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Formulation and evaluation of captopril Transdermal Patches

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ABSTRACT

The present study comprises of an investigation of captopril a potent ACE inhibitors used orally to treat hypertension, as a feasible candidate for transdermal drug delivery. The present research work was undertaking to formulate a Transdermal drug delivery system of captopril, to investigate the effect of different penetration enhancers, and to study the in vitro permeation characteristics of the drug through the excised rat skin. In the present study, Transdermal patches of captopril were formulated using EC, PVA, PVP, PEG6000. All the formulation were used in combinations and penetration enhancers like DMSO, DMF, PG used in each groups. The effect of penetration enhancer in permeation through rat skin, revealed that DMF showed better result. In vitro skin permeation studies indicated that PVA: PEG6000 matrix type film may be fabricated in to effective system and DMF showed better result. The penetration enhancer DMF demonstrated the highest flux of 0.102 mg/cm^2/hr and followed by PG 0.073 mg/cm2/hr from CE2 AND DE2 respectively.

Introduction

The treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various conventional dosage forms; like tablets, capsules, ointments, liquids, aerosols and injectables as drug carriers. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery systems several times a day. This results in a significant fluctuation of drug levels. Further the conventional dosage forms used for the control of infection, pain and fertility may cause side effects like nausea, vomiting, gastric irritation and toxicity if they are consumed for long duration. Continuous I.V. infusion has been recognized as a superior mode of systemic drug delivery that can be tailored to maintain a constant and sustained drug level within a therapeutic concentration range for as long as required for effective treatment. It also provides a means of direct entry into the systemic circulation of drugs that are subjected to hepatic first-pass metabolism and/or suspected of producing gastro-intestinal incompatibility. Unfortunately, such a mode of drug administration entails certain health hazards and therefore necessitates continuous hospitalization during treatment and requires close medical supervision. To duplicate the benefits of intravenous drug infusion without its potential hazards several technical advancements have been .They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a particular tissue. With the concept of delivering drug into the skin for both local effects in dermatology and through the integument for the systemic treatment of disease states. This latter process has been brought into sharp focus in recent years by the efforts of pharmaceutical field to develop Transdermal delivery devices to treat motion sickness, angina, hormone deficiency and hypertension. The novel drug delivery system has brought renaissance into the pharmaceutical industry for controlled drug delivery. The novel drug delivery systems includes transdermal drug delivery system, mucoadhesive drug delivery system, nasal drug delivery system etc. The transdermal route of drug delivery is gaining accolade with the demonstration of percutaneous absorption of a large number of drugs. This type of drug delivery with the intention of maintaining constant plasma levels, zero order drug input and serves as a constant I.V. infusion. Several transdermal drug delivery system (TDDS) have recently been developed aiming to achieve the objective of systemic medication through application to the intact skin.

Material and Methods

Captopril procured from Lupin Laboratories, Bombay, Polyvinyl alcohol gifted sample from Reidel chemicals, Delhi, Polyvinyle Pyrrolidone k30,PEG6000 purchased from Medispan Ltd, Chennai, Ethule cellolose purchased from S.D.Fine Chemicals, Delhi.

General Procedure For Fabrication The Drug Free Films

An area of 6 cm*6 cm was prepared on the glass plates by fixing (11 cm *8.5 cm *1.5 cm) with an adhesive . The films were casted to this compartments only.First the volume of polymer solution (to produce the film of specified thicknees) that occupies a said area on the glass plates was founds out by trial and error. As per the composition given in the table -1 which shown the optimized composition for casting the drug free film,the accurately measured quantities of the solvents and plasticizers were mixed well and then the polymer was dissolved in the mixture (containg solvents and plasticizers).

