\text{Weight of the extract X 100}}{\text{Weight of the drug powder}} = 26.68$$

2.3. Fabrication of cellulose/chitosan composite films: Different concentration (5 wt %, 6 wt %, 7 wt %, 10 wt % and 12 wt %) of cellulose acetate solution were prepared by dissolving calculated

amount in different solvents like acetone, acetic acid and DMSO at room temperature. The optimized solvent system was selected for the fabrication of all the films. The prepared solutions were casted into film on glass substrate and the films were made at different temperatures (room temperature, 60 ºC and 80 ºC). After the complete drying, films were peeled off from substrates. Similarly, various concentration (2 wt %, 3 wt %, and 4 wt %) of chitosan solution were prepared separately by dissolving desired amount in 30 wt % of acetic acid at room temperature. The prepared solutions were casted into film on glass substrate at room temperature and at 80 ºC.

After the complete drying, films were peeled off from substrates. Fabrication of cellulose/chitosan composite films was done by same solution casting method. For this, the prepared solutions (cellulose acetate and chitosan) were mixed in different ratios and casted into film. After the complete drying, films were peeled off from substrates. Cellulose acetate solution and chitosan solution were mixed in the ratio of 1:1, 2:1 and 3:1 along with 100 mg of the *T.chebula* extract named as composite C, composite D and composite E and casted into film.

Characterization studies:

Physical Appearance: All the films were visually inspected for color, clarity, flexibility and smoothness.

Thickness studies: The thickness of all the fabricated film was measured at five different points using digital micrometer (Mitutoyo Digimatic Micrometer, Coolant Proof Micrometer IP65). The average and standard deviation were calculated for each batch of the unloaded and drug-loaded films.

FT-IR Analysis: FT-IR spectra of the drug and the drug loaded cellulose/chitosan composite films were analyzed using IR Affinity (Shimadzu, Japan) spectrophotometer in the range of 4000 to 400 cm^{-1} to analyze the interaction between the drug and polymer matrix.

UV-vis studies:

UV-vis studies was carried out to study the absorption peak of the obtained extract in water which is analyzed by using UV-visible spectrophotometer with aid of PG spectrophotometer, using a 1x1 cm quartz cuvette cell in the range of 200-800 nm.

Folding Endurance Test:

Folding endurance is to find the flexibility, which is needed to handle the drug loaded cellulose based chitosan films conveniently and comfortably for the particular application. Folding endurance was determined by repeatedly folding the film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gives the value of folding endurance [17].

Moisture Content:

The fabricated films were marked, then weighed individually and kept in a vaccum desiccator (80 mmHg) at room temperature for 24 h. The films were weighed again until it showed a constant weight.

$$\text{Percentage of moisture content} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Final weight}} \times 100$$

Moisture Uptake:

A weighed film kept in a desiccator at normal room temperature for 24 h was taken out and exposed to 84 wt % relative humidity (saturated solution of potassium chloride) in a desiccator until a constant weight for the film was obtained.

$$\text{Percentage of moisture uptake} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

Drug content uniformity:

The fabricated films are cut into pieces (1x1 cm) and put in 100 mL dissolution medium (distilled water) used and placed in sonicator for 30 min then stirred continuously using a magnetic stirrer at room temperature for 3 h. The sample was withdrawn at the end of 3 h and the drug content is determined spectrophotometrically at 765 nm by Folin's colorimetric method.

***In vitro* release–dissolution studies:**

The patches were placed in phosphate buffer with pH 7.4. All dissolution studies were performed at

32 ºC, at 50 rpm, with each jar carrying 500 mL of PBS buffer. Samples were withdrawn at different time intervals [18].

Adjust the pH to 7.2 ± 0.2 and make up the solution to 1L.The total phenolic content in the sample was determined by using Folin-Ciocalteu colorimetric method based on oxidation-reduction reaction. In a test tube, 3 mL of the sample was added with 2 mL of Folin-Ciocalteu reagent (10 wt %) and 2 mL of 8 wt % Na_2CO_3 to get a total volume of 10 mL. The mixture was allowed to stand for 30 min at room temperature. The absorbance of the mixture was measured using UV-visible spectrometer at 765 nm [19].

