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COMPARSION STUDIES ON TRANSDERMAL FILMS OF NATURAL TAMARIND SEED POLYSACCHARIDE EXTRACT CONTAINING ANTI HYPERTENSION DRUG WITH PVA ,HPMC AND GUAR GUM.

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ABSTRACT

Objective of the study: The present study was to compare the transdermal film property of the natural Tamarind seed polysaccharide extract with the synthetic and natural polymers like PVA, HPMC and Guar gum. The transdermal films prepared by solvent casting method using Tamarind seed polysaccharide (TSP) alone and combinations with other polymers and film properties are evaluated. The release property of various film forming agent in increasing order are TSP>PVA>guar gum>HPMC. **Conclusion:** Tamarind seed polysaccharide (TSP) combination has showed the drug retardant property. The order of drug release for different formulation is given as follows F2>F1>F8>F7>F14>F11>F6>F5>F4>F3>F13>F12>F9>F10. Formulated Transdermal Films evaluated for various physicochemical parameters and *in vitro* permeation studies. Transdermal drug delivery system (TDDS) facilitates delivery of therapeutically effective amount of drug across a patient's skin with controlled rate.

KEY WORDS: Tamarind seed polysaccharide (TSP), Retardant property, PVA, HPMC and Guar gum.

INTRODUCTION

Transdermal drug delivery system (TDDS) is topically administered dosage form in the form of patches which deliver drugs for systemic effects at a predetermined, which deliver a therapeutically effective amount of drug across a patient's skin and controlled rate. Excipient is consider to be the heart of the formulation either in solid, liquid ,semi liquid dosage form which modify the release pattern of the drug which is essential for the therapeutic activity. Excipients may be synthetic, semi synthetic and natural. Natural Excipient is preferred

compared to other as they are inexpensive, readily available, safe, non-toxic, accomplished of chemical modifications, potentially biodegradable, however they favour microbial growth. Polysaccharides are the interesting compounds which are hydrophilic in nature[1]. The various polysaccharides used in drug delivery application are cellulose ethers, xanthan gum, locust bean gum and guar gum[2]. Tamarind seed polysaccharide (TSP) which is obtained from the seed kernel of Tamarindus indica, Tamarindus indica belonging to family leguminacy. Chemical constituents of tamarind are tartaric acid, citric acid and malic acids and potassium bitartrate, pectin, gum etc., The hydrophilic nature of TSP is due to xyloglucan .Tamarind polymer in pharmacy is used for targeted drug delivery system as magnetic microspheres, colon targeting, capsule preparation, anti tumour, antiviral, mucoadhesive buccalpatch, antioxidant, flocculating agent[3].Dissolution improvement[4] used in novel drug delivery methods[5].

Transdermal drug delivery systems (patches) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin also defined as medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. In fact, transdermal drug delivery system is a transport process of drugs through a multi-laminar structure, e.g. from the film to Subcutaneous then to the viable epidermis and finally penetrating into the blood. 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 .

Drug Requirements for the Transdermal Route

When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery, where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.It can be used in combination with other enhancement strategies to produce synergistic effects.Dose should be <10mg/daily , low molecular weight. Drug Alfuzocin HCl is having low molecular weight(425.9) with a dose <10mg per day having a Halflife10hours, partition coefficient is about 1.51,undergoing hepatic metabolism all this factors provide suitable for the development of transdermal films.

MATERIALS AND METHODS

TSP was isolated in laboratory by using acetone.PVA, HPMCE5LV,Guargum from Loba Chemicals private limited, sodium meta bi sulphate from lobachem laboratory reagents and fine chemicals, acetone and span20 from moly chem. Reagents and fine chemicals, propeylen glycol from lobachem laboratory reagents and fine chemicals, NaOH and potassium di hydrogen phosphate from Merck Specialities Private Limited.

METHOD

Isolation of natural tamarind seed polysaccharide extract

Tamarind seeds must be soaked in distilled water and boiled for 5 h and separate the outer dark layer. Add sufficient amount of water to the inner white portion and boiled to obtain the slurry. Solution in refrigerator so that most of the undissolved portion settles down. The supernatant liquid can be separated out by centrifugation at 5 rpm for 20 min. After this, the solution is concentrated on a water bath at 60°C reduce the volume to one-third of its initial volume. Solution is to be cooled and poured into 3 volumes of acetone by continuous stirring. Precipitates obtained must be washed with acetone and dried in vacuum at 50-60°C[6].

Preparation of Transdermal films

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.