Fabrication Of Different Types Of Film Devices For Transdermal Drug Delivery

Fabrication of PVA : PVP based conventional matrix typed film. Accurately weighed quantity of PVA and PVP were dissolved in dissolved in distilled water ,this gave the polymer concentration of 10% w/v in a ratio of 60:40and 80:20. Accurately measured quantity of glycerol (in the concentration

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of 8% w/w with respect to polymer weight) was addes to the distilled water and mixed before addition of polymers. When the polymers got dissolved completely, a viscous solution was obtained. Then the accurately weighed quantity of captopril was added stirred slowly (to avoid air entrapment) till the drug dissolved completely in the polymer solution. Then this solution was poured onto the leveled glass substract which was kept in an oven, maintained at 40 c .It was then allowed to dry completely for about 24 hrs. Then the film was removed, packed in an aluminium foil and stored in the desicator without dessicant, which was kept in the oven set at 25 till used.

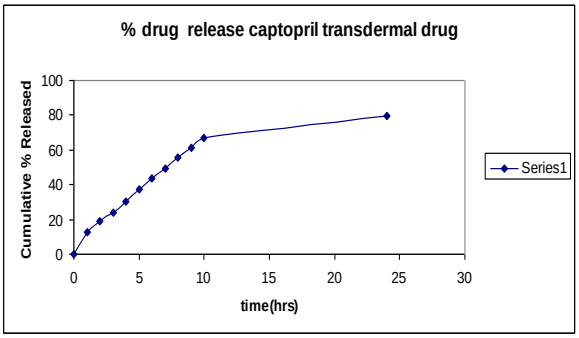

Figure 1. Permeation Profile of captopril from PVA:PVP(6:4) based conventional matrix type transdermal films through al;bino rat abdominal skin in saline phosphate buffer PH 6.4(CE2)

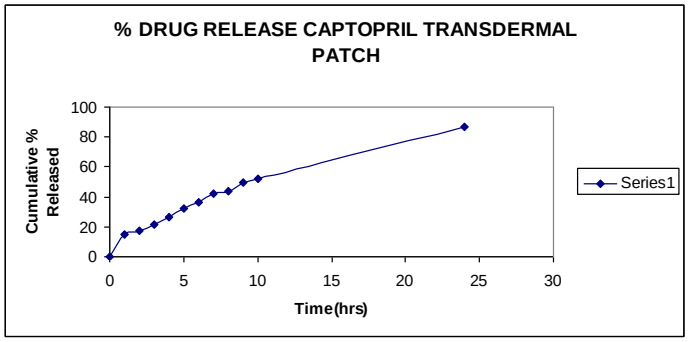

Figure 2. Permeation Profile of captopril from PVA:PVP(6:4) based conventional matrix type transdermal films through al;bino rat abdominal skin in saline phosphate buffer PH 6.4(DE2)

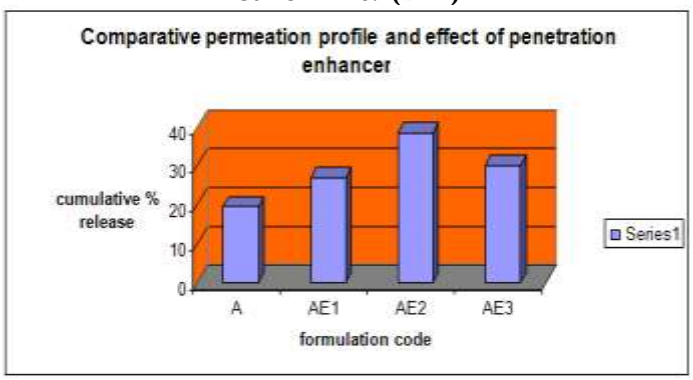

Figure 3. Comparative permeation profile and effect of penetration enhancer on A,A1,A2,A3,A4

Fabrication of PVA and PEG 6000 based conventional matrix type film for TDD

The composition are given in table, Accurately weighed quantity of PVA and PEG6000 was dissolved in 10 ml of water. The drug captopril was dissolved in remaining 5 ml of water and mixed with polymer solution on magnetic stirrer. Different types of polymeric matrix were prepared with different penetration enhancers. Dimethyle formamide in DE2, Dimethyl sulfoxide in DE1,Propylene glycol in DE3 were added and stirred vigorously to get uniform mixture. Then this clear drug polymer solution was poured onto the leveled glass substrate which was kept in an oven at 40 c.It was allowed to dry completely for about 12 hrs. Then the film was removed packed in an aluminium foil and stored in the dessicator.

