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Preparation of Diazipam Delayed Release Patch, for Anxiolytic Treatment

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Subject: Pharmaceutics

Abstract

Transdermal drug delivery systems are becoming more popular in the field of advance pharmaceutics.There are many types of TDDS in the modern pharmaceutics ,but the most attractive type for research is transdermal patches. The present study was carried out to develop matrix type transdermal patches containing Diazepam with Propylene glycol 10% is used as plasticizer and it can be act as chemical enhancer & Ethanol 10% is used as permeation enhancer. The adheser is used HPMC or EC which are most common . The possible drug(API) and polymer interactions were studied by FTIR studies and solubility of the ingredients in inert solvent. Designed transdermal patches were evaluated with regard to physicochemical characteristics.formulated patches were thoroughly studied for in-vitro permeation and stability.All data is convert in the form of graphs. All the formulated patches showed good physical stability.The sustain release action is determined by the dissolution study. The in-vitro permeation studies were performed using Franz diffusion cell.

Keywords: *Diazepam, Transdermal patches, Permeation enhancer, in-vitro permeation study, dissolution study, plasticizer*

Introduction

Transdermal drug delivery system1 [6] (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined & controlled rate. Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate release of medicaments, it, ease of termination, long duration of action and avoids hepatic metabolism.

Study has been carried out to provide an anxiolytic drug in Transdermal patches. The main objective is to evaluate the feasibility of controlled delivery of therapeutically effective amount of drug in matrix type drug delivery system. TDDS is become more popular now a days, the major penetration pathway of drug molecules through the stratum corneum of impact human skin is by diffusing through lipid envelopes of the skin cell. Diazepam possesses anxiolytic, skeletal muscle relaxant, amnestic anticonvulsant, hypnotic,and sedative properties.[7] The pharmacological action of diazepam enhances the effect of the neurotransmitter GABA by binding to the benzodiazepine site on the $GABA_A$ receptor (via the constituent chlorine atom) leading to central nervous system depression.[8]

Materials and Methods

Below are the materials used in the research: Diazepam, Ethanol, Propylene Glycol, Glycerol, EC, HPMC, KH2PO4, NaOH,Water

Equipment used for the reaearch: Franz Diffusion Cell, Magnetic Stirrer (Remi equipments Ltd., Vasai), UV/VIS Spectrophotometer, pH Meter (Hanna instruments, Italy) FTIR, Vernier caliper, Beaker , Dissolution apparatus

Reagents Preparation

Phosphate buffer [9] pH 7.4:

Place 50ml 0.2M KH2PO4 in 200ml volumetric flask and add 39.5 ml of 0.21M NaOH and then add distilled water to make up the volume.

Preparation of Standard Curve:

Diazepam is estimated by measuring the absorbance at 235nm. The standard curve of diazepam is prepared in phosphate buffer pH 7.4 and the standardization fellowed by Beers law.

Preformulation Studies of the drug:

The solubility10 of the selected drug was determined in distilled water, phosphate buffer of pH 7.4, methanol and chloroform. The partition coefficient7 was performed using n-octanol as oil phase and

phosphate buffer pH 7.4 as aqueous phase. FTIR8 by using FT-IR (Perkin-elmer 1600 series USA), and solubility in inert solvent obtained to know the possible interaction of drug and polymer.

Fabrication of Transdermal Patches:
Patches were casted on a glass or SS mould by solvent casting method. Five types of polymer patches were prepared. First two formulations were prepared by using HPMC and EC separate with 5% mix enhancer. Enhencer were ethanol and Propylene glycol. combination of enhancer were 10%. Next one formulations were prepared by using HPMC and EC in combination having drug and polymer using methanol,propylene glycol with ratio of 15%.Last two formulations were produced by the combination of HPMC and EC and combination of chemical enhancer with water.

Evaluation of Transdermal Patches11- 14

Physico-Chemical Evaluation
Thickness of the patch:
Thickness of the patch is measured from different points by using Screw Gauge in mm.

Water Vapour Absorption %15:
The films of 3.15 cm2 area were measured and weighed and then placed in a desiccator at 70% RH by using saturated potassium bromide solution. The films were taken out and weighed every day for a weak of storage.

Water Vapour Transmission %16:
The WVT % was calculated by using the following formula WVT = WL / S Where W is water vapour transmitted in g, L is thickness of film in cm and S is exposed surface area in cm2.

Drug content uniformity:
Patch is cut into required pieces and put these pieces into 100 ml dissolution or diffusion medium used respectively in which all drug is soluble in specific time and stirred continuously using a mechanical stirrer and the sample is withdrawn at the end of four hours and the drug content is determined spectrophotometrically at 235 nm.

