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Design of transdermal films of alfuzocin HCl by using a natural polymer tamarind seed polysaccharide extract

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ABSTRACT

Hydrophilic matrices involving natural polysaccharides are an interesting option for developing sustained release formulation. One of such polysaccharides is Tamarind seed polysaccharide (TSP) isolated from seedkernel of Tamarindusindica.TSP is used as the binder, mucoadhesive, antiviral, antitumor, floculant, gellingagent, suspendingagent, solubility enhancer. The main aim of this study is to use TSP as film forming agent. The TSP is isolated and characterised for identification tests,organoleptic characters, solubility, swelling index, microbiological tests andIR spectra and was found to be no incompatability with the alfuzocinHCl by the FTIR studies. The transdermal films of TSP were prepared (f1 tof8). The prepared films were evaluated for thickness, uniformity of weight,Drug content determination, moisture content, Percentage moisture loss, Folding Endurance, flatness, Water vapour transmission rate, In-vitro diffusion studies and all the values were found to be satisfactory. Among all formulationsf5 was found to be having good release and all other properties comparing to other formulations and it is following the super case II release. The order of release was found to be f5>f1>f6>f7>f8>f2>f3>f4.

INTRODUCTION

Gums have been wildly used as Tablet binders, emulgents and thickeners in cosmetics and suspensions as film-forming agents and transitional colloids. Polysaccharides are the choice of materials among them hydrophilic polymers used, because they are nontoxic and acceptable. The various polysaccharides used in drug delivery application are cellulose ethers, locust bean gum,xanthangumand guar gum. Another natural polysaccharide, Tamarind seed polysaccharide (TSP) obtained from the seed kernel of *Tamarindusindica*,possesses properties like high viscosity, broad pH tolerance, noncarcinogenicity, mucoadhesive nature, andbiocompatibility. It is used as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. TSP has advantages likeLow cost and natural origin. Free from side effects. Biocompatible and bio-acceptable.Environmental friendly processing.Local availability. Better patient tolerance as well as public acceptance. They improve the national economy by providing inexpensive formulations to people, using locally available materials[1].Tsp is used as the binder, mucoadhesive, antiviral, antitumor, floculant, gelling agent, suspending agent[2], solubility enhancer[3]

Drug AlfuzocinHCl is an Antihypertensive Agent with a Half life10 hours, partition coefficient is about 1.51 and Molwt:425.9 Dose:max10mg per day (2.5to10mg), undergoing hepatic metabolism all this factors provide suitable for the development of transdermal films .The mechanism of action of drug alpha(1)-adrenergic blocking agent that exhibits selectivity for alpha(1)- adrenergic receptors in the lower urinary tract. Inhibition of these adrenoreceptors leads to the relaxation of smooth muscle in the bladder neck and prostate, resulting in the improvement in urine flow and a reduction in symptoms in benign prostate hyperplasia. Alfuzosin also inhibits the vasoconstrictor effect of circulating and locally released catecholamine's (epinephrine and nor epinephrine), resulting in peripheral vasodilatation [4].

MATERIALS AND METHODS

Materials: TSP was isolated in laboratory by using acetone. sodium meta bi sulphate from lobachem laboratory reagents and fine chemicals, acetone and span20 from moly chem. Reagents and fine chemicals,propeylen glycol fromlobachem laboratory reagents and fine chemicals, NAOH and potassium dihydrogen phosphate from MerckSpecialitiesPrivate Limited.

Isolation of TSP[5]:
Tamarind seeds collected and dried in sunlight. The kernels were crushed into fine powder. 20 g of fine kernel powder added to 200 ml of cold distilled water to prepare slurry. The slurry obtained was poured into 800 ml of boiling distilled water and boiled for 20 min on a water bath to obtain a clear solution which must be kept aside overnight. The thin clear solution was then centrifuged at 5000 rpm for 20 min to separate all the foreign matter. Supernatant liquid was separated and poured into excess of absolute alcohol with continuous stirring. Precipitate obtained were collected by a suitable method and washed with 200 ml of absolute ethanol and dried at 50°C for 10 h.

Evaluation tests for TSP

Table :1Identification test for TSP[6]

TEST	OBSERVATION	REFERENCE
MOLISHTEST:(100 mg dried mucilage powder + Molisch'reagent+conc.H2SO4 on the side of a test tube)	Violet green colour observed at the junction of the two layers	Carbohydrate present
RUTHENIUM: Take a small quantityof dried mucilage powder, mount it on a slide with ruthenium red solution, and observe it under microscope.	Pink colour is observed	Mucilage present
IODINETEST: 100mg dried mucilage powder +1 ml 0.2 N iodine solution.	No colour observed in Solution	Polysaccharides present (starch is absent)
Enzyme test:: dissolve 100 mg dried mucilage powder in 20ml-distilledwater; add0.5mlof benzidine in alcohol (90%) Shake and allow to stand for few minutes	No blue colour produced	Enzyme absent (Distinction between dried mucilage and acacia)

Organoleptic characters of TSP:
The organoleptic characters of the polymer such as colour, odour, taste, shape e.t.c .are shown in Table no:2.