Antimicrobial studies:

100 mL of Luria agar was prepared by dissolving 1.3 g of Luria agar in 100 mL of distilled water. The Agar solution was poured in conical flask and plucked with non adsorbent cotton and sterilized at 120 ºC for 20 min. The sterilized media was poured into petridishes and allowed to get solidify. 1 mL of the culture of *E.coli* was added on the surface and distributed evenly using L rod. Small holes were made on the surface of solidified media using a puncher. The prepared films were cut into 1 cm x 1 cm and placed on the punched site. The plate was incubated for 24 h at 37 ºC. Same procedure was followed for *B.subtilis.*

RESULTS AND DISCUSSION:

We have investigated the *T.chebula* loaded cellulose/chitosan composite films for transdermal drug delivery application. Prior to fabricate the drug loaded films, there are many parameters involved in the optimization of the film fabrication such as solvent used, concentration of the polymer and temperature. All these parameters varied based on the properties of polymers. In this study, different concentrations (5 wt %, 6 wt %, 7 wt %, 10 wt % and 12 wt %) of cellulose acetate solution were prepared by dissolving in acetone or DMSO and casted into film on glass substrate at room temperature. cellulose acetate film was optimized at 7 wt% concentration with DMSO as solvent and casted over a glass substrate at 80 ºC. Similarly, chitosan film was optimized at 2 wt % concentration with 30 % acetic acid and 70 % water as solvent and casted over a glass substrate at room temperature. **Fig.1** shows the photographic images of fabricated drug loaded films of a) Cellulose acetate b) Chitosan c) Composite C d) Composite D and e) Composite E.

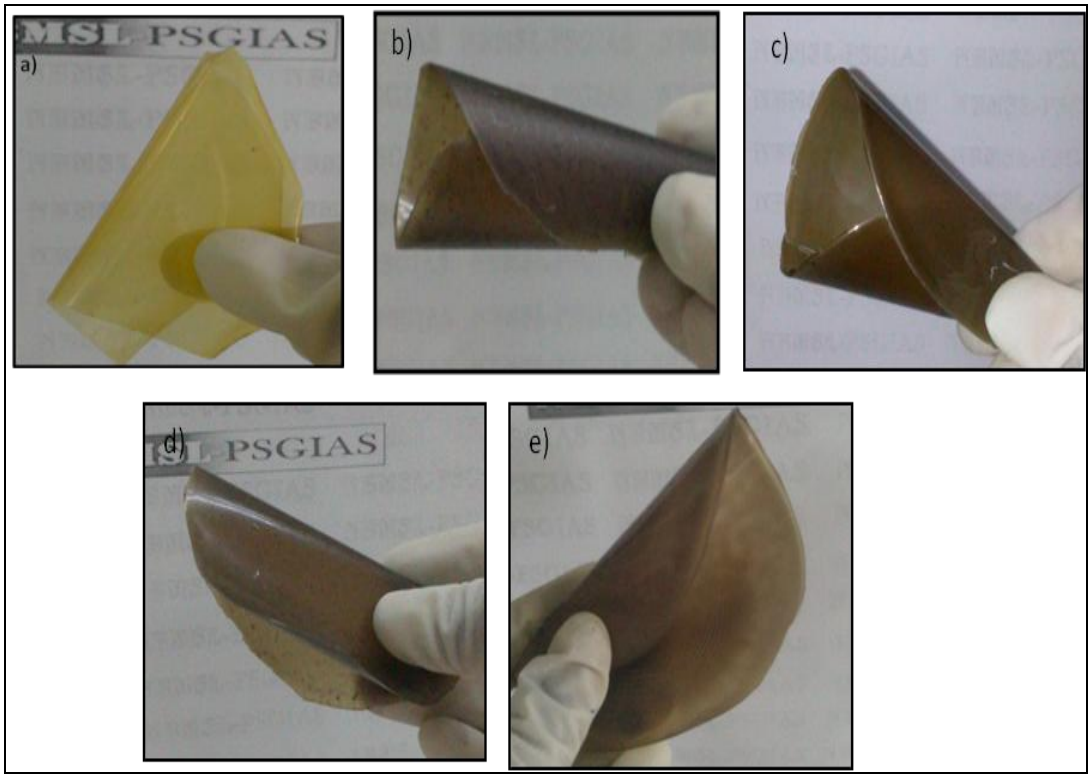

FIG.1: DRUG LOADED FILMS a) CELLULOSE ACETATE b) CHITOSAN c) COMPOSITE C d) COMPOSITE d AND e) COMPOSITE E

Fabrication of drug loaded cellulose/ chitosan composite films as follows. Cellulose acetate and chitosan was dissolved separately in the mixture of 30 % of acetic acid and 70 % of water. The prepared solutions were mixed well in the different ratios (1:1, 2:1 and 3:1) and allowed to stirrer vigorously at 80 °C until get the homogenous solution. Then 100 mg of drug was mixed into the all solutions separately and casted into film at room temperature. Among the ratios, 3:1 of cellulose /chitosan composite films were fixed as optimized condition for transdermal drug delivery applications.