Skin sensitivity test:
The skin sensitivity test was done on a healthy rabbit weighing between 2 to 2.5 kg. Drug intact polymeric film of 3.15 sq cms was placed on the left dorsal surface of the rabbit. The patch was removed after 24 hours with the help of alcohol swab. The skin was examined for irritation.

Stability studies :(Accelerated study)
All the films were exposed to two selected temperatures of 45°C and 70% RH in stability chamber. Transdermal films were kept in stability chamber for period of 4 weeks. The films were analyzed for the drug content at the end of every week. The averages of triplicate readings were taken.

In-vitro Diffusion Study:
The in-vitro diffusion study is carried out by using Franz Diffusion Cell (Ponmani & Co, Coimbatore).semi permeable membrane is used for diffusion. The Franz diffusion cell has two compartment ,one is receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.15 sq.cms.other compartment is donor . The semi permeable membrane is installed between the donor and the receptor compartment. A weighed amount of Transdermal patch is placed on one side of membrane. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket to maintain the temperature at 37 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The samples withdrawn are analyzed spectrophotometrically at 235 nm. The drug which is released note and draw a curve.

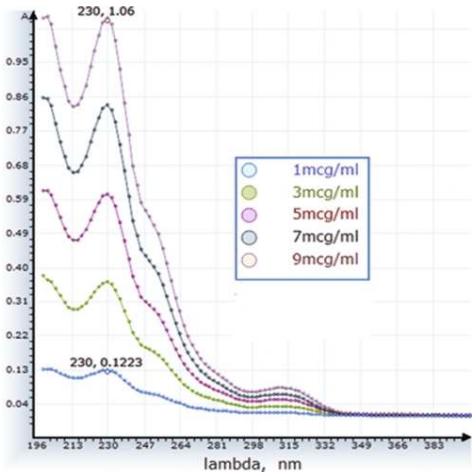
Table 1: formulation composition for 2000mg mixture

Formulation	Diazepam	HPMC (polymer)	EC	Propylene glycol 3-10% (enhancer)	Ethanol 3-10% (enhancer)	Water
D1	100mg	1600mg		100mg	100mg	
D2	100mg		1600mg	100mg	100mg	
D3	100mg	800mg	800mg	100mg	200ml	
D4	100mg	1000mg	600mg	50mg	50mg	100ml
D5	100mg	1200mg	400mg	100mg	50mg	50ml

Results

Table No: 2 Standard curve of diazepam in phosphate buffer pH 7.4.17

Sr no	mcg/ml	Absorbance
1	0mcg	0.00
2	1mcg	0.122
3	3mcg	0.391
4	5mcg	0.612
5	7mcg	0.865
6	9mcg	1.06



Compatibility Study:
The drug was identified and compatibility was confirmed by FTIR.

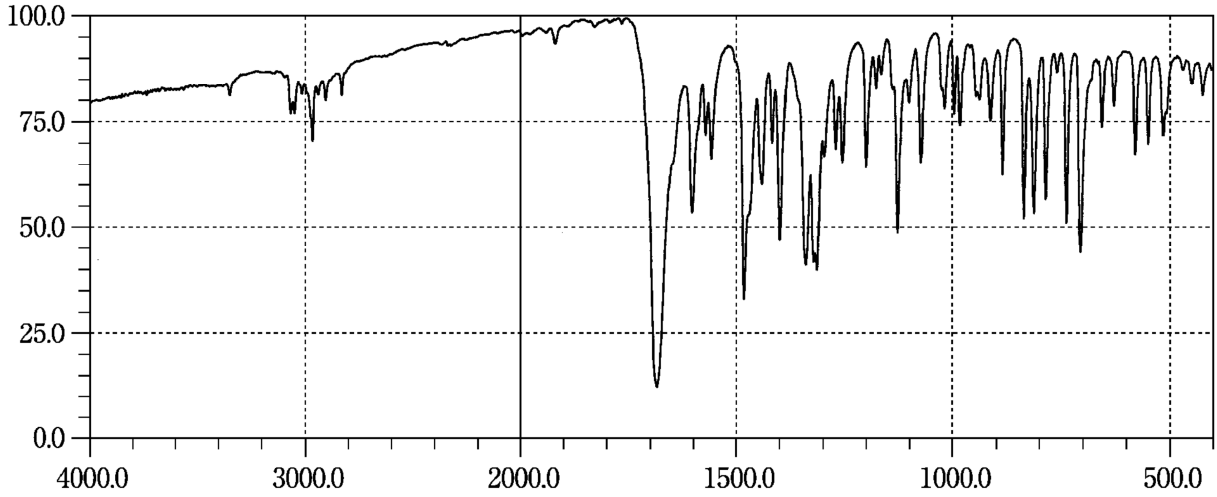


Table No: 3 Physico-chemical evaluations data of diazepam Transdermal patches.

