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FORMULATION AND EVALUATION OF PHYLLANTHUS AMARUS TRANSDERMAL PATCHES FOR ANTI-DIABETIC ACTIVITY

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ABSTRACT

The leaves of Phyllanthus amarus, have been used in traditional medicine by many Asian, Middle Eastern and Far Eastern Countries to treat headache, coughs, abdominal pain, diarrhea, asthma, rheumatism and other diseases. The whole plant are the most extensively studied, both phytochemically and pharmacologically. The aqueous extracts of the leaves have been shown to possess antioxidant, anti-inflammatory, anticancer, anti-diabetic, analgesic and antimicrobial activities. In this study, Transdermal Patches containing Phyllanthus amarus were prepared by Solvent Casting Technique using two different polymers, Pectin and Sodium alginate in various ratios using Polyethylene Glycol 400, Glycerine as Permeation enhancer and plasticizer. The prepared patches were studied and optimized with respect to physicochemical characters, drug-excipient interaction, in-vitro dissolution, release kinetics studies. The combination of Pectin and Polyethylene Glycol produces smooth flexible films. The In-vitro Dissolution studies revealed that the cumulative amount of drug released was decreased as the polymer content of the film increased. Based on in-vitro drug release studies, P6 [PA-Pectin] was found to be better formulation with reliable physicochemical characteristics as it released a maximum amount of drug release 79.32% at 24 hours and followed zero order kinetics. It is concluded as the optimized formulation for effective drug delivery and produce sustained drug delivery.

KEYWORDS: Transdermal patches, Phyllanthus amarus, Pectin, Sodium alginate, Solvent Casting Technique, Franz Diffusion Cell, Anti-diabetic activity.

INTRODUCTION

Potential of Novel Drug Delivery for Herbal Drugs

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases.

Transdermal Drug Delivery for Herbal Drugs

In conventional medicine system the oral route is highly taken but does not give effective or desired effect because of systemic circulation, the first pass metabolism taken more time to get bioavailable or give therapeutic effect. So Transdermal drug delivery has made an important contribution to medical practice. It is a medicated patch that delivers a specific amount of medication through the skin into the blood stream. An advantage of a transdermal drug delivery route over other types of medication delivery is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.

Transdermal Drug Delivery System

Transdermal drug delivery system (TDDS patch) are self-contained discrete dosage forms that, when applied to the intact skin, are designed to deliver the drug through the skin at a controlled rate of the systemic circulation. TDDS (Transdermal Drug Delivery System) improve beneficial value and drug safety by further site definite the way and temporal position in the body's vital to reduce the number and size of doses necessary to achieve the objective of systemic medication through topical application to the intact skin surface. TDDS has abundant advantages more than usual drug delivery route. Transdermal route or therapy is non-invasive that includes lack of first pass metabolism effect, high bioavailability and steady drug plasma concentration.

The main principle of developing unconventional drug delivery technologies is to offer more convenience for patients and increase the effectiveness and protection of drug.

Transdermal Patches

"A Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a predetermined rate over a period of several hours to days into the blood stream after application to the skin". Today the most common transdermal system present in the market mainly based on semipermeable membranes which were called as patches. Transdermal Drug Delivery System (TDDS), also known as "Transdermal patches"

MATERIALS AND METHODS

Materials

List of Reagents and Chemicals : Phyllanthus amarus, Pectin, Sodium Alginate, Polyethylene Glycol 400, Glycerine , Ethanol

List of Equipments: Electronic balance, Digital pH meter, Soxhlet Apparatus, Rotary Evaporator, Dessicator, Digital Vernier Caliper, Fourier transform infrared spectrometer, Magnetic stirrer, UV Spectrophotometer.

METHODS

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of drugs substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be man produced. The following Preformulation studies are carried out, Collection and Extraction of Phyllanthus amarus plant, finding the absorption maxima, physical appearance, solubility, standard curve, infrared spectroscopy studies (compatibility studies), standard UV Data of Phyllanthus amarus Plant Extract.