Solubility:
Solubility of the polymer in different solventswere studied and the results are shown in Table no :3

Swelling index:
One gram of TSP powder (#100 mesh passed) was accurately weighed and transferred to a 100ml stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100 ml mark with distilled water. The cylinder was Stoppered, shaken gently and set aside for 24 h.The volume occupied by the gum sediment was noted after 24 h. The results are shown in Table no:4

Microbiological test:
Tamarind seed is natural extract the scope for microorganisms is high. TSP is added to the inoculums of bacterial(Agar) and fungal medium(Sabouraud agar)along with micro organism with anti microbial(Na meta bisulphate) of various concs0.02%,0.05%,0.1%agent by pour plate method and incubated at 37^0c and 25^0c.The same above process is done without a microbiological agent as controls. There was no microbial growth in 0.1%con of Sodium Meta bisulphate.

IR-spectra[7]:
The pure drug, and combination of drug with polymer were mixed separately with IR grade KBr in ratio of 100:1 and corresponding pellets were prepared by applying 7.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400 cm-1.The IR spectrum forTSP,alfuzocinHCl and combinations are shown in following figure no: 1, 2,3

Preparation of transdermal films:
The matrix type transdermal films are prepared by solvent casting method. The desired concentrations of polymer solution was taken along with drug solution and other excipients were triturated in mortar and pestle and poured in

a petri dish and allowed to dry in hot air oven at 60^0c for 24 hours and the formulae for the films is shown in Table no.8.

Transdermal films have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types[8,9,10,11]

Evaluation of transdermsl films:
Physicochemical evaluation
Thickness:
The thickness of transdermal film is determined by screw gauge at different points of the film.

Uniformity of weight:
Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination:
An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Moisture content:
The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24h.The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following equation.

$$\%MOISTURECONTENT = \frac{initialweight}{finalweight} * 100$$

Percentage moisture loss:
The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula:

% Moisture Loss = (initial weight –final weight)/initial weight*100

Folding Endurance:
Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

% Flatness:
A transdermal film should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100

%FLATNESS=(L2-L1)/L1*100
I2 = Final length of each strip
I1 = Initial length of each strip

Water vapour transmission rate[9]:
Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm^2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

$$\%wvt = \frac{(final\ weight - initialweight)}{area * time} * 100$$

In-vitro diffusion studies[10,11]: The prepared transdermal films are evaluated for the diffusion studies by placing dialysis set up .The donor component containing the film along with diffusion membrane which are tied to the funnel, placed in the beaker containing pH 7.4 phosphate buffer of volume 50ml which acts as a receptor medium. The magnetic bead is placed in the beaker and the medium is maintained at 37±0.5^{0}c. The 1ml sample was removed at regular intervals of time and equal volume is replaced with buffer.

RESULTS AND DISCUSSION

Characterisation of polymer:

The identification tests for the polymer are shown in the Table.1. The results confirmed that the extracted substance is found to be possessing the polysaccharide characteristics.

Organoleptic characterisation of polymer

Table no: 2 Organoleptic characteristics

PARAMETER	TAMARIND SEED EXTRACT
Colour	Cream
Odour	Odourless
Taste	Tasteless
Shape	Irregular
Touch and Texture	Hard and rough

Table no:3 solubility studies

SOLVENT	SOLUBILITY PARAMETER
Cold Water	Sparingly soluble
Warm water	Quickly soluble forms colloidal solution
Acetone	Insoluble
Methanol	Insoluble
Ethanol	Insoluble
Ethanol	Insoluble

Table no: 4 Swelling index

TIME(hr)	Water(SI%)	Buffer(SI%)
1	20	20
2	30	30
4	40	30
24	50	40

IR SPECTRUM ANALYSIS:

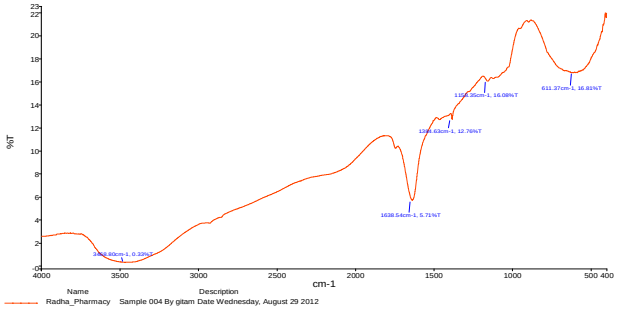

Figure no:1 IR-spectrum for TSP

Table no : 5 functional group analysis of TSP

GROUP	WAVE LENGTH
C=O	1638.54CM-1
C-H	1384.63CM-1
0H	3468.80CM-1

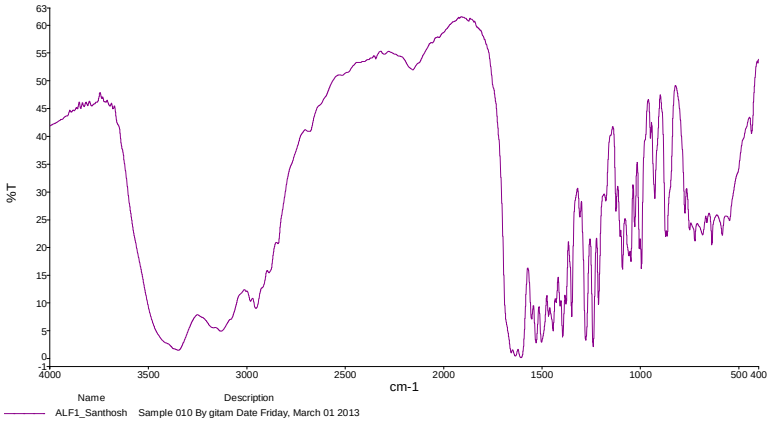

Figure:2 IR- Spectrum of AlfuzocinHCl.

Table no: 6 Functional group analysis of pure drug

GROUP	WAVENUMBER(cm^{-1})
R-NH_2	3348.88
R-NH-R	3131.3
C=O	1656
C-O-C	1552.97
CH_2bending	1466.86,1443.51
C-O	995.06
C-O-H	1394.83

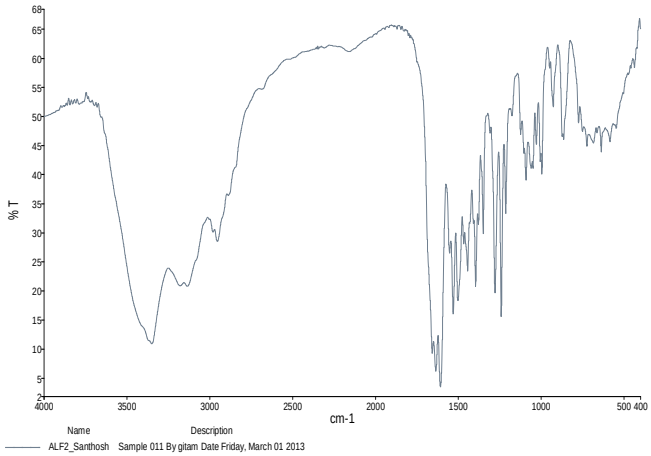

Figure:3 IR Spectrum for combination of AlfuzocinHCl : Tamarindpolymer

Table no: 7 functional group analysis of AlfuzocinHCL : TSP

GROUP	WAVENUMBER(cm^{-1})
R-NH_2	3349.61
R-NH-R	3134.44
C=O	1656.42
C-O-C	1552.5
CH_2bending	1466.72,1443.51.
C-O	995.62
C-O-H	1378.11

Table no: 8 FORMULATION TABLE

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Tamarind(mg)	500	600	700	800	500	600	700	800
% Propylene Glycol	5	5	5	5	5	5	5	5
% Span 20	3	3	3	3	5	5	5	5
%Sodium meta bisulphate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
AlfuzocinHCl(mg)	5	5	5	5	5	5	5	5
Water	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml

Table no:9 Evaluation test for transdermal films

Formulation code	Thickness	Weight (mg)	Constriction(%)	folding endurance	Moisture loss(%)
F1	0.23±0.01	780 ±5	2.9±0.4	135±8	2.56±0.24
F2	0.26±0.01	810±5.2	1.4±0.2	165±7	3.7±0.3
F3	0.27±0.01	920 ±5.7	4.4±1.0	210±5	4.34±0.2
F4	0.29±0.01	970 ±6	1.4±0.3	225±8	5.15±0.4
F5	0.22±0.01	830 ±8	1.4±0.2	132±5	3.61±0.6
F6	0.24±0.01	890±8.4	0±0.1	158±8	4.7±0.4
F7	0.26±0.01	970 ±9	2.9±0.7	206±7	5.15±0.10
F8	0.30±0.01	1240±10	1.4±0.5	218±9	11.2±1.2