Formulation	Thickness (mm)	Physical appearance	Weight (mg)	Moisture absorbed	Moisture lost
D1	0.250	++	198.26	2.34	1.45
D2	0.292	++	207.92	2.89	1.78
D3	0.301	++	212.31	1.78	1.12
D4	0.354	++	254.61	2.67	1.31
D5	0.344	++	234.64	2.45	1.49

Table No 4: Drug Content Uniformity

Formulation	% of drug in 3.15 sq.cm			
	1	2	3	Mean
D1	95.93%	96.67%	98.56%	97.05%
D2	96.78%	94.78%	95.97%	95.84%
D3	91.90%	98.47%	94.78%	95.05%
D4	97.67%	92.68%	97.78%	96.04%
D5	98.58%	97.89%	93.89%	96.78%

Skin sensitivity Test:

Skin irritation test on rabbit showed no sign of skin reaction or sensitivity and erythema so the fabricated Transdermal patch was suitable for further studies.

Table No 5 In-Vitro diffusion studies of various formulations

Sr no	Time hr	D1 %	D2 %	D3 %	D4 %	D5 %
1	0	0	0	0	0	0
2	2	12.23	10.13	12.23	7.23	9.31
3	4	18.78	27.34	23.13	12.12	18.67
4	6	23.45	32.77	30.34	19.45	26.34
5	8	29.34	45.98	50.56	34.34	36.56
6	10	34.45	50.56	58.34	50.13	45.35
7	12	39.87	65.45	69.12	55.34	52.89
8	14	41.49	78.56	75.34	63.23	57.45
9	16	43.75	88.98	80.66	67.12	62.12
10	18	46.31			69.56	67.34
11	20	49.45			72.34	72.32
12	22	57.23			74.13	78.23
13	24	66.97			79.23	82.12

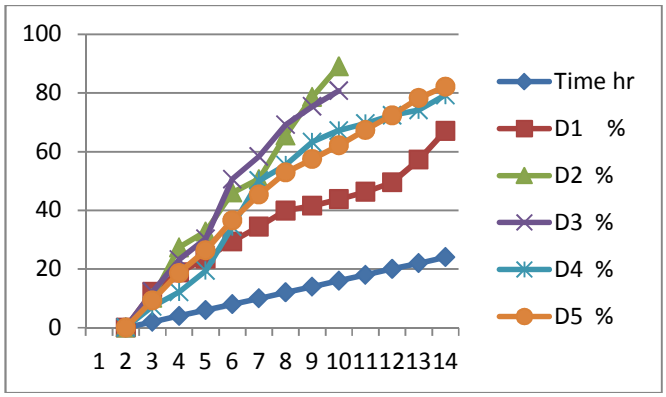


Table No: 6 Cumulative % and Kinetic Values obtained from different formulations

Formulation	Drug % in 24 h	Zero order plot Regression	1st order plot Regression	Higuchi order plot Regression
D4	82.12%	0.997	0.907	0.989
D5	79.23%	0.879	0.786	0.986

Discussion

The calibration curve of pure diazepam (fig no.1) was plotted with phosphate buffer pH 7.4. The compatibility between Drug and polymer was studied by using FTIR absorption spectra and check the solubility of the material used in the patch with inert solvent and check the crystallization and precipitation. The preliminary study conducted on compatibility between diazepam with HPMC and EC revealed that there is no interaction between the drug and polymer as from FTIR spectra and physically no interaction seen in the solution of the diazepam and

HPMC,EC, Ethanol and propylene glycol . The polymers are the important part of the Transdermal delivery system. The widely used polymers for the fabrication of Transdermal patches are Cross-linked polyethylene glycol (PEG) networks, Hydroxy Propyl Methyl Cellulose (HPMC), Acrylic-acid matrices, Ethyl cellulose (EC), , Organogels, Polyvinylpyrrolidine (PVP),Ethyl vinyl acetate (EVA) copolymers, and Chitosan etc. Among these polymers, HPMC and EC combination was selected for preparation of diazepam Patches. Since, HPMC is effective polymer as rate controlling for sustained release and HPMC also acts as stabilizing agent. Hence, it is commonly employed in formulation of patch. The physico-chemical characteristics
such as thickness of the patch, weight of the patch, percentage of moisture absorbed, percentage of moisture lost, and drug content analysis were found to be within the acceptable limits. The patches also contain ethanol which also act as preservative

Conclusion

The Fabricated Transdermal patch showed good controlled release properties. The results of the present study show that diazepam can be considered for Transdermal patch containing HPMC & EC as polymers & ethanol as permeation enhancer and propylene glycol plasticizer as well as chemical enhancer for controlled release of the drug over a period of 24 hrs for the management of anxiolytic. The Transdermal drug delivery system have a promising future in effective Transdermal delivery system. The combination of the chemical enhancer show effective permeation in the skin of diazepam.

"Cite this article"

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