International Journal of Scientific Research in Science and Technology
Print ISSN: 2395-6011 | Online ISSN: 2395-602X (www.ijsrst.com)
doi : https://doi.org/10.32628/IJSRST

Preparation, Evaluation and Characterization of Antihypertensive Drug for Matrix Transdermal Patches

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Article Info
Volume 9, Issue 3
Page Number : 140-147

Publication Issue
May-June-2022

Article History
Accepted : 01 May 2022
Published : 12 May 2022

ABSTRACT

Nicorandil belongs to the elegance of potassium channel activators, which exert their transfer through arterio-dilating and vasodilating properties and represents a unique form of compound for use withinside the treatment of angina pectoris. It has a short ½ of existence and the usual oral dosage routine is 5-40mg taken to 4 times a day. V G Jamakandi et al., employed solvent casting technique to formulate HPMC patches containing specific grades of HPMC polymer (6 cps, 15 cps and K4M) as matrix base, polyethylene glycol as plasticizer and DMSO as penetration enhancer. Prepared matrix type patches were evaluated for their physicochemical characterization followed through in-vitro and ex-vivo studies on porcine ear pores and skin. The quit end result shows transdermal patch with 6 cps 2% w/v HPMC,30% w/v PEG 400 and 6%w/v DMSO as a penetration enhancer showed a maximum release (44.7%) and it offers least resistance for the drug movement due to its immoderate hydrophilic nature and immoderate water permeability value to water. Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems .

Keywords : TDDS, Nicorandil , transdermal patch , PVA membrane, Skin permeation

I. INTRODUCTION

More current technique to drug transport is to supply the drug into systemic circulate at a predetermined rate that is referred to as controlled release drug transport system. Such structures helped to conquer the aspect results related to traditional system of medication, which require multidose therapy [1, 2.]The improvement of technology for release of drug at controlled rate into systemic circulate the use of pores and skin as port of access has end up famous for numerous reasons [3].Transdermal drug transport system (TDDS) are adhesive drug containing System of described surface region that supplies predetermined quantity of drug to the intact pores and skin on the preprogrammed rate [4, 5]. The transdermal transport has received significance withinside the current years. The TDDS has ability benefits of keeping off hepatic first pass metabolism, keeping steady blood ranges for longer time period ensuing in a reduction of dosing frequency, progressed bioavailability, reduced gastrointestinal inflammation and advanced affected person compliance [6].

The advantages of the use of transdermal drug transport consist of advanced systemic bioavailability attributable to bypassing the primary hepatic metabolism. Variables because of oral management, which includes pH, the presence of meals or enzymes, and transit instances can all be eliminated.The intention withinside the improvement of latest transdermal drug transport system is to achieve a managed, predictable, and reproducible release of the drug into the blood move of the affected person. The transdermal system acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is managed through the tool in place of through the pores and skin, transport of the drug is greater reproducible, leading to smaller interand intrasubject versions due to the fact the drug release from the system may be managed appropriately than the permeability of the pores and skin.[1,2] . The relief of chest pain stays one of the number one goals withinside the control of sufferers with angina pectoris. Beta blockers, calcium antagonists, and nitrates are indicated and are broadly used for this purpose, however these types of agents have boundaries and are consequently now no longer a whole solution to the problem. Nicorandil belongs to the elegance of compounds referred to as potassium channel activators, which might be characterised through their arteriodilating and venodilating properties, and represents a unique form of compound to be used withinside the treatment of angina pectoris.[3] Nicorandil has a brief ½ of lifestyles and the standard oral dosage routine is 5–40 mg taken to 4 instances a day. To decrease the frequency of administration and to enhance affected person compliance, a once-every day matrix-type transdermal drug transport system (TDDS) of nicorandil is desirable.[4] The purpose of the prevailing observe is to formulate, represent, and compare nicorandil transdermal patches.Since the early 1980s, transdermal patch dosage form of transdermal therapeutic system (TTS) has been to be had commercially. Such a system gives lots of vast medical advantages over different traditional structures. Therefore the TTS is of specific medical importance for the prevention and long-time period treatment of persistent sicknesses like high blood pressure 7. Some of the antihypertensive pills have already been formulated and evaluated as transdermal patches however maximum of them nevertheless been unexplored. Transdermal components of antihypertensive drug is promising component in close to future.Mortality from coronary heart

sicknesses will increase dramatically with age. Hypertension is one of the important reasons of coronary heart ailment and, in current years, the age adjusted high blood pressure and hypertensive ailment demise rates were growing 8. Consequently, the prevention and treatment of high blood pressure is of essential social importance 9. Hypertension is described conventionally as a sustained growth in blood strain 140/90 mm Hg, a criterion that characterizes a collection of patients whose chance of high blood pressure-associated cardiovascular ailment is excessive sufficient to benefit clinical attention .

