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FORMULATION AND DEVELOPMENT OF TRANSDERMAL PATCH OF TIZANIDINE HYDROCHLORIDE

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ABSTRACT

Tizanidine Hydrochloride, is an centrally acting myotonolytic skeletal muscle relaxant. It undergoes first pass metabolism on oral administration resulting in less bioavailability (40%).Present research work was carried out to formulate and develop transdermal patch of Tizanidine hydrochloride which will overcome the limitation of bioavailability. In the present study transdermal patches were prepared by solvent-casting method using hydrophilic polymer HPMC E-5 LV, chitosan, *Moringa oleifera* gum and Propylene Glycol as plasticizer. The six formulations were prepared and evaluated. Accelerated stability studies of drug containing films, were performed according to ICH guidelines. It was found that, *Moringa oleifera* gum has potential to modify drug release rate and posses good film former and adhesive property. The transdermal patch has shown promising drug release within 12 hr (84.36%), good stability and no irritancy.

KEYWORDS

Tizanidine Hydrochloride, Transdermal patch and *Moringa oleifera* gum.

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INTRODUCTON

Today about two third of drugs (available in market) are taken orally, but these are not as effective as required[1]. Conventional oral dosage forms are required to be administered in multiple doses at a specific time interval in aspecific amount for an effective therapy. Administration of the drugs in multiple dosage has several drawbacks such as inconvenient administration, chances of overdose if administered prior to time interval, lack of patient compliance, skip of dose by the patient, fluctuation of drug plasma level, first pass metabolism, to avoid such complications transdermal drug delivery

systems are designed[2]. Transdermal therapeutic systems are self-contained, discrete dosage forms which, when applied to the intact skin deliver the drug, through the skin at a controlled rate to the systemic circulation[9]. Thus, it is anticipated that transdermal drug delivery system deliver drug at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port of entry of drug.

Tizanidine Hydrochloride, is an centrally acting myotonolytic skeletal muscle relaxant. It undergoes first pass metabolism on oral administration resulting in less bioavailability (40%) hence there is need to develop formulation to overcome limitation of bioavailability. Thus the main objective of the present study was to formulate and develop transdermal patch of tizanidine hydrochloride.

Anatomy of skin[3-7]

Human skin comprises of three distinct but mutually dependent tissues, the stratified, vascular, cellular epidermis, underlying dermis of connective tissues and Hypodermis.

Principles of transdermal permeation[7]

The various steps involved in transport of drug from patch into systemic circulation are as follows:

- Diffusion of drug from drug reservoir to the rate controlling membrane.
- Diffusion of drug from rate limiting membrane to stratum corneum.
- Sorption by stratum corneum and penetration through viable epidermis.
- Uptake of drug by capillary network in the dermal papillary layer.

Transdermal patches[8,9]

A transdermal patch is also known as skin patch which is used to deliver the specific amount of dose through skin and it directly goes into the blood stream.

MATERIAL AND METHODS

Material

Tizanidine Hydrochloride was gifted by Blue cross, Nashik. *Moringa oleifera* gum was naturally collected from stem of plant of *Moringa oleifera*. HydoxyPropyl Methyl Cellulose and Chitosan were purchased from local market.

Moringa oleifera gum

Collection and authentification

The *Moringa oleifera* tree was identified. The tree trunk was incised working from the base up towards the branches. The incisions were 10-15 mm long and 4-5 mm deep. The gum then started seeping out from the incisions and coagulated in 10-20 days. The gum was collected after drying and authenticated by Ayurved Seva Sangh's Ayurved Mahavidyalaya, Ganeshwadi, Panchvati, Nashik

Isolation and purification of gum

The dried gum was ground, and passed through sieve no 80 and (10 g) was stirred in distilled water (250 ml) for 6- 8 hr at room temperature. The supernatant was obtained by centrifugation. The washing of residue was done with water and the washings were added to separate supernatant. The procedure was repeated four more times. Finally the supernatant was made up to 500 ml and treated with twice the volume of acetone by continuous stirring. The precipitated material was washed with distilled water and dried at 50-60°C under vacuum.

Evaluation of *Moringa oleifera* gum

The gum was evaluated for loss on drying, pH determination, test for Tannin, test for Starch, test for Sucrose and fructose, Swelling power test as per official procedure in IP[12].

