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Formulation and Evaluation of Benazepril Emulsomes Containing Transdermal Patch

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KEYWORDS
Benazepril hydrochloride, Transdermal patch, Permeation enhancer, In-vitro permeation study.

ABSTRACT

Transdermal drug delivery is an alternative route of administration that offers avoidance of the associated drawbacks of orally and parenterally administered hydrophobics. However, owing to the extremely specific set of physicochemical characteristics required for passive transdermal drug permeation. The purpose of this research was to develop a transdermal therapeutic system containing drug Benazepril hydrochloride (BZ). Benazepril, an angiotensin-converting enzyme (ACE) inhibitor, is a prodrug which, when hydrolyzed by esterases to its active Benazeprilat. Benazeprilat, the active metabolite of Benazepril, competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II. Emulsomes containing phosphatidylcholine (soya-lecithine), cholesterol and either of the solid lipid were prepared and optimized for the lipid ratios. Hence it was desired to develop formulations which would be avoid the problems of toxicity and rapid elimination of drug. The transdermal route for the treatment eliminates major side effects and showed better effect to diseased suffering person. The aim of present work is to development of new approach as matrix type polymeric transdermal patch for management of hypertension of cardiac patients.

INTRODUCTION

Transdermal drug delivery systems (TDDs) avoid gastrointestinal degradation and hepatic first-pass metabolism, providing good drug bioavailability and patient compliance. One emerging type of TDDs is the wearable patch worn on the skin surface to deliver medication through the skin. They can generally be grouped into passive and active types, depending on the properties of materials, design principles and integrated devices [1]. Transdermal drug delivery system (TDDS) offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects, offers multi-day dosing, penetrate the skin barrier and reach the target site [2]. Because of its great advantages, it has become one of the highly research field among the various drug delivery system. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects [3]. Hypertension, a cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Global Burden of Disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries. Transdermal systems are ideally suited for diseases that demand chronic treatment. Despite the suitability of

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TDDS in the treatment of chronic disease like hypertension, the high cost of antihypertensive patches than conventional products made the target patients to think twice. In spite of the high cost of transdermal patches for hypertension treatment, antihypertensive patches with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs [4]. Benazepril hydrochloride (BH) is chemically (3- [[1-(ethoxy-carbonyl)-3-phenyl-(1S)propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine -1-acetic acid monohydrochloride) is a medication used to treat high blood pressure (hypertension) congestive heart failure, and chronic renal failure [5].

Identification test by FTIR spectroscopy [6]: Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound.

Loss on drying: Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrumentby knob then take 1 gm sample (powder) andset the temp at 100°C-105°C for 5 min and constant reading set the knob and check % moisture.

Determination of pH: Upon cleavage of its ester group by the liver, benazepril is converted into its active form benazeprilate, a non-sulfhydryl angiotensin- converting enzyme (ACE) inhibitor. The empirical formula of BH is $C_{24}H_{28}N_2O_5 \cdot HCl$ with a molecular weight of 460.96 g/mole[5]. So ouraim to develop a transdermal drug delivery system for BH to reduce the dose frequencies and minimize the side effects [7].

Material and Methods:

Characterization of drug molecules:

Organoleptic evaluation: It refers to the evaluation by sensory characters-taste, appearance, odor, feel of the drug.

Solubility (at room temperature): Solubility is determined in different solvents like water, methanol 0.1 N HCL, 0.1 N NaOH and different buffers. 1g of the powder was taken and dissolved in 100ml of distilled water with sonication and filtered, pH of the filtrate was checked with standard glass electrode.

Melting point: A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt andthe temperature when all the powder getsmelted [8].

Flow properties: Compressibility index (C.I.) is an importantmeasure that can be obtained from the bulk and tapped densities. Hausner ratio indicates the flow properties of the powder andis measured by the ratio of tapped density to bulk density. The angle of repose is a relatively simple technique for estimating the flowability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resultingcone is measured.

Moisture content: The titrimetric determination of water is based upon the quantitative reaction of waterwith an anhydrous solution of sulphur dioxideand iodine in the presence of a buffer that reactswith hydrogen ions.

Development of Transdermal patches: The obtained drug containing emulsomes were stored under normal room temperature for the prepartion transdermal patches were prepared using solvent casting method. The transdermal films containing benazepril hydrochloride were formulated by using different polymeric combinations of poly vinyl alcohol and poly vinyl pyrrolidone.