Drug compatibility studies

The physical stability of the excipient with drug extract has to be determined. The drug extract is mixed with the components used in the formulation in 1:1 ratio. These sample mixture is then placed in two closed containers each at room temperature 25±1℃ and accelerated temperatures 45±1℃ for 4 weeks. The mixture were then observed for any specific changes by visual observations.

Development of Transdermal Patch

Transdermal patches of all batches were prepared by Solvent Casting Method using aqueous extract of Phyllanthus amarus with two different polymer in six different ratios (1:0.25, 1:0.5, 1:0.75, 1:1, 1:1.25 & 1:1.5). Weighed quantity of polymer was dissolved in calculated quantity of water and heated on a water bath. Calculated amount of Phyllanthus amarus extract was added to the above mixture and stirred well until a homogenous mixture was formed. Then calculated amount of PEG 400 was added as a plasticizer. Glycerin was added as a permeation enhancer. After mixing, the drug and polymer solution was allowed to stand for 15 min to remove air bubbles and the resulting solution was poured into a petridish and air dried at room temperature in a dust free environment for 24hrs. An inverted funnel was covered over the petridish to enhance the evaporation of the solvent. The patches were then peeled off from the petridish with the help of a knife and packed in an aluminium foil and kept in desiccator.

RESULTS AND DISCUSSION

In-vitro Drug Release Studies

In-vitro drug release study of the prepared Phyllanthus amarus Transdermal patches was carried out using dialysis Franz Diffusion Cell. Amount of drug released in different time intervals were observed. In-vitro drug release profile data of Phyllanthus amarus Transdermal patches containing Pectin (P1- P6), Sodium alginate (S1-S6) are given in table.

Transdermal patches of Phyllanthus amarus were taken for In-vitro Release study. The formulation **P6** has a release of **79.32%** at **24 hours**. So, in accordance with the Physicochemical Evaluation and In-vitro Release studies, the formulation **P6** may be concluded as optimized formulation for effective drug delivery.

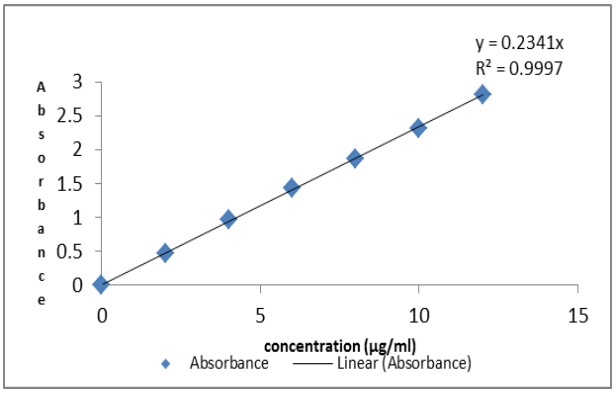

Fig. 1: Calibration Curve of Phyllanthus Amarus Plant Extract in UV Spectroscopy.

Table 1: Composition of Phyllanthus amarus Transdermal Patches with Pectin.

Formulation Code	Phyllanthus amarus (Pa) Extract (in ml)	Pectin (in g)	PEG 400 (in ml)	Glycerin (in ml)	Water
P1	2	0.39	1	1	q.s
P2	2	0.79	1	1	q.s
P3	2	1.18	1	1	q.s
P4	2	1.58	1	1	q.s
P5	2	1.97	1	1	q.s
P6	2	2.37	1	1	q.s

Table 2: Composition of Phyllanthus amarus Transdermal Patches with Sodium alginate.

Formulation Code	Phyllanthus amarus (Pa) Extract (in ml)	Sodium Alginate (SA) (in g)	PEG 400 (in ml)	Glycerin (in ml)	Water
S1	2	0.39	1	1	q.s
S2	2	0.79	1	1	q.s
S3	2	1.18	1	1	q.s
S4	2	1.58	1	1	q.s
S5	2	1.97	1	1	q.s
S6	2	2.37	1	1	q.s

Table 3: In-vitro drug release profile of Phyllanthus amarus Transdermal patches (P1- P6).

