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"FORMULATION AND IN-VITRO EVALUATION OF TRIAMTERENE TRANSDERMAL PATCHES"

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ABSTRACT

Triamterene (2,4,7-triamino-6-phenylpteridine) is an antihypertensive drug used for the management of hypertension[31-32] and also for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and the nephritic syndrome; also in steroid induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism.

Triamterene is commercially available in the form of capsules, after oral administration the drug, it undergo first pass metabolism which leads to poor bioavailability i.e. 30%[34]. The poor Bioavailability of the drug can be improved by designing a new/ novel drug delivery system and designing of transdermal drug delivery system is one among them.

In the present research work, we have prepared transdermal patches of triamterene with an objective of improved bioavailability by bypassing pre-systemic metabolism and as a result it improves therapeutic efficacy of the drug. Transdermal patches released the drug in a controlled manner for longer period of time which intern reduces the frequency of dosing which improves the patient compliance.

Keywords: Transdermal patches, controlled delivery, drug-in-adhesive patches, specific dose, transdermal delivery.

INTRODUCTION

INTRODUCTION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Management of illness through medication has entered an era of rapid growth. Today there are a host of drugs from combination virtually every condition known to man and variety of means by which these drugs are delivered to the human body for therapy such as tablets, capsules, injections, aerosols, creams, ointments, suppositories, liquids, etc. often referred as conventional drug formulations.

The disadvantages of this kind of therapy are:

Drug concentration in the body follows a peak and through profile leading to greater chances of adverse effects or therapeutic failure.Therapy is insufficient and costly since large amounts of drug are lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdose[1].In response to these advances, several transdermal drug delivery system have been developed to achieve the objective of systemic medication through application on the intact skin.

One of the solution developed is transdermal drug delivery systems, which can deliver

medicine via the skin portal to systemic circulation at predetermined rate and maintain clinically effective concentration over a prolonged period of time.

This route of drug administration avoids the hazards and discomforts associated with parenteral therapy, and improve patient compliance, as it is easy to apply a patch.The bioavailability of the drug increases as variation in absorption when it is taken orally and its first-pass metabolism by the liver is avoided[3].Continuous intravenous infusion at a programmed rate has been recognized as a superior mode of drug delivery not only to bypass the hepatic first-pass elimination, but also to maintain a constant prolonged, and therapeutically effective drug level in the body.

However, such a mode of drug delivery contains certain risk and therefore necessitate hospitalization of patients and close medical supervision of medication. Recently, there have been increasing awareness that the benefits of intravenous drug infusion can be closely duplicated without its potential hazards, by continuous transdermal drug administration through intact skin.

MATERIALS AND METHODS

Method

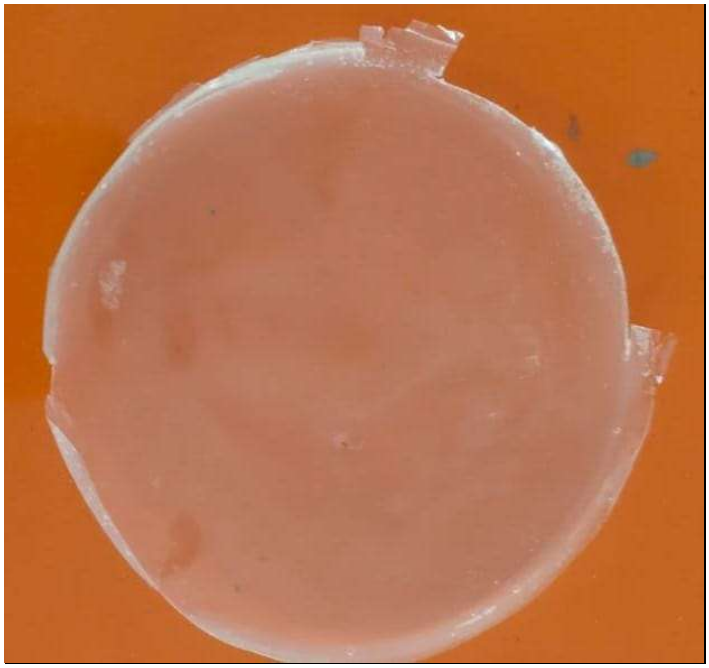
Accurately weighed quantities of HPMC, HEC and EC were soaked in the 1/3rd of water for 24 hours. Calculated quantity Plasticizer was added to the soaked solution, then the resultant mixture was poured into 9.3 cm petridish. The polymeric solution was dried at 37°C for 24 hours and the dried polymeric patches are cut into 1.5x2.5 sq.cm rectangular films. The transdermal patches were also prepared using the combination of polymer such as HPMC and HEC following the same procedure.