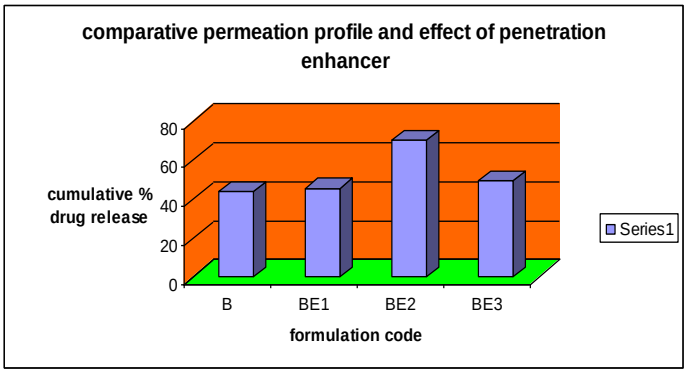

Figure 4. Comparative permeation profile and effect of penetration enhancer on B,B1,B2,B3,B4

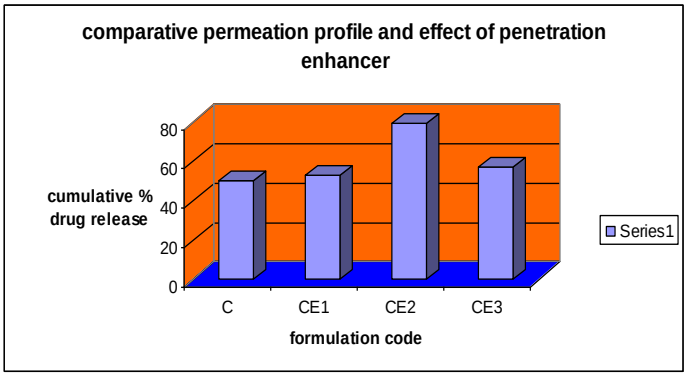

Figure 5. Comparative permeation profile and effect of penetration enhancer on C,C11,C2,C3,C4

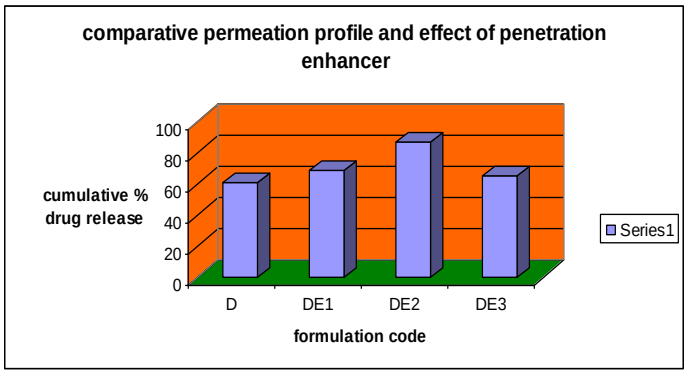

Figure 6. Comparative permeation profile and effect of penetration enhancer on D,D1,D2,D3,D4

Fabrication of EC and PVP based conventional matrix type film

The composition are given in table .Accurately weighed quantity of EC and PVP was dissolved in 10 ml of chloroform. Captopril was dissolved in remaining 5 ml of chloroform and mixed with polymer solution DMSO 20% W/W IN AE1,DMF 20% W/W IN AE2,PG20% W/W in AE3 was added and stirred vigorously. The clear polymer solution was pourd onto the leveled glass substrates which was kept in leveled glass in room temperature. It was allowed to dry completely for about 12 hrs. The film was removed ,packed in an aluminium foil and stored in the desicator till used.