S.No.	Time (hrs)	Cumulative percentage drug release (%)					
		P1	P2	P3	P4	P5	P6
1.	0	0	**0**	0	0	0	**0**
2.	1	6.78	4.2	3.6	2.83	2.55	**1.87**
3.	2	12.31	10.6	8.56	4.78	5.83	**3.95**
4.	3	17.21	15.65	12.89	5.64	9.65	**5.23**
5.	4	25.89	24.96	18.56	8.15	11.26	**6.98**
6.	5	31.1	30.54	26.45	12.45	20.38	**8.53**
7.	6	35.54	34.34	31.53	19.82	25.46	**12.32**
8.	7	40.68	38.75	35.46	22.38	30.25	**18.03**
9.	8	45.7	43.23	42.41	28.48	34.5	**23.54**
10	10	51.77	49.58	47.23	38.73	40.26	**40.01**
11.	12	62.1	55.25	52.36	49.24	50.89	**48.43**
12.	18	78.38	73.46	70.86	67.28	69.87	**61.24**
13.	24	97.68	93.52	89.21	86.25	82.52	**79.32**

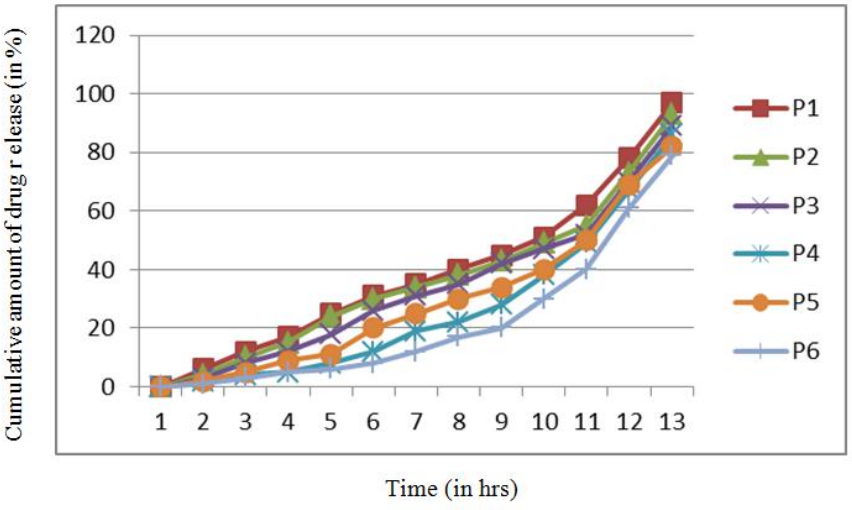

Fig 2: In-vitro drug release profile of Phyllanthus amarus Transdermal patches (P1- P6).

Table 4: In-vitro drug release profile of Phyllanthus amarus Transdermal patches (S1- S6).

S.No.	Time (hrs)	Cumulative percentage drug release (%)					
		S1	S2	S3	S4	S5	S6
1.	0	0	0	0	0	**0**	**0**
2.	1	10.92	9.23	8.14	7.56	4.48	**3.98**
3.	2	13.95	12.32	11.04	10.23	8.98	**4.78**
4.	3	17.86	15.26	14.42	13.26	11.21	**5.64**
5.	4	22.89	20.45	19.86	16.89	14.96	**7.15**
6.	5	30.98	27.32	25.24	21.96	20.54	**11.45**
7.	6	41.04	36.43	32.99	28.54	25.34	**14.82**
8.	7	47.68	44.12	42.52	32.95	29.45	**19.38**
9.	8	55.25	50.65	47.01	38.97	34.23	**25.48**
10	10	64.67	63.73	57.65	49.52	44.58	**37.73**
11.	12	70.21	68.34	67.63	57.46	52.25	**49.24**
12.	18	80.71	78.52	75.71	72.32	69.89	**67.28**
13.	24	96.24	92.12	86.84	83.45	75.37	**70.87**