Table no:10Evaluation test for transdermal films

Formulation code	%moisture content	%Watervapourtransmission rate (wvt)	% Drug content
F1	102.63 ±1.09	0.11±0.2	40
F2	103.84±1.07	0.10±0.01	60
F3	104.45±1.06	0.09±0.02	70
F4	105.75±1.05	0.08±0.01	70
F5	103.70±1.03	0.10±0.02	94
F6	104.43±1.04	0.09±0.01	60
F7	105.19±1.03	0.09±0.01	80
F8	112.72±1.07	0.08±0.01	40

Table no:12 Correlation coefficient 'r'values in the analysis of release data of transdermal films as per various kinetic models

FORMULATION	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSMEYER – PEPPAS	n VALUE
F1	0.955	0.970	0.901	0.903	1.01
F2	0.865	0.900	0939	0.949	0.5
F3	0.919	0.833	0.812	0.688	0.2
F4	0.816	0.925	0.888	0.932	0.1
F5	0.994	0.952	0.949	0.981	1.3
F6	0.957	0.952	0.930	0.895	0.2
F7	0.978	0.962	0.917	0.989	1.3
F8	0.979	0.963	0.921	0.935	1.6

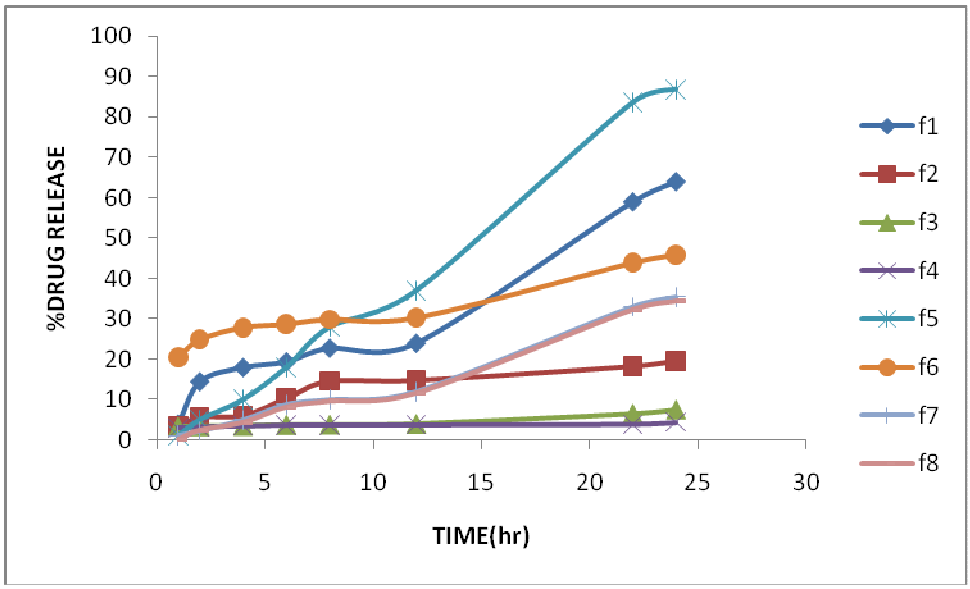

Figure:4 Release profiles of the formulations F1-F8

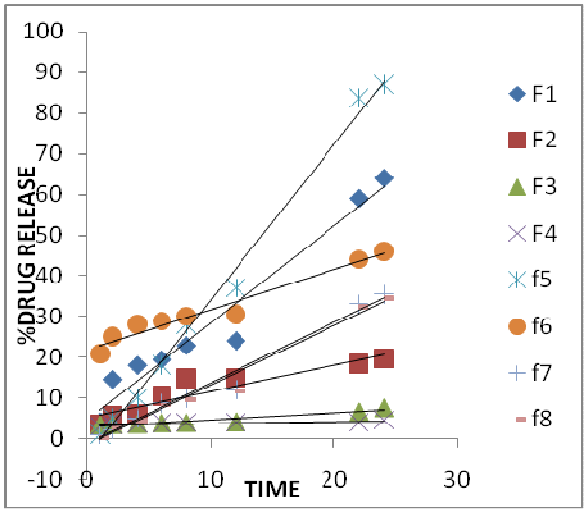

Figure no:4 Zero order plot

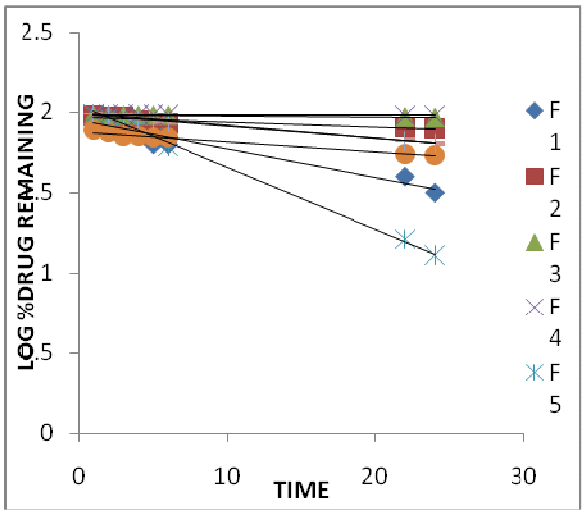

Figure no:5 First order plot

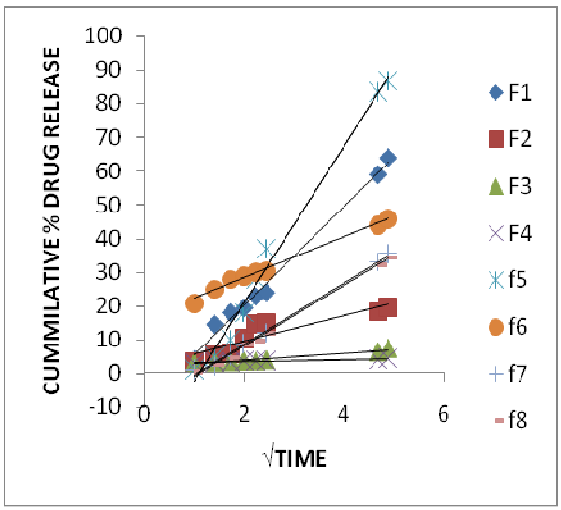

Figure no:6 Higuchi plot

TSP isolated and its characterisation was confirmed by the Molish test, iodine test, ruthenium test, andenzyme test and found to be slowly soluble in water.TSPalsohaving swellingindexabout50%inwaterand40%inbuffer. FTIR spectra shows no interaction of the drug with thepolymer. Transdermal films wereprepared b y using solvent casting method for alfuzocin Hcl. Formulations(F1toF4) containingTSP with 3% penetrating enhancer, and (f5 to f8) with 5% penetrating agent. The prepared films were evaluated and thickness ranges from 0.23±0.01mm to 0.30±0.01mm.weight of a films were found to be between 780 ±5mg to 1240±10mg. It was found that as con of polymer increased the weight of the film also increases. Folding endurance was found between 132±5 to 225±8**.