Compatibility Studies

A compatibility study for Tizanidine Hydrochloride was carried out with potential formulation excipients i.e.Chitosan, *Moringa oleifera* gum, PG and HPMC. These samples were mixed together as per formula, stored for 30 days at elevated temperature and humidity conditions of 40 ± 2 ^{0}C / 75 ± 5 % RH. After30days IR spectra of these stored samples was obtained.DSC was performed to check if any large shift of exothermic peak of drug in mixture. Mettler DSC 820 (SHIMADZU60).The assay of drug was performed using U.V. Spectrophotometer.

Formulation of Transdermal patch of Tizanidine Hydrochloride

The composition of Tizanidine Hydrochloride transdermal patches is given in Table No.1

Preparation of transdermal patches

Solvent casting technique

The transdermal patches prepared by solvent casting technique are of matrix diffusion controlled systems.

Procedure for patches containing Chitosan and HPMC

For (F1 to F3): The polymer was weighed and stirrerd in distilled water for 2 hrs. Then Propylene glycol was added to the polymeric solution, mixed thoroughly by means of Magnetic stirrer. Tizanidine Hydrochloride 6mg was added prior dissolving in sufficient of water then the resulting solution was poured in to petri plate. This petri plate were kept into hot air oven for 12hrs at 45° C, the patches were removed and stored in desiccator for further use.

Procedure for patches containing *Moringa oleifera* gum and HPMC

For (F4 to F6): The drug reservoir was prepared by dissolving *Moringa oleifera* gum and HPMC in distilled water. Propylene glycol and Tizanidine Hydrochloride6mg dissolved in sufficient amount of water was added under slow stirring. It was poured in petri plate. Which was kept in hot air oven for1 hrs at 45°c, and then the patches were removed and stored in desiccator.

Physicochemical evaluation of transdermal patches[11]

The transdermal patches were evaluated for.

Uniformity of weight

Three different patches from individual batch were weighed average weight was calculated.

Thickness of the patch

It was measured by usingvernier caliper at different points and average value was calculated.

Percentage Moisture loss

It was calculated for three different patches from individual batches by keeping them in desiccators containing calcium chloride at 37°c for 24 hrs.

Folding Endurance

This was determined by repeatedly folding one film at the same place till it broke.

Drug content determination

It was determined by cutting patch of size 1cm^2 diameter and dissolving it in Phosphate buffer of pH 7.4. The medium was stirred, filtered and analyzed for drug content at 318nm by UVspectrophotometeter.

***In-vitro* drug release studies**

Preparation of rat Abdominal Skin

The male rats were sacrificed by excess Diethyl ether inhalation and hair on the abdominal skin was removed with a razor. The shaved skin was excised from the animal and kept in the beaker containing distilled water covered with Aluminum foil.

In-vitro Drug Release

The fabricated film was placed on the rat skin and attached to the diffusion cell such that the cell's drug releasing surface was towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±10^{0}C. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UVspectrophotometer at 318 nm.

Kinetics of drug release

The cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log (Q0-Q) v/s t], Higuchi's square root of time (Q v/s t1/2) and KorsemeyerPeppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t.

Skin irritation study

The skin irritation study was conducted with prior permission of Institutional Animal Ethical committee (IPEC) under the purview of Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), on male Wistar rats. The dorsal side of rat was applied with hair remover cream, under anesthesia, 24 hr. before the beginning of experiment. The animals were divided into 4 groups. Each group was consisting of 5 rat: Group I served as control, Group II was applied 0.5 ml of a 0.8% V/V aqueous formalin solution topically as a standard irritant. Group III was applied with diclofenac transdermal patch as standard, Group IV was treated with medicated Patch. The application site was examined for edema

and erythema after 24 and 72 hr, and graded (0-4) according to visual scoring scale always by the same investigator, the final score represents the average of 24 and 72 hr. reading. The erythema scale was: 0- none, 1- slight, 2- well define, 3-moderate, 4- scare formation. Edema scale was: 0-none, 1- slight, 2- well define, 3-moderate, 4-severe.

Stability study for F4

Stability studies of formulation F4 was done as per ICH guidelines. In which the formulation was stored at 45^0c and 75%RH for 90daysand evaluated for physical changes, hardness, friability, drug content and percentage drug release.