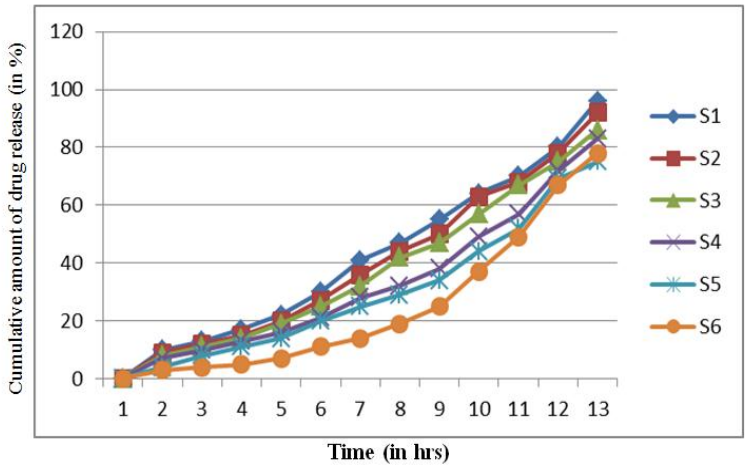

Fig. 3: In-vitro drug release profile of Phyllanthus amarus Transdermal patches (S1- S6).

Table 5: In-vitro Drug Release kinetics values.

S. No.	Formulation code	Time (in hrs)	Sq.root of Time	Log Time	Cumulative % Drug release	Log Cumulative % Drug Release
1.	**P6**	0	0	-	0	-
2.		1	1	0	1.87	0.27184
3.		2	1.414	0.3010	3.95	0.59659
4.		3	1.732	0.4771	5.23	0.71850
5.		4	2	0.6020	6.98	0.84385
6.		5	2.236	0.6989	8.53	0.93094
7.		6	2.449	0.7781	12.32	1.09061
8.		7	2.645	0.8450	18.03	1.25599
9.		8	2.828	0.9030	23.54	1.37180
10.		10	3.162	1.000	40.01	1.60216
11.		12	3.464	1.0791	48.43	1.68511
12.		18	4.242	1.2552	61.24	1.78703
13.		24	4.898	1.3802	79.32	1.89938

SUMMARY AND CONCLUSION

Main objective of this study was to formulate 2 different polymer batches P (P1, P2, P3, P4, P5, P6) and S (S1, S2, S3, S4, S5, S6) of Ethanolic extract of Phyllanthus amarus transdermal patches by Solvent Casting Technique using Pectin and Sodium alginate respectively as polymer to target diabetic cells and release the drug in a controlled manner. Preformulation studies were carried out with various formulation parameters. Drug- Polymer ratios and permeation enhancers were optimized to get thin, transparent, smooth, stable and high permeable transdermal patches. The FTIR graphs of drug,

excipients and formulations showed that there is no extra peak or broadening of peaks were observed and thus it indicates that there is no incompatibility between drug and excipients. UV spectra gave the maximum absorption peak at 664 nm.All the batches were evaluated for Percentage Moisture uptake, Percentage Moisture content, Thickness, Folding Endurance, Percentage Drug content, Flatness, Surface pH, Percent Elongation, Tensile strength and Adhesive strength. **P6** is selected as an optimized formulation by the evaluation parameters and in-vitro diffusion release, showed **79.32 % at the end of 24 Hours**. From the results of weight uniformity and thickness, it can be inferred that all the formulations exhibited uniform weight and thickness. This indicates that the polymeric solution of the drug is well dispersed in patches.It follows zero order kinetics and also follows Higuchi's and Korsmeyer - Peppas model as release mechanism. The Phyllanthus amarus transdermal patches can be formulated by cost effective Solvent Casting method using Pectin as polymer. The formulated Phyllanthus amarus transdermal patches can be used in the treatment of different types of diabetics.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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