Physicochemical Evaluation:

Thickness: The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Formulation Table 1

S.No	Polymer combination	Casting solvent	Plasticizer	%w/v polymer solution for casting	Substrate for casting the patches	Special remarks
1	EC+PVP	chloroform	Dibutyl phthalate 8%	10%	Glass	A glass funnel was kept invertly over the glass plate for controlled drying
2	PVA+PVP 8:2	Distilled water	Glyserine 8%w/w	10%w/v	Glass	Film casting was done in the oven set at 50 0 c for 12 hrs
3	PVA+PVP 6:4	Distilled water	Glyserine 8%w/w	10%w/v	Glass	Do
4	PVA+PEG 6000 8:2	Distilled water	Glyserine 8%w/w	10%w/v	Glass	do

Formulation Table-2

S.No	Code.no	Drug captopril(mg)	Polymer(gms)				Enhancer % w/w			plasticizer	Casting solvent
			PVA	PVP	EC	PEG-6000	DMSO	DMF	PG		
1	A	70	-	0.1525	0.6050	-	-	-	-	Dibutyl phthalate	chloroform
2	AE1	70	-	0.1525	0.6050	-	20%	-	-	-do-	-do-
3	AE2	70	-	0.1525	0.6050	-	-	20%	-	-do-	-do-
4	AE3	70	-	0.1525	0.6050	-	-	-	20%	-do-	-do-
5	B	70	1.2705	0.3176	-	-	-	-	-	glycerine	Distilled water
6	BE1	70	1.2705	0.3176	-	-	20%	-	-	-do-	-do-
7.	BE2	70	1.2705	0.3176	-	-	-	20%	-	-do-	-do-
8.	BE3	70	1.2705	0.1376	-	-	-	-	20%	-do-	-do-
9	C	70	0.9529	0.6352	-	-	-	-	-	-do-	-do-
10	CE1	70	0.9529	0.6352	-	-	20%	-	-	-do-	-do-
11	CE2	70	0.9529	0.6352	-	-	-	20%	-	-do-	-do-
12	CE3	70	0.9529	0.6352	-	-	-	-	20%	-do-	-do-
13	D	70	1.2705	-	-	0.3176	-	-	-	-do-	-do-
14	DE1	70	1.2705	-	-	0.3176	20%	-	-	-do-	-do-
15	DE2	70	1.2705	-	-	0.3176	-	20%	-	-do-	-do-
16	DE3	70	1.2705	-	-	0.3176	-	-	20%	-do-	-do-

Table 3. Evaluation of physical characteristics of patches and the changes in their physical characteristics on storage

SL.NO	CODE NO.	WEIGHT VARIATION TEST	THICKNESS UNIFORMITY TEST	DRUG CONTENT
1	A	20.68	190	1.473
2	AE1	20.44	200	1.563
3	AE2	20.56	190	1.496
4	AE3	20.60	190	1.486
5	B	31.36	185	1.796
6	BE1	31.42	190	1.714
7	BE2	31.05	185	1.763
8	BE3	31.25	185	1.730
9	C	26.25	160	1.734
10	CE1	26.18	165	1.709
11	CE2	26.22	160	1.712
12	CE3	26.05	160	1.710
13	D	21.05	178	1.894
14	DE1	21.83	175	1.890
15	DE2	21.73	170	1.878
16	DE3	21.85	174	1.886

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

In vitro permeation studies of films for TDD

Drug release system

A modified Franz diffusion cell which also called as Keshary Chien cell was fabricated to study the permeation of captopril from matrix type film across the freshly exercised rat skin. Keshary Chien cell is a vertical type diffusion cell consit of two cylindrical compartments in vertical arrangements. A donor compartment which was exposed to an ambient temperature and a receptor compartment which was maintained at 37^0C by a water bath (thermostate). The fabricated Keshary Chein type diffusion cell. The solution hydrodynamics in the receptor compartment was kept constant by the constant rotation of magnetic beads.