Preparation of the nicorandil transdermal patch

Nicorandil belongs to the elegance of potassium channel activators, which exert their movement through arterio-dilating and vasodilating properties and represents a singular kind of compound to be used withinside the treatment of angina pectoris. It has a brief ½ of lifestyles and the standard oral dosage routine is 5-40mg taken to 4 instances a day. V G Jamakandi et al., hired solvent casting approach to formulate HPMC patches containing unique grades of HPMC polymer (6 cps, 15 cps and K4M) as matrix base, polyethylene glycol as plasticizer and DMSO as penetration enhancer. Prepared matrix type patches had been evaluated for their physicochemical characterization accompanied through in-vitro and ex-vivo research on porcine ear pores and skin. The end result indicates transdermal patch with 6 cps 2% w/v HPMC,30% w/v PEG 400 and 6%w/v DMSO as a penetration enhancer confirmed a most release (44.7%) and it gives least resistance for the drug movement because of its excessive hydrophilic nature and excessive water permeability value to water 45

The solvent-casting approach[5] become used to formulate the HPMC patches containing extraordinary grades of HPMC polymer, poly ethylene glycol (PEG 400) as plasticizer, and nicorandil. The drug polymer (5 mg/ml) answer become transferred into a pitcher Petridish containing mercury. The petridish become then stored in an air circulate drier and maintained at a temperature of 45–50oC for 6 hours. Poly vinyl acetate (PVA) membrane become used because the backing membrane. One surface of the drug reservoir matrix become barely moistened with water and located towards the PVA membrane and allowed to dry at 45–50oC for 2 hours. The patches did now no longer endure a rate controlling membrane. This served as a matrix-type transdermal delivery system in table 1 .

Table 1 : Preparation of Nicorandil Transdermal patches

Formulation	Polymer (2%w/v)	Solvent system	Plasticizier PEG40 % w/v	Permeation enhancer DMSO w/v%w/v	Drug mg
NicHPMC1	HPMC 6CPS	8:2	30	-	5
NicHPMC2	HPMC25CPS	8:2	30	-	5
NicHPMC3	HPMCKHM	8:2	30	-	5
NicHPMC4	HPMC6CPS	8:2	30	6	5
NicHPMC5	HPMC15CPS	8:2	30	6	5
NicHPMC6	HPMCK4M	8:2	30	6	5

Characterization of the transdermal patches for Nicorandil

Physical appearance

All the transdermal patches had been visually inspected for color, clarity, flexibility, and smoothness. Folding persistence a strip of film (4 × 3 cm) become reduce calmly and again and again folded on the identical area until it broke. The variety of instances the film can be folded on the identical area with out breaking gave the value of the folding persistence.[12,13]

Thickness of the films

The thicknesses of the drug-loaded polymeric films had been measured at 5 extraordinary factors the use of a virtual micrometer (Mitutoyo, Japan).[13,14] The common and popular deviation of 5 readings had been calculated for every batch of the drugloaded films.

Weight uniformity

The films of various batches had been dried at 60oC for four hours earlier than testing. Five patches from every batch had been appropriately weighed in a virtual balance.[13] The common weight and the usual deviation values had been calculated from the character weights.