Preparation of casting solutions: The films were prepared by method as solvent casting method. The polymer mixture was prepared by dissolving weighed quantities of polymers in water. The drugs were dissolved in methanol as solvent, which added to the prepared polymeric solution with Propylene Glycol 400 (10% w/v) as plasticizer and Tween 80 (5% v/v) were added respectively. The solution of mixture (20 ml) was poured into Petri plates, kept it in the hot air for drying.

Preparation of transdermal patches: The optimized prepared emulsomal formulation (1 ml) was thoroughly mixed to polymer mixture of casting solution to form a homogeneous mixture with thermostable heating mantle at 60°C. The solution of poymer mixture (20 ml) was poured into Petri plates containing mercury as base, kept it in the hot air for drying upto 24 h for solvent evaporation. The patches were removed by peeling and cut into square dimension of 2 cm × 2 cm (4 cm2). These patches were kept in desiccators for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers [9].

Evaluation of Transdermal Patches:

Thickness: The thickness of patches was measured at

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three different places using an Absolute Digimetic (Mitutoyo) from Medreich Lab, Bangalore.

Folding endurance: This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance.

Percentage of moisture content: The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constantweight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Percentage of moisture uptake: A weighed film kept in desiccators at room temperature for 24 h was taken out and exposed to 81% relative humidity (a saturated solution of aluminium chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [10].

Drug content analysis: The drug content of multilayered transdermal patch containing benazepril hydrochloride emulsomes was determined for identified the specific quantity of drug presence in prepared patch. Patch (2 cm2) was cut into pieces and keep into a 100 ml volumetric flask containing 100 ml phosphate buffer pH 7.4 for 24 hours with occasional shaking. After shaking, filtered and prepared suitable dilution with phosphate buffer pH 7.4. The blank was prepared with drug-free patch. The solutions were observed by UV spectrophotometer at wavelength 305 nm [11].

In *Vitro* skin permeation study: The in vitro skin permeation experiments were conducted using a Franz diffusion cell (receptor compartment capacity: 100 ml: surface area: 3.799 cm^2). Full thickness skin from dorsal region of Swiss albino mice, whose hair had been removed by razor, was used as membrane. The mice were sacrificed by cervicaldislocation and dissected skin was used immediately. The receiver compartment was filled with 100 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the center of the mouse skin and then the skin was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of dermis side skin just touches the receptor fluid surface. The whole assembly was kept on a water bath maintainedat 37± 0.5ºC. The samples were withdrawn at different time intervals up to 10 h and analyzed for drug content. Receptor phase was replenished with an equal volume of buffer solution at each time interval [12].

Result and Discussion: The present work comprises the formulation and evaluation of emulsomal containing benazepril hydrochloride transdermal patches for sustained or extended release for a prolonged period of time. Organoleptic studies of drug material conclude the specific color, odor and taste of pure drug. Solubility study of drug molecule has been done in various solvent such as water, phosphate buffer pH 6.8 and 0.1N HCl solution. We were found that a solubility of drug material is good in a 0.1N HCl solution. Identification of benazepril hydrochloride by FTIR spectroscopy and pure drug-excipients were analyzed and which clearly indicates thatthere was very slight interaction between drug and excipients. In case of pure drug sharp peakswere observed at 1735.39 (C=O stretching), 1669.76 (strong C=C stretching), 1519.74 (weak C=C stretching), 1363.08 (C-H bending), 1321.65 (C-N stretching), 1204.21 (C-N stretching), 1003.44 (C-O stretching) and 838.39cm^{-1} (=C-H bending). Whereas, in case drug-excipient sharp peakswere observed at 1793.54 (C=O stretching), 1645.16 (C=C stretching), 1490.09 (C-N stretching), 1361.15 (C-H bending), 1242.14 (C- N stretching), 946.20 (=C-H bending) and 842.36 cm^{-1} (=C-H bending). The percentage of loss on drying for BH was found 0.0039 % w/w respectively. The pH determination of drug molecule was done by digitalpH meter and found to be 4.29. The melting point of the drug sample range ofthe drug is 198ºC. The bulk density and tapped density of drug material was 0.412 g/cm^3 and 0.396 g/cm3. The compressibility index of BZ was found 20.673 % and Hausner ration was found 1.260**.** The Angle of repose of drug is 43.56 °. The Moisture content of drug is 0.75%. The thickness of the films was measured by using an absolute Digimetic (Mitutoyo) at five different positions. The moisture content was determined by keeping patches in a desiccators containing activated silica. The percentage moisture uptakewas calculated as the difference between initial and final weight with respect to final weight. The moisture content in the patches ranged from1.671± 0.012 to 5.690 ± 0.015. The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. The results of moisture uptake studies for different formulations were