UV-VIS studies:

The obtained extract of *T.chebula* was diluted with distilled water and analyzed using UV-visible spectrophotometer. The UV-visible spectra of *T.chebula* extract was shown in figure 2. It shows the absorption peaks at 215 nm and 270 nm which correspond to the presence of polyphenols, tannin and carbohydrates [20].

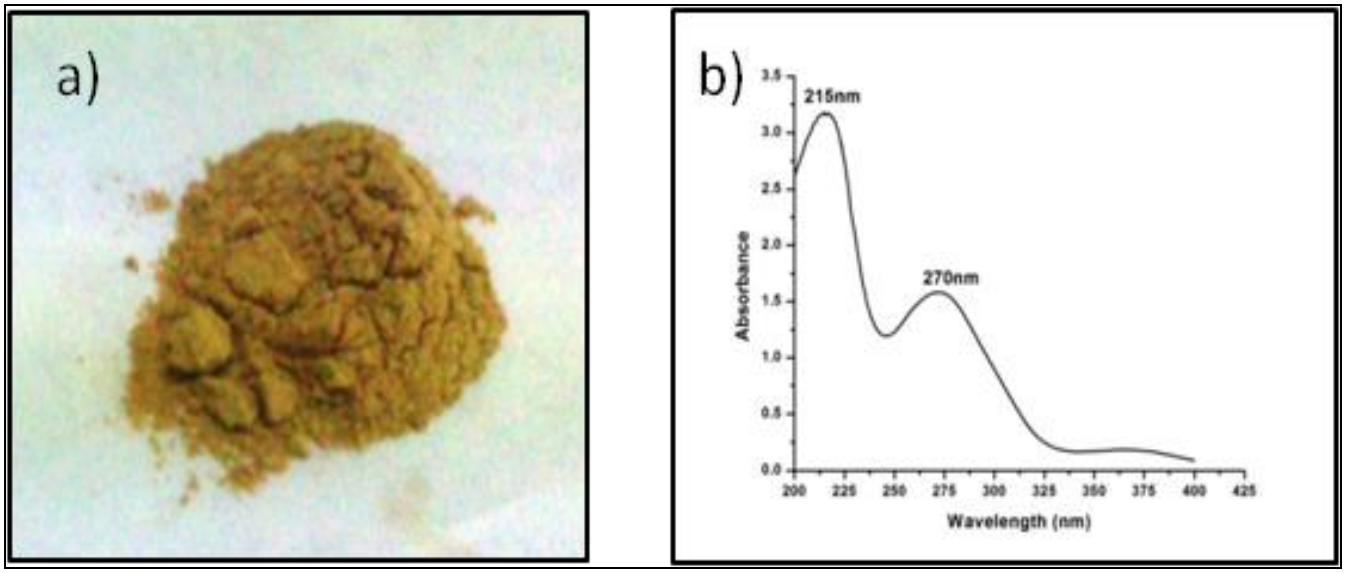

FIG. 2. (a) PHOTOGRAPHIC IMAGE OF *T.CHEBULA* POWDER (b) UV-VISIBLE SPECTRUM OF *T.CHEBULA* EXTRACT IN WATER

FT-IR analysis of *T.chebula* extract and drug loaded films: The FT-IR spectra of *T. chebula* extract is shown in **Fig. 3 A**. The peaks observed at 3394.72 cm^{-1}, 1720.50 cm^{-1}, 1612.40 cm^{-1} and 1442.75 cm^{-1} which are attributed to the presence of -OH group, -C=O group, -NH group and -C=C group, respectively. The peaks obtained at 2924.09 cm^{-1} and 2854.65 cm^{-1} indicates the presence of aromatic -CH vibration in *T.chebula* extract. The peaks obtained at 1350.17 cm^{-1}, 1203.58 cm^{-1} and 1033.85 cm^{-1} which are the characteristics of -CF alkyl halide group. Based on the FT-IR results, it was found that the extract of *T. chebula* contains -OH, -CH, -C=O, -NH, -C=C, =CH and -CF functional groups, which confirms the presence of polyphenols, tannin and carbohydrates [20].