EVALUATION OF TRANSDERMAL FILMS[7,8]

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:

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 is dissolved in 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. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated. The percent moisture content is calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initialweight}}{\text{Finalweight}} * 100$$

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:

$$\%\text{Moisturecontent} = \frac{\text{Initalweight} - \text{Finalweight}}{\text{Finitalweight}} * 100$$

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.

$$.\%\text{Flatness} = \frac{L1-L2}{L1} * 100$$

L2 = Final length of each strip

L1 = Initial length of each strip

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.

Water vapour transmission rate

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 2.25cm^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.

$$\text{WVP}\% = \frac{\text{Final weight} - \text{Initialweight}}{(\text{Area} * \text{Time})} * 100$$

***In vitro* permeation studies**

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimetre square at each time interval is calculated. Design of system,

patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e. ,drug permeated per cm^2 per second

RESULTS AND DISCUSSION

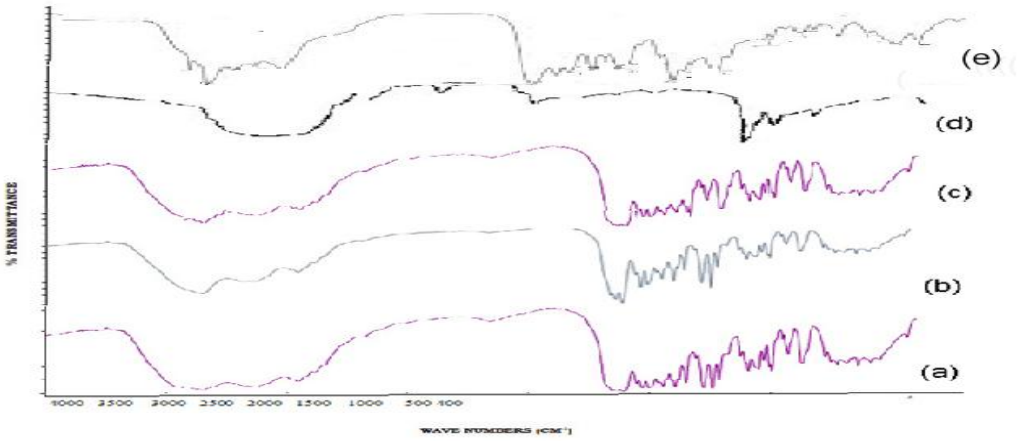

Fig.no 1:-FT-IR Spectra of (a)TSP ; (b)1:1 ratio of Drug,TSP (c) PVA (d) Guar Gum (e) HPMC E5 LV

Table.No:1-Formualtion of Transdermal films Using TSP, HPMC, PVA and Guar Gum.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
TSP(%)	5	5	-	-	-	-	-	-	2.5	2.5	2.5	2.5	2.5	2.5
HPMC E5 LV(%)	-	-	5	-	-	5	-	-	2.5	-	-	2.5	-	-
Guar gum(%)	-	-	-	5	-	-	5	-	-	2.5	-	-	2.5	-
PVA(%)	-	-	-	-	5	-	-	5	-	-	2.5	-	-	2.5
Propeyelen Glycol(%)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Span 20 (%)	3	5	3	3	3	5	5	5	3	3	3	5	5	5
Sodium metabi sulphate (%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Alfuzocin Hcl(mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Water(ml)	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Table no: 2: Evaluation of tamarind films

FORMULATION	Thickness (mm)	Weight (mg)	Constriction (%)	folding endurance	Moisture loss (%)	Drug content (%)	watervapour transmission (%)	Moisture content (%)
F1	0.23+0.01	780	2.9	135	2.56	94	0.11±0.2	102.63±1.09
F2	0.29+0.01	830	1.4	132	3.61	90	0.10±0.02	103.70±1.03
F3	0.28+0.01	910 ±4	2.9±0.3	26±3	2.16±0.2	60	0.11±0.02	105.27±1.05
F4	0.29+0.01	1000 ±8	32.8±0.9	43±4	5 ±0.5	60	0.08±0.01	103.07±1.09
F5	0.32+0.01	670 ±6	1.4±0.4	277±10	2.9 ± 0.4	70	0.10±0.02	103.07±1.08
F6	0.30+0.01	940 ±7	2.9±0.5	20±2	7.4 ±0.8	60	0.11±0.01	108.04±1.04
F7	0.33+0.01	1090±10	32.8±1.0	48±4	5.5 ±0.5	60	0.09±0.05	105.82±1.06
F8	0.27+0.01	790 ±9	0±0.2	244±8	7.5 ±0.7	70	0.11±0.01	109.72±1.07
F9	0.19+0.01	890 ±6	1.4±0.2	90±4	4.4 ±0.4	60	0.08±0.01	104.70±1.09
F10	0.28+ 0.01	880 ±7	2.9±0.4	181±5	4.7 ±0.8	60	0.01±0.001	104.76±1.16
F11	0.26+0.01	870 ±8	1.4±0.3	69±3	2.21±0.20	70	0.02±0.001	102.35±1.10
F12	0.24+0.01	960 ±7	1.4±0.2	85±7	5.2 ±0.4	60	0.09±0.001	105.49±1.13
F13	0.26+0.01	1080 ±9	2.9±0.3	176±10	6.4 ±0.5	60	0.02±0.001	106.93±1.21
F14	0.25+0.01	920 ±10	2.9±0.6	93±7	2.17±0.10	70	0.03±0.001	102.00±1.00

