RESERVOIR TYPE TRANSDERMAL DELIVERY SYSTEMS OF PENTAZOCINE HYDROCHLORIDE

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ABSTRACT

Topical delivery of pentazocine hydrochloride (Pz) is of great interest for the treatment of moderate to severe pain of various origins like post surgical, trauma, cancer, burns and colics. The purpose of the study was to formulate and evaluate reservoir type transdermal delivery systems (TDS) of pentazocine hydrochloride. In the present study reservoir device was prepared using membrane cellulose acetate: PVP and ethyl cellulose: eudragit RL 100 and aqueous alcoholic gel system of HPMC as reservoir.

Ethyl cellulose and cellulose acetate membrane released the drug from reservoir in controlled manner over 24 hours. Permeation flux of drug depends on the presence of concentration of penetration enhancer and type of rate controlling membrane used. CA membrane was found to be less retarding compared to EC. Both showed formation of pores during dissolution studies. The statistical comparison using one way ANOVA followed by post hoc student 't' test showed significant improvement in permeation flux data at ($P<0.05$).

Key words: *Transdermal, reservoir, topical delivery, pentazocine hydrochloride.*

INTRODUCTION

With the successful development of several technologies to deliver the drug at a controlled rate

to the systemic circulation through skin[1], membrane controlled TDS utilizes a microporous or polymeric membrane to control the drug flux by the size and tortousity of pores in the membrane through which the drug permeate by dissolution and diffusion[2]. Several materials can be used as rate controlling membrane examples being ethyl vinyl acetate, copolymer, and polyvinyl alcohol co-polymers high-density polyethylene, polyester elastomers. Poly (2 hydroxy ethyl methacrylate) ethyl cellulose, cellulose acetate, eudragit etc[3, 5]. In general the membrane should be permeable only to the drug, penetration enhancers and other formulation excipients should be retained. Alternatively, membranes have been designed in such a way that they allow differential permeation of enhancer and the drug[6]. Some times, membrane is useful when the drug is present in the adhesive and enhancer is formulated in the reservoir[7, 8].

A variety of materials can be used in the drug reservoir ranging from simple formulations such as mineral oil to complex formulation such as aqueous alcoholic gels. A requirement of reservoir system is that it should be capable of permitting zero-order release of the drug over delivery period. This requires the reservoir material to be saturated with drug over the period of product application, which can be achieved by formulating the drug in suspension.

Pentazocine Hydrochloride **(Pz)** (l, 2, 3, 4, 5, 6-Hexahydro-6, ll dimethyl-3(-methyl but-2-enyl)-2-6 ano-3-benzazocine-y-ol-hydrochloride) is an analgesic of the nalorphine type and was the first mixed agonist-antagonist to be widely used. It is a white or cream, odorless, powder consisting of racemic mixture of D and L isomers. It is used widely in cases of

moderate to severe pains of various origins like post surgical, trauma, cancer, burns, colics, as well as a preanaesthetic and anesthetic supplement.
Long term administration of Pentazocine is required in most cases. Pentazocine undergoes extensive hepatic metabolism and have plasma half-life of only 2 hours due to extensive presystemic elimination. Secondly due to low molecular weight and lipophilicity it is a good candidate for transdermal drug delivery system, to reduce the hepatic first pass metabolism and dosing frequency. In the present study Cellulose acetate (CA): PVP and ethyl cellulose: eudragit RL 100 membranes were used to prepare reservoir device using aqueous alcoholic gel system of HPMC as reservoir for delivery of pentazocine.

EXPERIMENTAL

Pentazocine hydrochloride was generously supplied as gift sample by Concept Pharmaceuticals Ltd, Aurangabad, Eudrajit RL 100 was procured from Rohm Pharma, West Germany, PVP was purchased from BDH, Mumbai, Hydroxy propyl methylcellulose, Warner Hindustan Ltd, Hyderabad, Cellulose acetate and Ethyl cellulose was procured from Sigma Chemical Company, USA and Loba Chemie Indoaustranol Co., Mumbai. All other chemicals were of analytical reagent grade and were used as received

Formulation of pentazocine drug reservoir:Drug reservoir for the reservoir type system consisted of 1% HPMC gel along with penetration enhancer. Pentazocine was completely dissolved in mixture of water and methanol (1:1) at room temperature followed by sequential addition of DMSO or IPM. The solution was mixed for 10 minutes in a closed container to prevent any significant loss of volatile component. Hydroxy propyl methylcellulose was then added to the solution and mixed for 5 hours to form gel.

Preparation of rate controlling membrane: Ethyl cellulose film: Ethyl cellulose along with Eudragit RL100 and dibutyl phthalate was used to prepare rate-controlling membrane. Casting a dispersion of polymer, in chloroform, which is used as casting solution on mercury substrate, formed the film[9]. The plasticizer was used at a level of 20% of the polymer weight. The dry films were stored in dessicator until use[10].
Similarly Cellulose acetate along with PVP was used for membrane fabrication on mercury substrate using dibutyl phthalate as plasticizer and choloform as casting solution (Table 1 and 2).