Preparation of triamterene polymeric patches:

Based on the physical observation of the blank patches, totally 9 formulations out of 15 were selected to incorporate drug triamterene. The polymers HPMC and HEC alone and in combination were used to prepare triamterene transdermal patches. Accurately weighed quantities of HPMC, HEC were soaked in the 1/3rd of water for 24 hours. Calculated quantity Plasticizer and drug were added to the soaked solution, then the resultant mixture was poured into 9.3 cm petridish. The polymeric solution was dried at 37°C for 24 hours, the dried polymeric patches are cut into 1.5x2.5 sq.cm rectangular films. The formulation details of triamterene transdermal patches is shown in the following table no-4.

SL.NO.	MATERIALS	Batch No.	SOURCES
1	Triamterene	TCI/GH 01	Yarrow chem, Mumbai
2	HPMC	E02Z/0502/1103/13	SD Fine chemicals, Mumbai
3	HEC	SK21-0912	Loba Chemicals, Mumbai
4	EC	H10Z/0210/2108/13	SD Fine chemicals, Mumbai
5	Ethanol	SLC22-23	SD Fine chemicals, Mumbai
6	Propylene glycol	1P03-202203133	SD Fine chemicals, Mumbai
7	Glycerin	0411B1-RG-H1	SD Fine chemicals, Mumbai
8	Methanol	25.3561509	SD Fine chemicals, Mumbai

Figure-9 practically perfomed transdermal patch



RESULT AND DISCUSSION

The transdermal patches of triamterene prepared were evaluated for the following parameters:

1.Physical Appearance: It includes visual inspection of films and evaluation of texture by feel or touch.

2.Thickness uniformity: The thickness of the films was measured by using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at different spots of the patch and average was taken.

Formulation code	Thickness (nm)			Mean± SD
	I	II	III	
TTP_1	1.8	0.75	1.8	1.45 ±0.60
TTP_2	1.85	0.4	1.75	1.33 ±0.80
TTP_3	1.89	0.4	0.75	1.01 ±0.77
TTP_4	1.1	0.65	1.15	0.96 ±0.27
TTP_5	1.15	0.75	1	0.96 ±0.20
TTP_6	0.98	0.6	0.9	0.82 ±0.20
TTP_7	1.2	0.95	1.9	1.35 ±0.49
TTP_8	1.6	0.6	0.95	1.05 ±0.50
TTP_9	0.7	0.92	0.95	0.85 ±0.13

3. Weight Variation: Three films were taken from each batch and their individual weights were determined by using electronic balance

Formulation code	Weight Variation (gm)			Mean± SD
	I	II	III	
TTP_1	0.078	0.077	0.055	0.07±0.013
TTP_2	0.106	0.084	0.114	0.101±0.015
TTP_3	0.082	0.065	0.094	0.080±0.014
TTP_4	0.071	0.095	0.049	0.071±0.023
TTP_5	0.114	0.169	0.120	0.134±0.030
TTP_6	0.053	0.097	0.046	0.065±0.027
TTP_7	0.175	0.163	0.162	0.166±7.23
TTP_8	0.152	0.062	0.072	0.095±0.049
TTP_9	0.102	0.130	0.152	0.128±0.025

4.Folding Endurance: The flexibility of the transdermal patch can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patch was determined by repeatedly folding a small strip of patch (approximately 2x2 cm) at the same place till it broke. The number of time patch could be folded at the same place with breaking gives the value of folding endurance.

Formulation code	Folding endurance			Mean± SD
	I	II	III	
TTP_1	79.00	78.00	78.00	78.33± 0.58
TTP_2	77.00	77.00	77.00	77.00± 0.00
TTP_3	78.00	79.00	78.00	78.33±0.58
TTP_4	78.00	78.00	78.00	77.67±0.58
TTP_5	79.00	79.00	77.00	78.33±1.15
TTP_6	75.00	76.00	76.00	75.77±0.58
TTP_7	77.00	76.00	77.00	76.67±0.58
TTP_8	78.00	78.00	76.00	77.33±1.15
TTP_9	77.00	76.00	77.00	76.67±0.58

7.Drug Content uniformity studies: This study was carried out to know the uniform and complete dispersion of drug throughout the formulation. In this test, three films were used and each patch was dissolved in methanol and volume was adjusted to 50 ml. Aliquots were taken and measured for the drug content at 365 nm against methanol as blank using UV-spectrophotometer.