RESULTS AND DISCUSSION

Evaluation of isolated and purified *Moringa oleifera* gum

The evaluation of *Moringa oleifera* gum was carried out, the evaluation test results are shown in Table No.2.

Drug-Polymers Interaction Studies

Infrared Spectroscopy

Drug-excipients interaction study showed no interaction between Tizanidine Hydrochloride and selected polymers as there was no significant shift of peaks in IR spectrum.

Differential Scanning Calorimetry

DSC analysis was performed by taking 2 to 5 mg sample. Results have shown that the sharp exothermisc peak was observed of the drug individually at 282^0C, corresponding to its melting point (282^0C -290^0C).Thus the Tizanidine Hydrochloride was found to be compatible with the selected excipients.

Evaluation of transdermal patches

Physical appearance

All patches from F1-F6 were found to be smooth in nature and had good appearance.

Weight Uniformity

The average weight and thickness of all the films is given in Table No.3.Weight variation values (mg) of different Tizanidine Hydrochloride films were found to be in the range of 625± 0.0247 to 734± 0.0433 mg.

Thickness

The average thickness of all the films is given in Table No.3 the average thickness of all the transdermal patch ranged from 0.99± 0.0212 to 2.36± 0.04716 mm.

% Moisture loss

The value of % moisture loss was found to be between0.99-2.36 for all formulations.

Drug content uniformity

Tizanidine HCl has shown maximum absorbance at 319nm in phosphate buffer pH7.4 hence percentage drug content was determined by UV spectrophotometer in phosphate buffer.

Folding endurance

The number of folding required to break or crack a film was taken as the folding endurance. The folding endurance was found to be increased with an increasing concentration of chitosan and *Moringa oleifera* gum.

***Ex Vivo* Drug Release Studies**

Ex Vivo skin permeation study shows a drug release profiles are shown in Figure No.1 and Figure No.2. And drug release was successfully observed for all patches. The drug release profile shown in Table No.4

Kinetics of Drug Release

The kinetic Drug release study was performed for all batches of transdermal patches. From this, drug release profile of optimised batch F4 is given below. The release data of formulation F4 was fitted into release rate equations such as zero-order, first order, Higuchi's square root time dependent diffusion and Korsmeyer-peppasexponential equation. It was found it follows Zero-order with diffusion controlled mechanism. By fitting in the Korsemeyer–Peppas equation the release kinetics follows Fickian and non-fickian kinetics. As the range of 'n'valueforKorsemeyer- Peppa's equation is 0.726.

h. Accelerated Stability Studies

In the results of stability studies performed on batch F4, after the 90 days, it was found that there was no change in appearance of the films and negligible change in thickness.

i.Skin irritation study

Skin irritation test was performed on Wistar Rats for F4 formulation and there were no signs of redness or erythma observed for 72hrs after application of patch[10].

Table No.1: Composition of Tizanidine Hydrochloride transdermal patches

S.No	Ingredients	Formulation code					
1		F1	F2	F3	F4	F5	F6
2	Tizanidine HCl(mg)	6	6	6	6	6	6
3	HPMC(mg)	200	200	200	200	200	200
4	Chitosan(mg)	30	75	120	-	-	-
5	*Moringa oleifera* gum	-	-	-	30	75	120
6	Propylene Glycol(ml)	0.5	0.5	0.5	0.5	0.5	0.5
7	Distilled water(ml)	10	10	10	10	10	10
8	Acetic acid(ml)	q.s	q.s	q.s	-	-	-

Table No.2: Evaluation of isolated and purified *Moringa oleifera* gum

S.No	TEST	OBSERVATION
1	pH	4.7(Acidic)
2	LOD	47.5%
3	Test for Tannin	Absent
4	Test for Starch	Absent
5	Test for Sucrose and Fructose	Absent
6	Swelling power	30.28 ml

Table No.3: Physicochemical evaluation parameters of Tizanidine Hydrochloride transdermal patch