Similarly, FT-IR studies were carried out for drug loaded films in order to identify the presence of drug in the fabricated films, which are illustrated in **Fig. 3 B**. The peaks obtained at 3500 to 3000 cm^{-1}, 1735.93 cm^{-1}, 1612.40 cm^{-1} and 1442.75 cm^{-1} attributed to the presence of -OH group, -C=O group, -NH group and -C=C group, respectively. The peaks observed at 2924.09 cm^{-1} and 2854.65 cm^{-1} indicates the presence of -CH group. The peaks obtained at 1350.17 cm^{-1}, 1203.58 cm^{-1} and 1234.44 cm^{-1} indicates the presence of -CF alkyl halide and acetyl group.

The peaks obtained at 1049.28 cm^{-1} indicates the presence of -CH alkane group. From FT-IR analysis, it was concluded that the drug was bonded physically to the polymer matrix. Hence, the drug release can be done efficiently by adjusting the ratio between cellulose acetate and chitosan.

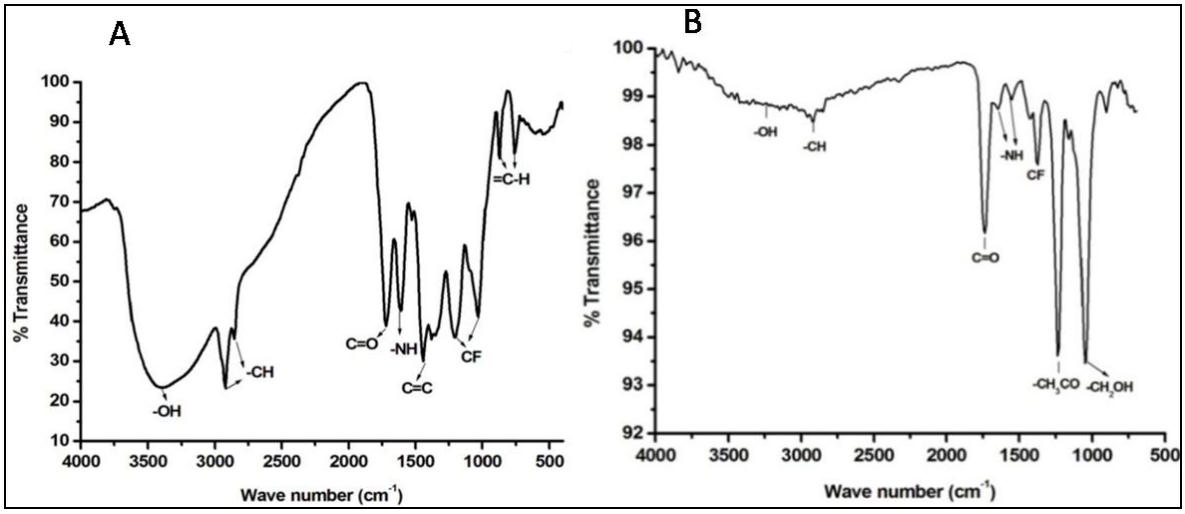

FIG.3:FT-IR SPECTRA OF (a) *T.CHEBULA* EXTRACT (b) *DRUG* LOADED COMPOSITE FILM

Physico-chemical characterization studies:

The moisture content of fabricated film was determined by keeping the drug matrix patches in a vaccum desiccator at 80 mmHg for 24 h, which are shown in **Table 1**. The percentage moisture content was calculated from the weight differences relative to the final weight. The moisture content in the formulations was found to be same with the increasing concentration of hydrophobic polymer, cellulose acetate. Moisture contents in the formulations prepared were found to be low and moderate in chitosan.

TABLE 1: RESULTS OF VARIOUS PHYSICO- CHEMICAL CHARACTERISTICS OF FABRICATED FREE FILMS AND DRUG LOADED FILMS

S. No	Films	*Thickness of the film (mm)	*Folding endurance	*Percentage Moisture lost (%)	*Percentage Moisture uptake (%)
1	Cellulose acetate	0.0856 ± 0.002	205	-	-
2	Chitosan	0.0442 ± 0.008	289	-	-
3	Composite C	0.1962 ± 0.020	26	-	-
4	Composite D	0.124 ± 0.0018	30	-	-
5	Composite E	0.1384 ± 0.003	31	-	-
	Drug loaded films				
6	Cellulose acetate	0.0814 ± 0.006	336	3.353	0.329
7	Chitosan	0.1102 ± 0.002	279	4.423	27.35
8	Composite C	0.1156 ± 0.020	76	2.477	9.363
9	Composite D	0.1086 ± 0.008	79	2.796	0.778
10	Composite E	0.1476 ± 0.003	77	2.713	0.996