**As the conc of polymer increase the folding endurance of the films also increased. The flatness of the film is found to be between 0±0.1% to 4.4±1.0% of constriction.0% constriction indicates 100% flatness. The moisture loss is between2.56±0.24 to 11.2±1.2%.As the conc of polymer increased the moisture loss also increased as the loss is low indicating stability of films which prevents from brittle during storage.The moisture content is found to be between102.63 ±1.09% to 112.72±1.07%.As the con of polymer increased the moisture content is also found to be increased up to small content. The % wvt is between0.08±0.01% to 0.11±0.2%. As the con of the polymer increased the rate of % wvt is decreased. The drug content is found to be between 40% to 94%.Thediffusionstudywascarried outbyusingthedialysissetupanditisobservedf1andf5having good releasing behaviour. As the con of the polymer increased the release rate was decreased .i.e. from formulationf1 t of4 itis found to be decrease in drug release amount due to increase in polymercon. The role of penetrating enhancer is to enhance the rate of release. Comparing the formulationf1,f2,f3,f4and f5, f6, f7, f8 the rate of release has been increased as the penetrating enhancer increased. Based on the correlation coefficient values it was found that formulations F3,F5,F6,F7,F8 following zero order drug release and formulations F1, F2, F4 are following the first order drug release. The regression values of the all the formulations in Higuchi equation was found to be > 0.812 indicating that drug release was diffusion controlled. As per the Peppas equation the release exponent 'n' value < 0.5 for formulationsF2, F3, F4 and F6 shows Fickian diffusion and remaining all formulations 'n' value > 1 shows supercase transport II.

CONCLUSION

The transdermal films are prepared for the drug AlfuzocinHCl with good controlled release by using the natural polymer tamarind seed polysaccharide extract. Based on drug release data the formulationf1and f5are having better release as most of the drug was released within 24 hrs compared too the formulations. The order of release is as followsf5>f1>f6>f7>f8>f2>f3>f4. In conclusion, the present data confirm the feasibility of developing transdermal films by using tamarind seed polysaccharide extract as film forming agentonan industrial scale.

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