Table no:3 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	0.937	0.895	0.905	0.7
F2	0.994	0.952	0.945	0.988	1.3
F3	0.900	0.843	0.781	0.651	0.2
F4	0.833	0.848	0.924	0.969	0.2
F5	0.945	0.877	0.913	0.885	0.2
F6	0.990	0.967	0.907	0.907	0.4
F7	0.691	0.735	0.793	0.811	0.2
F8	0.917	0.930	0.911	0.885	0.3
F9	0.966	0.843	0.932	0.971	0.6
F10	0.932	0.418	0.824	0.742	0.2
F11	0.948	0.942	0.840	0.861	1.0
F12	0.966	0.843	0.891	0.914	0.6
F13	0.993	0.787	0.949	0.904	0.3
F14	0.964	0.944	0.885	0.951	0.7

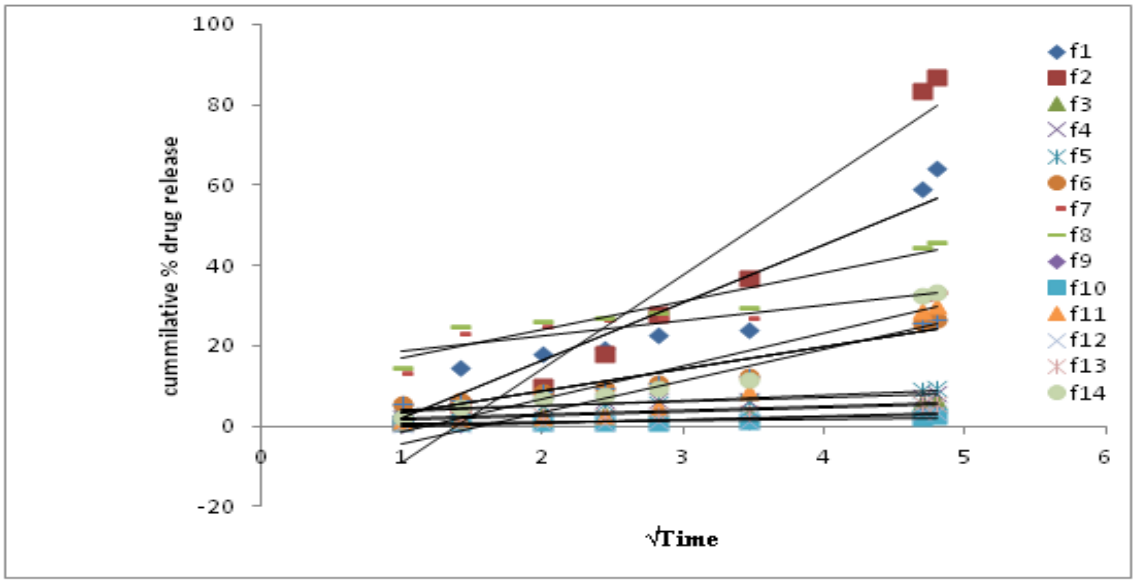

Fig.2: Dissolution plots of Various formulations from F1 to F14

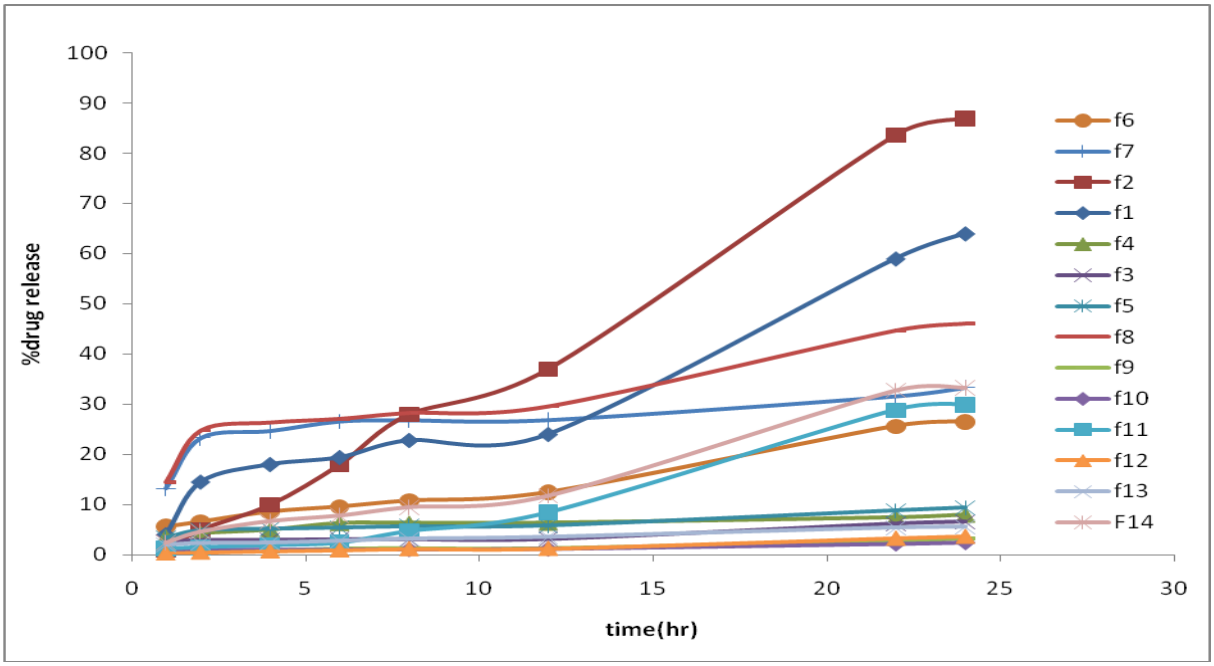

Fig.3: Dissolution plots of Various formulations from F1 to F14

CONCLUSION AND DISCUSSION

Tamarind seed polysaccharide is extracted and the 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.1 matrix type films .F1 to F8 Formulation containing alone polymers without any combination with varying amounts of penetrating agents 3%,5%.F9 t0 F14 containing mixed combination of polymer with varying amount of penetrating agent. The IR spectrum containing TSP and Alfuzocin HCL shows the comparability . The thickness of the film is found to be between 0.19±0.01mm to 0.33±0.01mm. the % of moisture loss is found to be between 7.5% to 2.17%. the weight of the films are found to be between 670mg to 1080mg .The folding endurance is found to be between 26 times to 277 times. The % of constriction is found to be between 0% to32.8%. Transdermal films are prepared by solvent casting method using TSP, PVA, HPMC, guargum alone and its combinations. The F2 formulation is the best out of fourteen formulation with 86%of drug release following zero order, first order ,higuchi, korsmeyer – peppas having the regression value(0.994, 0.952, 0.945,0.988) and the n value