*Indicates average of three values

Similarly, the percentage moisture uptake was calculated from the weight difference relative to the initial weight after exposing the prepared patches to saturated potassium chloride solution. The percentage moisture uptake was also found to decrease with increasing concentration of hydrophobic polymer, cellulose acetate. The moisture uptake was up to 27 wt% for chitosan film. The results of various physico-chemical characteristics of films are summarized in **Table 1**. Folding endurance measurements were carried out for the fabricated films. The films was folded repeatedly continuously at the same point until it breaks. The folding endurance was high for cellulose acetate and chitosan film. In the composite film, the folding endurance was considerably decreased due to the crystals present in cellulose acetate. The crystals of cellulose acetate were dispersed in chitosan which gives brittle nature to the composite film.

***In- vitro* drug release studies:**

In order see to the release profile of drug from films, drug release study was carried out in 5

formulations for 24 h using PBS. **Fig. 4** shows the drug release profile of *T.chebula* loaded cellulose/chitosan composite films. The drug was released within 24 h in cellulose acetate film, chitosan film and in the composite C & D. But the drug release was reduced to 77 wt % for Composite E. From this it was concluded that, as the cellulose acetate concentration increases the drug release was considerably reduced from 97 wt % to 77 wt %. By tuning the concentration of the cellulose acetate drug release can be controlled. The drug release can be considerably increased when the pH was reduced.

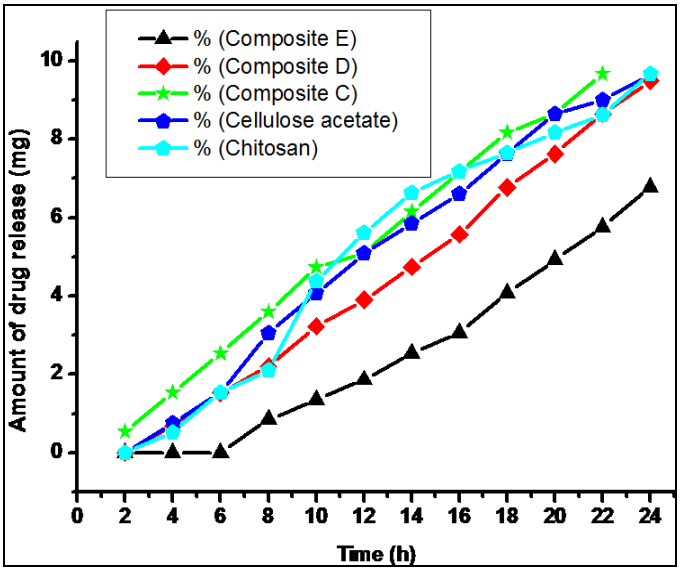

FIG. 4: DRUG RELEASE PROFILE OF *T.CHEBULA* LOADED CELLULOSE/ CHITOSAN COMPOSITE FILMS

Antimicrobial studies:

Antimicrobial activities are evaluated for *T.chebula* drug loaded cellulose, chitosan and composite of cellulose/chitosan films against *E.coli* and *B. subtilis*. **Fig. 5** shows antimicrobial activity of drug loaded cellulose acetate, chitosan and composite of cellulose acetate/chitosan films and abbreviations are as follows; drug loaded cellulose acetate film named as ks-1, drug loaded chitosan film named as ks-2, 1:1 ratio of cellulose acetate/chitosan was named as ks-3. Similarly, 2:1, 3:1 are named as ks-4, ks-5 and pure chitosan film named as ks-6. From the **Fig. 5**, it was found that drug loaded cellulose acetate and their composites showed good antimicrobial activity against *E.coli* and *B. subtilis.* It can be concluded that the drug was efficient in inhibiting the growth of the microorganism and cellulose acetate plays no role in inhibition. There was a significant increase in MIC value of drug loaded chitosan in against the microorganism especially against gram negative bacteria, *E.coli*. Chitosan possess good antimicrobial activity and there are two suggested mechanism are: (1) The binding of cationic chitosan to sialic acid in phospholipids, and consequently restraining the movement of microbiological substances, and (2) penetration of oligomeric chitosan into the cells of microorganisms and prevention the growth of cells by preventing the transformation of DNA into RNA. When more amount of chitosan (positively charged) is adsorbed on the cell surfaces result in greater changes in the structure of the cell wall and in the permeability of the cell membrane. As a result, Gram-negative bacteria due to their more negatively charged cell surfaces are more susceptible to chitosan, and sensitivity of the Gram-positive bacteria was highly variable and the mode of action of chitosan is more complex than simple interaction of chitosan with cell membrane, and it involves a number of events, which may ultimately lead to a killing process [21]. Chitosan with highest molecular weight ranging from 500-10,000 Da had the strongest bactericidal and fungicidal activities against most pathogens tested [22].