Formulation code	Drug content (%)			Mean± SD
	I	II	III	
TTP_1	101.94	91.66	96.80	96.8±5.14
TTP_2	94.29	99.4	91.80	95.16±3.87
TTP_3	96.80	91.80	92.91	93.83±2.62
TTP_4	81.52	96.80	91.66	89.99±7.77
TTP_5	94.29	84.16	99.4	92.61±7.75
TTP_6	92.91	99.4	86.6	92.97±6.40
TTP_7	99.4	81.52	91.80	90.90±8.97
TTP_8	94.29	84.16	91.80	90.08±5.27
TTP_9	92.91	81.52	86.6	87.01±5.70

8.Drug-Polymer Interaction: IR spectral analysis is one of the most important analytical tools in knowing drug-polymer interaction. IR spectral study was carried out using Perkin-Elmer Spectrophotometer by KBr-pellet method. In the development of transdermal drug delivery system, so many excipients are used as formulation additives for different purposes. The additive used must be inert and should not react chemically with the drug. This drug-polymer chemical interaction was assessed by number of techniques

A) Drug polymer interaction studies:

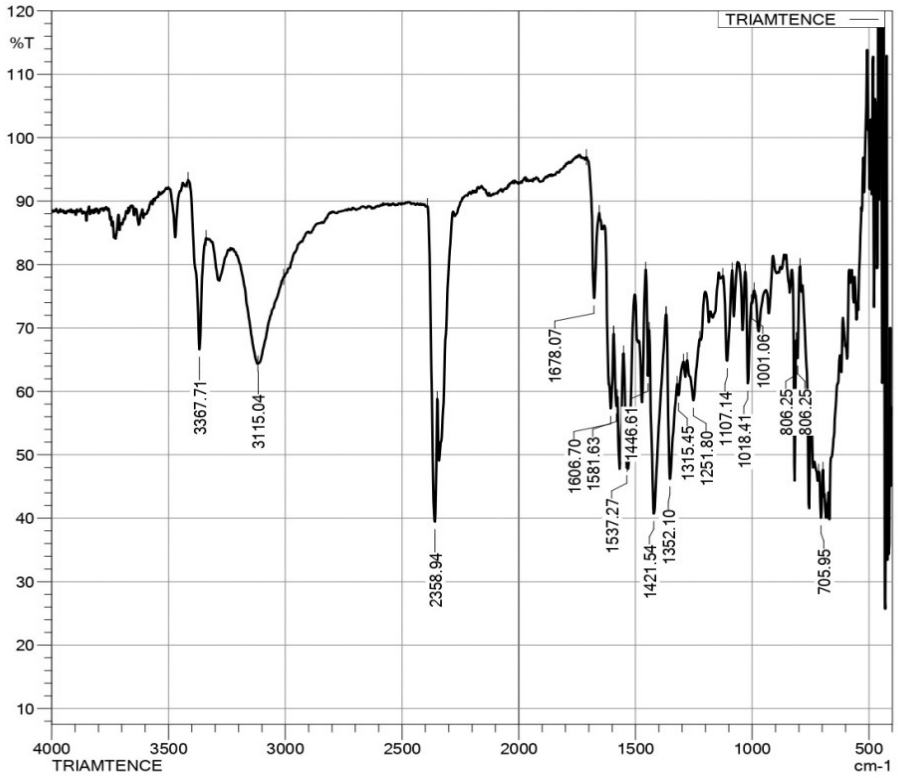


Figure.12: IR spectrum of Triamterene (pure drug)