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shown with % uptake for different formulations ranges from 2.569± 0.22 to 7.895± 0.22. Low moisture uptake protects the material from microbialcontamination and bulkiness. The drug content analysis of different formulations was done and ranged between 95.857 ± 0.2073 to 97.770 ± 0.1992%. The *in vitro* permeation studies are predictive of *in vivo* performance of a drug. **Conclusion:** In the present study, an attempt was made to deliver a novel ant diabetic drug, Benazepril hydrochloride through transdermal route in the form of transdermal patches. Transdermal patches of matrix were prepared out of which matrix type of patches was found to be satisfactory. The composite patches demonstrated facilitated drug loading and encapsulation efficiency of drugs along with extended drug release profiles. Release curves were also subjected to model fitting, and it was found that drug release was optimally adapted to the Higuchi square root model for each drug. They performed a time-dependent and diffusion-controlled release from the patches and followed Fick's diffusion law by the Korsmeyer-Peppas energy law equation. The drug–polymer interaction results suggested no interaction between drug and polymers was observed. The best formulation BEMT3 showednegligible change in % drug content and permeation. The present study showed that matrix Transdermal patches of Benazepril hydrochloride exhibited better in vitro performance.

These studies were performed for different formulations across mice skin using phosphate buffer, pH 7.4 as an *in vitro* study fluid in the receptor compartmentof a Franz diffusion cell. The results of these studies concluded that formulation BEMT3 exhibits better drug permeation (87.18%) as compared to its others.

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Table 1: Composition of various formulation of emulsomes

Formulation Code	Lipid content (X_1)			Amount of surfactant (X_2) (%) (Span 60)	Addition of sonication time (X_3) (Min.)
	Cholestrol (CH) (mg) X_a	Phospholoipids (Lecithine) (LN) (mg) X_b	Triglycerides (Stearylamine) (STL) (mg) X_c		
BEM1	25	75	50	2.5	5
BEM2	50	75	25	2.5	5

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BEM3	25	75	50	5	10
BEM4	50	75	25	5	10
BEM5	25	75	50	7.5	15
BEM6	50	75	25	7.5	15

Table 2: Formulation composition of benazepril hydrochloride emulsomes transdermal patches

S. No.	F. code	PVA (mg)	PVP (mg)	Plasticizer (Propylene Glycol 400) % W/V	Methanol (ml)	Water (ml)
1	BEMT1	600	400	10	10	20
2	BEMT2	600	400	10	10	20
3	BEMT3	600	400	10	10	20
4	BEMT4	600	400	10	10	20
5	BEMT5	600	400	10	10	20
6	BEMT6	600	400	10	10	20

Table 3: Various characterization of prepared BZ emulsomes containing transdermal patch

S. No.	F. code	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Percentage Elongation (%mm2)	Tensile Strength N/mm2	Swellability (%)	Surface pH	Drug Content	Moisture Content (%)	Percentage Moisture uptake (%)
1	BEMT1	0.23±0.03	48.66±1.165	87-84	82.01±0.02	3.19±0.23	26.91±0.13	6.1 ± 0.11	84.21±3.2	4.96±0.14	4.99±0.27
2	BEMT2	0.24±0.02	47.23±1.154	85-80	91.74±0.11	4.26±0.12	29.12 ± 0.24	6.5 ± 0.12	89.78±2.1	4.89±0.17	4.93±0.37
3	BEMT3	0.23±0.03	50.33±1.155	96-91	105.12±0.12	5.29±0.21	35.42 ± 0.17	6.3± 0.13	91.23±0.2	4.15±0.13	4.83±0.36
4	BEMT4	0.24±0.01	49.33±1.156	101-99	102.21±0.011	6.03±0.11	24.03 ± 0.14	6.4 ± 0.15	89.13±1.3	3.28±0.18	3.89±0.38
5	BEMT5	0.25±0.01	49.60±0.144	89-80	98.21±0.014	4.13±0.11	22.18 ± 0.12	6.5 ± 0.22	87.21±0.15	4.62±0.13	4.87±0.26
6	BEMT6	0.26±0.02	51.32.±1.154	98-97	107.01±0.024	4.02±1.12	25.13 ± 0.11	6.6 ± 0.13	89.02±0.07	3.63±0.13	4.67±0.25