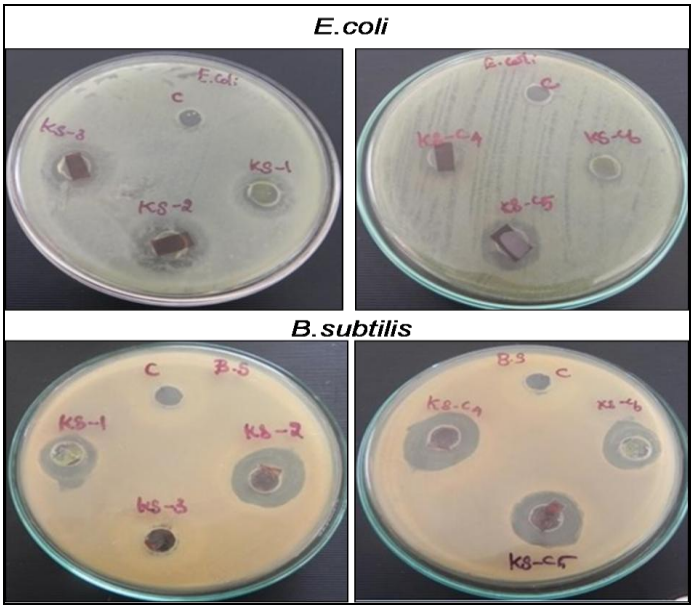

FIG.5: ANTIMICROBIAL ACTIVITY OF DRUG LOADED CELLULOSE ACETATE, CHITOSAN AND COMPOSITE OF CELLULOSE ACETATE/CHITOSAN FILMS AND ABBREVIATIONS ARE AS FOLLOWS; DRUG LOADED CELLULOSE ACETATE FILM NAMED AS ks-1,DRUG LOADED CHITOSAN FILM NAMED AS ks-2, 1:1 RATIO OF CELLULOSE ACETATE/CHITOSAN WAS NAMED AS ks-3. SIMILARLY, 2:1, 3:1 ARE NAMED AS ks-4, ks-5 AND PURE CHITOSAN FILM NAMED AS ks-6.

The zone of inhibition of drug loaded cellulose, chitosan and composite of cellulose acetate/chitosan films were shown in table 2. The pure chitosan films possess good antimicrobial activity with the zone of inhibition 12 mm *for E.coli* and 18 mm for chitosan whereas cellulose acetate film posses no antimicrobial activity. In case of composites, the drug release was more in composite C than composite D & E. So, the antimicrobial value of composite C is higher than composite D & E.

TABLE 2: *T.CHEBULA* EXTRACTS LOADED FILMS AGAINST *E. COLI AND B. SUBTILIS*

Drug loaded films	Zone of Inhibition (mm)	
	E. coli **(Gram negative)**	***B. subtilis*** **(Gram positive)**
Cellulose acetate	18.0	16.6
Chitosan	24.2	21.0
Composite C	21.6	6.0
Composite D	13.0	22.4
Composite E	18.4	21.2

Stability:

The stability of fabricated drug loaded patches were observed for the physical changes in the films such as color, appearance and drug content at a regular interval of seven days for one month. All the films were stable at 37 ºC with respect to their color, appearance and uniformity of drug content.

CONCLUSION: In this paper, we have developed *T.chebula* loaded cellulose/chitosan composite films. Various parameters with respect to film formation, drug loading, drug release and stability have been evaluated. It was observed that 95 wt % of drug was released within 24 h and the drug concentration was constantly increasing which is an important parameter for transdermal drug delivery. The film has a potential to increase the drug delivery rate if the pH reduces, so it can efficiently reduce the micro organism present on the skin.

The antimicrobial studies with *E.coli* and *B. subtilis* indicates that the composite film has good potential to inhibit the growth of micro organism. The *in-vitro* drug release studies suggests that cellulose blended composite films could be effectively used for diabetic wound healing applications. The *in-vivo* drug delivery studies will be carried out in the near future.

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