is about 1.3 seem to be following supercase-2.The release pattern TSP>PVA>guar gum>HPMC. TSP in combination has decreased the release in combination can be used as release retardant. The order of drug release for different formulation is given as follows F2>F1>F8>F7>F14>F11>F6>F5>F4>F3>F13>F12>F9>F10.

TSP as new novel excipient for formulation Transdermal films and will be feasible in pilot scale development.

Release Kinetics

The release pattern for the films and best fitting model is determined based on the correlation coefficient for various Transdermal films containing TSP, HPMC, PVA, Guargum alone and in the combination is shown in Table no 3.The release of drug is about 80% to 2.5% the n value is found to be between 0.2 to 1.3 .The percent of drug release in F2 formulation is found to be 86% following zero order, first order ,higuchi, korsmeyer – peppas having the regression value(0.994, 0.952, 0.945,0.988) and the n value is about 1.3 seem to be best fitting model. The release pattern of the films suggested that the release of drug from TSP>PVA>guar gum>HPMC, as the con of penetrating agent improved the diffusion of drug is also improved. the release rate in 5% is more than the 3% penetrating agent. The combination of TSP with the PVA, HPMC, guar gum the release rate is decreased compared to the individual formulation i.e. when they are formulated without the TSP both with 3% and 5% release. This indicates that the TSP can be used as the transdermal films alone or with combination of hydrophilic polymers which controls the release rate of drug and used for the prolonged or sustained release . The order of drug release for different formulation is given as follows F2>F1>F8>F7>F14>F11>F6>F5>F4>F3>F13>F12>F9>F10 .

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