Percentage moisture uptake

The weighed movies had been stored in a desiccator at room temperature for 24 hours after which uncovered to 84% relative humidity the use of a saturated answer of potassium chloride.[15] Finally, the movies had been weighed and the percentage moisture uptake become calculated the use of the formula:

Percentage moisture uptake = [Final weight – Initial weight/Initial weight] × 100 (3)

Percentage moisture content material

The organized films had been weighed in my view and stored in a desiccator containing fused calcium chloride at room temperature for 24 hours.[15] The films had been once more weighed and the proportion moisture content material become calculated the use of the formula:

Percentage moisture content material = [Initial weight – Final weight/Final weight] × 100. (4)

Water vapor transmission

The film become constant over the glass vial with an adhesive containing 3 g of fused calcium chloride as a desiccant.[13] then, the vial become positioned in a desiccator containing saturated solution of potassium chloride (relative humidity 84%). The vial become taken out periodically and weighed.

Stability research

Stability research had been carried out in step with the International Conference on Harmonization (ICH) suggestions through storing the TDDS in a balance chamber (Thermo Lab., Mumbai, India).[2] The samples had been withdrawn at 0, 30, 60, and 90 days and the drug content material become analyzed through a UV spectrophotometer method.

II. EVALUATION OF TRANSDERMAL PATCH5

Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance affected individual compliance through delivering smaller amount of drug at a predetermined price. This makes evaluation studies even greater important in order to ensure their favored performance and reproducibility under the precise environmental conditions. These studies are predictive of transdermal dosage paperwork and can be categorised into following types:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

Skin irritation check

Skin irritation check grow to be finished on seven healthy albino rabbits weighing amongst 2.0 and three.5 kg.[2,13,16] Aqueous solution of formalin 0.8come used as the standard irritant. Drug-free polymeric patches of 4.874 cm2 have been used as check patches. Standard irritant grow to be carried out on the left dorsal ground of each rabbit and drug-free patches have been carried out on the right dorsal ground of the rabbit. The patches .have been removed after a period of 24 hours with the help of an alcohol swab. The pores and pores and skin grow to be examined for erythema/edema.

Drug content material material

Transdermal system of specific place (three.066 cm2) grow to be decrease into small quantities and taken proper right into a 50 ml volumetric flask and 25 ml of phosphate buffer pH 7.4 grow to be added,[17] gently heated to 45oC for 15 minutes, and Keep for twenty-4 hours with occasional shaking. Then, the volume grow to be made as a good deal as 50 ml with phosphate buffer of pH 7.4. Similarly, a easy grow to be completed the usage of a drug-free patch. The solutions have been filtered and the absorbance grow to be measured at 260 nm. In vitro drug release studies a paddle over disc assembly (USP 23, Apparatus 2) grow to be used for the assessment of release of drug.[2] The TDDS patch grow to be established on the disc and placed at the bottom of the dissolution vessel. The dissolution medium grow to be 900 ml phosphate buffer of pH 7.4. The system grow to be equilibrated to 37 ± 0.5oC and operated at 50 rpm. The samples (5 ml Aliquots) have been withdrawn at appropriate time periods up to 8 hours and analyzed on a UV spectrophotometer at 260 nm.

In vitro pores and pores and skin permeation studies

Preparation of the pores and pores and skin barrier: Fresh full-thickness (75–80 mcm) porcine ear pores and pores and skin grow to be used for the check. The pores and pores and skin grow to be immersed in water at 60oC for a period of 5 minutes. The epidermis grow to be peeled from the epidermis. The isolated epidermis (25 ± 5 mcm thick) grow to be all of sudden rinsed with hexane to remove surface lipids and then rinsed with water and used immediately.The in vitro pores and pores and skin permeation[18-20] from the prepared polymeric patches for the duration of the porcine ear pores and pores and skin barrier grow to be studied the usage of a Keshary Chien diffusion cell. Fifty-four milliliters of phosphate buffer of pH 7.4 grow to be used as an elution medium. The patches to be studied have been placed in many of the donor and the receptor compartment on this type of way that the drug releasing ground faced toward the receptor compartment. The elution medium grow to be magnetically stirred for uniform drug distribution at a speed of 60 rpm. The temperature of the whole assembly grow to be maintained at 37 ± 1oC through thermostatic arrangements. An aliquot of 1 ml grow to be withdrawn at a suitable c program languageperiod and an identical volume of easy buffer grow to be replaced. The amount of drug permeated for the duration of the pores and pores and skin grow to be determined on a UV spectrophotometer at 260 nm. The flux (mcg/cm2) grow to be calculated from the slope of the plot of the cumulative amount of drug permeated consistent with cm2 of pores and pores and skin at normal state toward time the usage of linear regression analysis. The values are tabulated in Table 5. The records have been tabulated and prepared into severa classical equations to indicate the kinetics and mechanism of diffusion [3] .