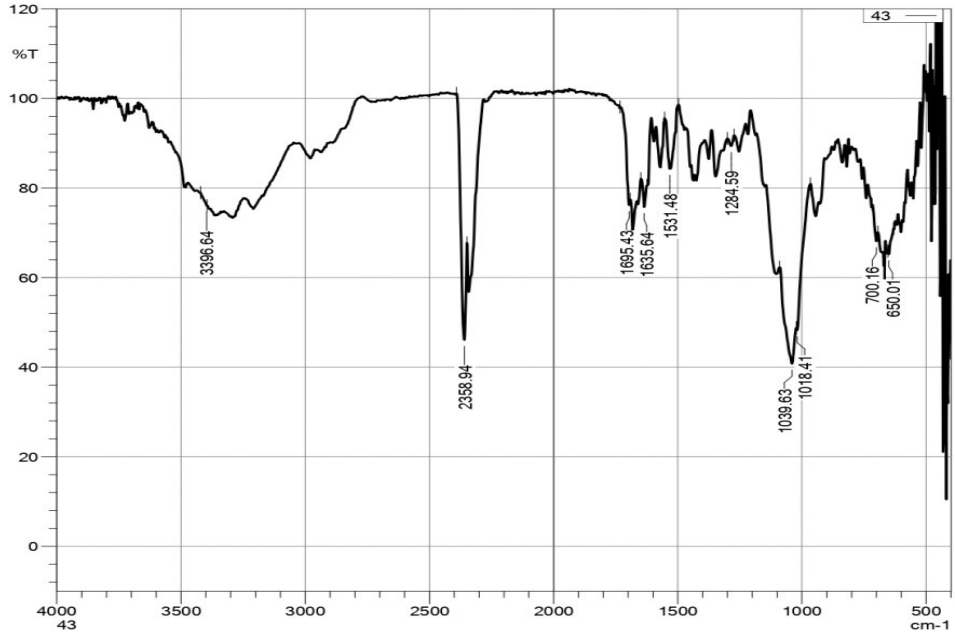


Figure.13: IR spectrum of Triamterene and HPMC

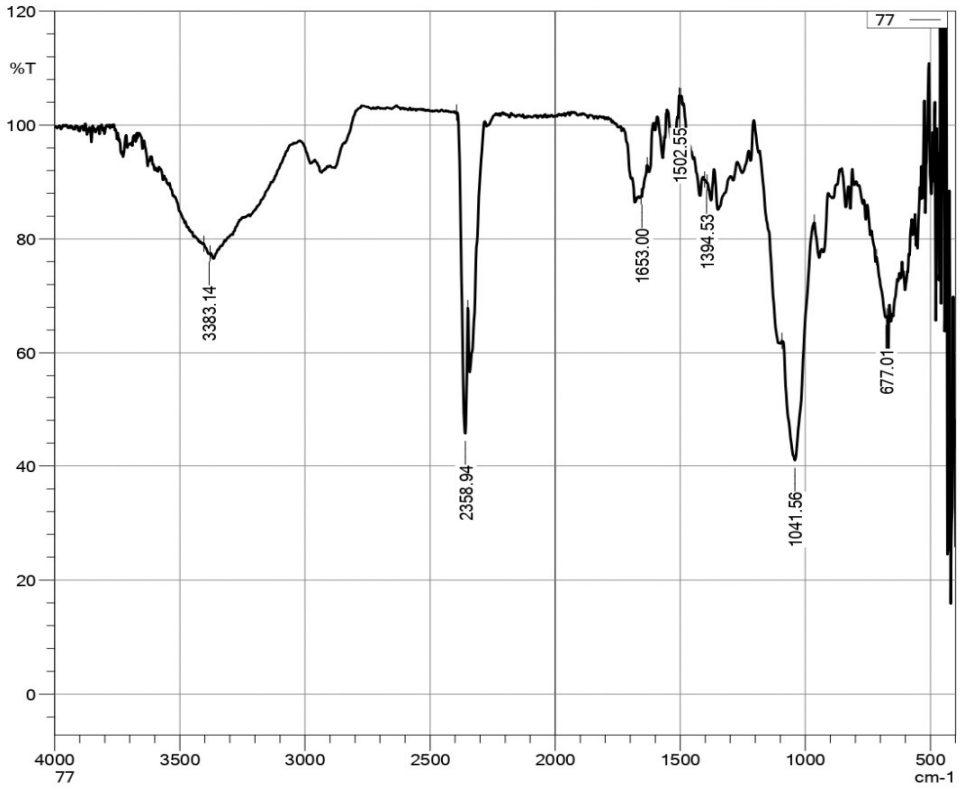


Figure.14: IR spectrum of Triamterene and combination of HPMC-HEC

9.in vitro drug release studies

The in vitro drug release from different transdermal patches were studied by using the classical standard cylindrical tube of 25 mm diameter using commercial semipermeable membrane. The membrane tied to one end of open cylinder and is acted as donor compartment. A transdermal patch was placed inside this donor compartment and this compartment it was in contact with the receptor compartment containing 250 ml 7.4 pH phosphate buffer. The content of the receptor compartment was stirred continuously using magnetic stirrer and temperature was maintained at 37+0.5°C.

Sample of 2 ml were withdrawn from the receptor compartment at periodic intervals and the same was replaced by equal volume of fresh buffer solution. The sample were analyzed for drug content spectrophotometrically at 365 nm against reference standard using pH 7.4 phosphate buffer as blank. The drug release was calculated with the help of standard calibration curve.