Prepation of skin

Albino rats of both sexes weighing between 150-200 gm were used for this study. The hair from the abdominal region were removed one day prior to in vitro study first by using scissors then by using depilator after giving chloroform inhalation to rats. Special care was taken while removing the hairs as not to destry the stratum corneum. A piece of full thickness skin sample (2.5*2.5 cm) was excised from the hairless abdominal region. The dermal side of the skin was cleaned off any adhering subcutaneous tissues and blood vessels and the skin free of any adhering subcutaneous tissues blood vessels were used for permeation study.

In vitro permeation studies for the conventional matrix type films

Freshly exercised skin(with stratum corneum intact) prepared as above ,was mounted on the receptor compartment of the permeation cell, with the stratum corneum facing upwards and the dermis side facing upwards and the dermis side facing downwards into the receptor compartments. Film measuring 2*2 cm were cut using a razor blade and the film were weighed on an analytical balance. Then the film was placed on the skin in intimate contact with stratum corneum. A sheet of aluminum foil was kept over the film which acted as the backing membranes as well as to fix the film properly in intimate contact with the skin.

The donar compartment was kept on the receptor compartment and secured tightly with help of rubber bands. Phosphate buffered saline PH6.4 was used as the receptor fluid. It was filled into to receptor compartment through the sampling port and checked for the absence of any air bubbles under the skin. The cell was then kept in a water bath, Previously heated to 37^0c and maintained at 37^0c by a thermostat throughout the period study. A micro magnetic bead was used band rotated at a constat speed for maintaining the hydronamic of the receptor fluids constantly throughout the study.

The amount of drug that was released from TTS and permeated through the skin was determined by removing samples of 1 ml periodically. The samples were immediately replced with same volume of drug free phosphates buffered saline PH 6.4 to keep the volume in the receptor compartment constant and also to ensure as intimats contact between the dermal surface of the skin and the receptor solution. For every 4/5 hrs. fresh drug free phosphate buffered saline PH 6.4 in the order to maintain the sink condition as well as to maintain the terbidity free solution medium. As the skin specimen degraded with time the contents getting leached out from the skin to the medium was increasing thus increasing the turbidity in the elusion medium. The aliquot removed were assayed spectrophotometrically. The samples were diluted to the required extent and the absorbance were noted at the wave length 203.5 nm using drug free phosphate buffered saline PH 6.4 as reagent blank. From the standard curve , the concentarion were noted and the amount of drug released / sq cm was then plotted agnist the time.

Conclusion

In an attempt to optimize the permeation of the drug through rat abdominal skin, four different types of matrix system (PVA:PVP 8:2,EC:PVP,PVA:PEG 6000,PVA:PVP 6:4) were used in formulating transdermal patches of captopril .Effect therapeutic concentration can be maintainged constant by delivering the drug at a constant rate for determined periods. In the present study, the effective concentration were maintained for 24 hrs. by incorporating 1.94 mg/cm2 dose. In human beings the dose can be increased accordingly to the release rate of the drug. The formulations were evaluated in vitro to quantity the permeation of drug through excised albino rat abdominal skin. The effect of penetration enhancer in permeation through rat skin, revealed that DMF showed better result. In vitro skin permeation studies indicated that DMF showed better result. In vitro skin permeation through rat skin, revealed that DMF showed better result. In vitro skin permeation studies indicated that PVA:PEG6000 matrix type film may be fabricated in to effective system. The penetration enhancer DMF demonstrated the highest flux of 0.102 mg/cm2/hr. and followed by PG 0.073 mg/cm2/hr from CE2 and DE2 respectively. The penetration enhancer DMF and PG enhanced the transport of captopril from the patch by a factor of 1.970 and 1,543 respectively with comparison with control patch. In conclusion, DMF was found to be the best enhancing agent to enhancer the transdermal permeation of captopril from the patches in comparison to DMSO and propylene glycol.

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