In vivo studies

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account throughout in Vitro studies can be fully explored throughout in vivo studies. In Vivo evaluation of TDDS can be completed the usage of:

•Animal models

•Human volunteers

Animal models

The maximum common animal species used for evaluating transdermal drug transport system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.

Human models

The final stage of the development of a transdermal device includes collection of pharmacokinetic and pharmacodynamic records following application of the patch to human volunteers. Clinical trials had been completed to assess the efficacy, chance involved, facet outcomes, affected individual compliance etc.

III. Result

Matrix-type transdermal patches of nicorandil have been prepared the usage of three wonderful grades of HPMC (6 cps, 15 cps, and K4M) to get the popular drug release profile. The prepared patches have been subjected to folding staying power, thickness of the movie, weight uniformity, drug content material material, percentage moisture uptake, percentage moisture content material material, water vapor transmission, stability studies at tremendous temperature, and pores and pores and skin irritation check and their values are confirmed . Partition coefficient of nicorandil withinside the octanol/water system grow to be decided to be 0.07226. Solubility and permeability of nicorandil have been evaluated at different values of pH with phosphate buffer. It grow to be seen that solubility accelerated with increase withinside the pH. The permeability studies of nicorandil through the porcine ear pores and pores and skin showed that the flux of nicorandil and permeability coefficient (P) grow to be decided to be 26.235 mcg/cm2/hour and 0.0000526, respectively.

IV. FUTURE TECHNOLOGIES AND APPROACHES

- thermal poration is the formation of aqueous pathways for the duration of stratum corneum through the application of pulsed heat, this method has been used to supply traditional pills and to extract intestinal fluid glucose from human subjects
- jet injectors are receiving accelerated interest now days, that is opening doors for advanced system design for controlled, needle free injection of drug solutions for the duration of the pores and pores and skin and into deeper tissue.
- small needle is inserted a few millimeters into pores and pores and skin and drug solution is flowed through the needle into the pores and pores and skin at controlled quotes the usage of a micro-infusion pump that is contained within a big patch affixed to pores and pores and skin, morphine has been delivered to humans the usage of this method.
- throughout the past decade different theories had been advise in addressing the combinations of hemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.
- transpharma is focused on products for which our generation will provide clear blessings over existing therapies. Such blessings could consist of enhancing safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.
- the viaderm system may be carried out to the transport of community medications for topical applications in the fields of dermatology and cosmetics. The viaderm system may moreover allowenhanced immunisations, providing a nonpainful, stable and effective opportunity to current intramuscular or subcutaneous vaccination methods. Altea therapeutics is currently in clinical development of a transdermal patch designed to deal with a first rate unmet need through preventing off periods and provide an advanced

restoration opportunity for handling parkinsons ailment.

V. CONCLUSION

A lot of improvement has been completed withinside the place of Transdermal Patches. Due to huge benefits of the Transdermal Drug Delivery System, this system interests plenty of researchers. Many new researches are going on in the present day to incorporate newer pills through this system. Various gadgets which help in growing the price of absorption and penetration of the drug are moreover being studied. However, withinside the present time due to advantageous risks like big drug molecules cannot be delivered, huge dose cannot be given, the price of absorption of the drug is less, pores and pores and skin irritation, and etc. the usage of the Transdermal Drug Delivery System has been limited. But, with the invention of the new gadgets and new pills which can be incorporated through this tool, it used is growing all of sudden in the prevailing time.

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Cite this article as :

Mr. Saurabh Jawahar Sanghavi, Abhishek Suna, Ms. Pratibha Pradip Deshmukh, Vikash Singh Bhadouria, Jyotsna Kharbanda, Divya Thirumal, Ishan Shah, Kurhade Rupesh Ramdas , "Preparation, Evaluation and Characterization of Antihypertensive Drug for Matrix Transdermal Patches ", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 9 Issue 3, pp. 140-147, May-June 2022.
Journal URL : https://ijsrst.com/IJSRST229324