H) **IN-*VITRO* RELEASE DATA OF TRIAMTERENE PATCHES**

Table 13 – *In-vitro* Drug Release plots of Triamterene patch prepared using HPMC in the concentration of 4% (TTP1) 5%(TTP2) and 6% (TTP3) with propylene glycol (10%) as plasticizer.

Time (hr.)	Square Root	Log time	Cumulative % drug release ± SD			Amount of remaining			Log % drug release			Log % drug remaining		
			TTP1	TTP2	TTP3	TTP1	TTP2	TTP3	TTP1	TTP2	TTP3	TTP1	TTP2	TTP3

	of time													
00	0.000	0.000	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000	100	100	100	0.000	0.000	0.000	2.000	2.000	2.000
01	1.000	0.000	4.96± 1.15	5.23± 1.00	5.78± 2.00	95.04	94.77	94.22	0.6954	0.7185	0.7619	1.9779	1.9766	1.9741
02	1.4142	0.3010	10.74 ±1.00	9.37± 3.05	10.19 ±2.08	89.26	90.63	89.81	1.0310	0.9717	1.0081	1.9923	1.9572	1.9533
03	1.7321	0.4771	20.12 ±2.08	18.46 ±2.08	19.56 ±2.51	79.88	81.54	80.44	1.3036	1.2662	1.2913	1.9024	1.9113	1.9052
04	2.000	0.6021	29.76 ±3.05	27.28 ±1.52	28.11 ±3.00	70.24	722.72	71.89	1.4736	1.4358	1.4488	1.8465	1.8616	1.8566
05	2.2361	0.6990	35.83 ±1.52	35.00 ±2.08	36.10 ±3.51	64.17	65.00	63.9	1.5542	1.5440	1.5575	1.8073	1.8129	1.8055
06	2.4495	0.7782	44.37 ±1.06	43.27 ±2.08	44.09 ±1.52	55.63	56.73	55.91	1.6470	1.6361	1.6443	1.7453	1.7538	1.7474
07	2.6458	0.8451	53.47 ±3.05	50.98 ±3.00	53.47 ±2.08	46.53	49.02	46.53	1.7281	1.7073	1.7281	1.6677	1.6903	1.6677
08	2.8284	0.9031	64.21 ±3.21	62.84 ±3.00	64.77 ±4.72	35.79	37.16	35.23	1.8076	1.7982	1.8113	1.5537	1.5700	1.5469

CONCLUSION

In the present research work initially the blank polymeric patches we are prepared using HPMC, HEC and EC in different concentration and evaluated for the various parameters to select suitable polymer and its concentration to get a smooth , uniform and complete patch. From the preliminary observation of the blank polymeric patches finally hydroxy propyl methyl cellulose in three different concentrations i.e. 4, 5 and 6% w/v and HPMC-HEC in six different ratios were used to prepare triamterene transdermal patches.

Triamterene transdermal patches prepared were evaluated for various parameters such as thickness, weight variation, folding endurance, moisture uptake, moisture loss, drug content uniformity, drug polymer interaction, in-vitro drug release studies.

1.Thickness :- The results of thickness study reveals that the polymers HPMC and HEC in the said concentration able to produce transdermal patches by solvent casting technique. The results reveals that the patches prepared are uniform in thickness with a minimal SD value.

2.Weight Variation :- The results of weight variation test suggest that the patches prepared are weighing uniformly with a minimum.

3.Folding Endurance:- The patches prepared were subjected to folding endurance to check the integrity of the patch prepared. The results reveals that the patches possess a good integrity.
5.Drug content uniformity:- Triamterene transdermal patches prepared we are subjected to drug content uniformity studies to ascertain the uniform dispersion of the drug throughout the patch the results of the study reveals that the drug triamterene is uniformly dispersed throughout the patch (lower SD value) in all formulations.
6.Drug polymeric interaction studies:- Triamterene transdermal patches prepared using HPMC and HEC were subjected to IR spectral analysis to check any chemical interaction of the polymer with the drug. The IR spectral analysis shows that the characteristic peaks of the drug triamterene are retained in the patches also. It suggest that there is no chemical interaction of the drug with the polymer in developing transdermal patches.
7. *In-vitro* drug release studies:- Finally triamterene transdermal patches were subjected to in-vitro drug release studies for a period of 8 hours. The various patches prepared released the drug in the range of 60.08±3.05 to 67.25± 2.51

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