FC	Weight Uniformity (mg)	Thickness[b] (mm)	% moisture loss	Drug content uniformity[b] (mg)	Folding endurance[b]
F1	633± 0.1071	0.260± 0.01	2.36± 0.04716	105.8 ± 7.07	152 ± 2
F2	634± 0.0240	0.271± 0.00854	1.466± 0.0387	109.5 ± 6.30	158 ± 1.595
F3	625± 0.0247	0.279± 0.0524	1.116± 0.1587	102.59 ± 8.70	165.3 ± 2.38
F4	664±0.00552	0.0733± 0.00067	2.25± 0.02	105.82 ± 4.85	208 ± 1.581
F5	697±0.01977	0.0783± 0.00735	1.286± 0.0360	110.33 ± 10.41	210.6 ± 2.310
F6	734± 0.0433	0.0887±0.00961	0.99± 0.0212	105.30 ± 8.847	217 ± 3.08

Table No.4: drug release profile of F1- F6 for *Ex Vivo* skin permeation study

S.No.	Timein hrs	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
1	2	17.63886	16.75943	15.37746	21.78474	18.26702	16.88506
2	4	28.51238	26.01543	22.32496	38.70435	27.33457	25.9055
3	6	40.59512	36.2922	32.53891	48.98112	43.15489	33.52827
4	8	50.76196	48.73613	45.72094	57.34199	55.41038	41.60647
5	10	65.04328	56.46884	55.46377	70.74387	68.60811	61.3057
6	12	83.98872	74.34639	70.98572	84.36562	77.59715	76.41934

Table No.5: Kinetic parameters of Tizanidine Hcl transdermal patch

FC	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	N
F1	0.987	0.977	0.987	0.987	0.85107887
F2	0.988	0.975	0.988	0.985	0.816341
F3	0.988	0.987	0.988	0.974	0.860057
F4	0.991	0.934	0.991	0.993	0.72679585
F5	0.994	0.955	0.994	0.988	0.840374
F6	0.963	0.990	0.963	0.956	0.820347

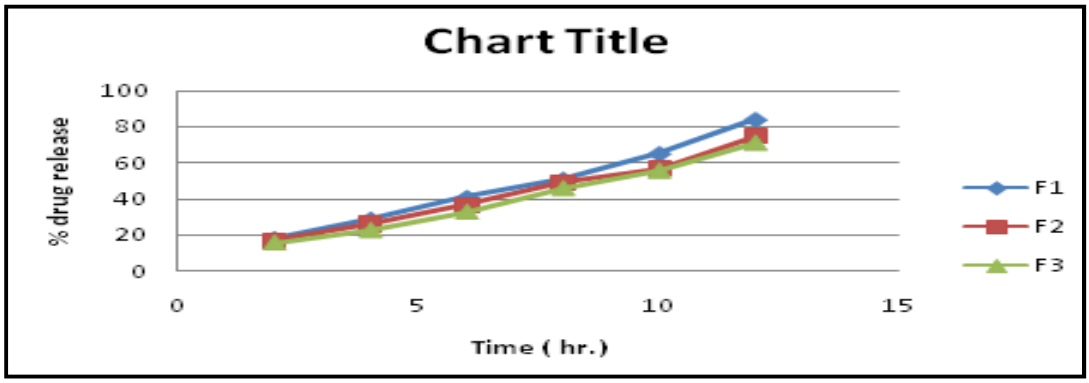

Figure No.1: Comparative *Ex Vivo* skin permeation study of F1 – F3 transdermal patches of Tizanidine Hydrochloride

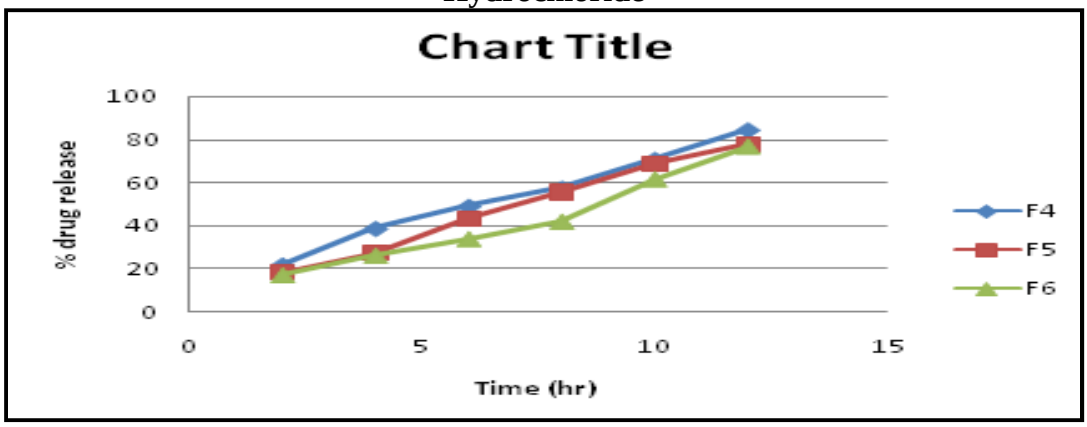

Figure No.2: Comparative *Ex Vivo* skin permeation study of F4 – F6 transdermal patches of Tizanidine Hydrochloride

CONCLUSION

The six formulations transdermal patches were prepared by solvent-casting method and evaluated for physical parameters along with *Ex vivo*skin permeation studies and skin irritation studies. It was found that, folding endurance was increased with an increase in chitosan and *Moringa oleifera* gum concentration. Optimized batch F4 showed good folding endurance i.e. 208. *Ex Vivo* skin permeation study has shown drug release 84.36% within 12 hr, It has shown no irritancy in skin irritation studies. There was no significant change in the physical parameters when stored at temperature and humidity conditions of 40 ± 2ºC / 75 ± 5% RH in stability studies carried out as per ICH guidelines.

Thus, *Moringa oleifera* gum has potential to modify drug release rate and posses good film former and adhesive property.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Sachan R, Bajpai M, Transdermal Drug Delivery System: A Review, *International Journal of Research and Development in Pharmacy and Life Sciences*, 3(1), 2013, 748-765.
2. Vikas C Jhawat, Vipin Saini, Sunil Kamboj, Nancy Maggon. Transdermal Drug Delivery System Approaches and Advancements in Drug Absorption through Skin", *Int. J. Pharm. Sci. Rev. Res.*, 20(1), 2013, 10, 47-56
3. Patel K and Patel H, Patel V. Formulation and Characterization of Drug in Adhesive Transdermal Patches of Diclofenac Acid, *International Journal of Pharmacy and Pharmaceutical Sciences*, 4(1), 2012, 296-299.
4. Popli H, Sharma S N. Drug delivery system, *Eastern Pharmacist*, 1990, 47.
5. Saini N, Bajaj A. Review Article Recent Trend on Transdermal Drug Delivery System and Advancements in Drug Delivery through Skin, *International Journal of Research in Pharmaceutical and Biosciences*, 4(1), 2014, 5-14.
6. Tortora G, Grabowski S, The Integumentary system. In: Principles of Anatomy and Physiology, *John Wiley and Sons Inc*, 9th Edition, 2006, 150-151.
7. Wilson K J, Waugh A, Ross and Wilson: Anatomy and Physiology in Health and Illness, *Churchill Livingstone*, 8th Edition, 1996, 360-366.
8. Sidharth M Patil, Muddasar G Bagawan. A Review: Transdermal Drug Delivery System – Basic Understanding for Development, *International Journal of Institutional Pharmacy and Life Sciences*, 3(6), 2013, 2249-6807.
9. Gazzi S, Chegonda K K, Chandrashekhara R G, Kumar B V and Prabhakar R Veerareddy. Formulation and Evaluation of Bioadhesive Buccal Drug Delivery of Tizanidine Hydrochloride Tablets, *American Association of Pharmaceutical Scientists PharmSciTech*, 10(2), 2009, 530-39.
10. Indian Pharmacopoeia, Government of India Ministry of Health and Family Welfare, *published by The Indian Pharmacopoeia Commission Ghaziabad*, 7th Edition, 3, 2014, 3228.
11. Mohd Amjad, Mohd Ehtheshamuddin, Chand S, Hanifa, Sabreesh M, Asia R and Kumar G S. Formulation and Evaluation of Transdermal Patches of Atenolol, *Advance Research in Pharmaceuticals and Biologicals*, 1(2), 2011, 109-19.
12. Draize J, Woodward G, Calvery H. Methods for the study of irritation and toxicity of the substances applied topicallyto the skin and mucous membrane, *J Pharmacol Exp Ther*, 82(3), 1994, 377-379.

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