Characterization of rate controlling filmsThickness: Thickness of film was determined using screw gauge at five separate points. Five randomly selected films of each polymeric membrane were tested for thickness.

Determination of water vapor transmission (WVT): The WVT of various films was studied at different relative humidities. The film of known thickness was fixed over the glass vial containing 3gm of fused calcium chloride as desiccant maintained at 52% or 84% RH. The vial was taken out periodically and weighed, for a period of 72 hours. The experiment was triplicated and average values were calculated.

Drug diffusion studies: The diffusion of Pentazocine through the free films was studied using Franz diffusion cells with the help of Aerosab. Polymer film was sandwiched between two compartments namely donor and receptor. 20 ml of distilled water was used as receptor fluid. 2% ethanol was added to the receptor compartment to maintain the sink condition. 5 ml of 2% w/v solution of drug was poured into the drug compartment. The receptor fluid was agitated using magnetic stirrer at a speed of 300 rpm. Temperature was maintained at 37 ± 1°C. Samples were withdrawn periodically from the receptor compartment. The amount of drug diffused at various time intervals was determined spectrophotometrically at 278 nm.

After each sampling, equal volume of drug free solution was added to the receptor compartment to ensure constant volume of receptor fluid (Table 3 and 6).

In-vitro Skin Permeation studies: Franz diffusion cell was used for the study. The magnetic stirrer was set at 300 rpm. Distilled water was used as receptor solution and whole assembly was maintained at 37 ± 2°C. Hairs from the abdominal region of healthy albino male rat were carefully removed from excised skin. The dermal side of the skin was thoroughly cleaned off any adhering tissues or blood vessel. Skin samples were allowed to equilibrate with receptor solution for half an hour. Skin sample was mounted carefully on modified Franz diffusion cell with epidermal side facing the donor compartment. Rate controlling membrane was placed in intimate contact with skin. The donor compartment was then charged with saturated gel system of the drug and immediately closed with cotton to prevent loss of volatile components from the solution. At specific time interval, 2 ml of receiver fluid was withdrawn from receiver compartment and replaced with fresh receiver fluid. The drug concentration in receiver fluid samples was assayed by UV double beam spectrophotometer (Table 9 and 10).

Scanning electron microscopy studies: For SEM study, the film was mounted on an aluminum stabs using double sticky cellophane tape and gold coated in a vacuum evaporator and observed under scanning electron microscope for topographical studies.

Statistical analysis: One way ANOVA followed by post hoc student 't' test was used for statistical comparison of permeation flux data at $P<0.05$ (Table 4, 5, 7 and 8).

TABLE-1: FORMULATION OF PENTAZOCINE RESERVOIR SYSTEM WITH 10% ENHANCER

Formulation Code	Drug reservoir with 10 % enhancer	Rate controlling membrane
PR1	HPMC + DMSO	-
PR2	HPMC + DMSO	Semipermeable membrane
PR3	HPMC + DMSO	Cellulose acetate: PVP
PR4	HPMC + DMSO	Ethylcellulose + Eudragit. RL100
PR5	HPMC + IPM	-
PR6	HPMC + IPM	Semipermeable membrane
PR7	HPMC + IPM	Cellulose acetate: PVP
|PR8	HPMC + IPM	Ethyl Cellulose + Eudragit RL100

RESULT AND DISCUSSION

Reservoir type transdermal systems contain a simple drug solution separated from out side by a release rate controlling membrane that offers diffusion resistance to the drug. The drug release rate from such system defined by fick's law of diffusion. The diffusion process is governed by permeability constants of drug in both the membrane and the skin. If the system membrane is much more permeable than the skin then the drug absorption rate is essentially controlled by skin. If the opposite holds true, then the drug absorption rate is controlled by membrane in the system. The presence of skin always adds to diffusion resistance of drug[11, 12].

In order to design a liquid reservoir transdermal system, the permeability of pentazocine through skin, semipermeable membrane, ethyl cellulose : eudragit RL 100 and cellulose acetate membrane were evaluated. The HPMC based Pentazocine gel containing DMSO or IPM as penetration enhancers were used as reservoir for membrane transport studies[13].

Cellulose acetate in combination with PVP (2:1) possessed good film forming properties. It was observed that the incorporation of PVP into CA free films markedly increased the permeability without losing its integrity. The improvement in film permeability may be due to leaching out of water soluble polymer, thus increasing the porosity of the film and hence the permeability.

Phuaproadit et al[14]. reported that addition of Eudragit RL 100 to ethyl cellulose (EC) membrane containing 20% dibutyl phthalate increased the permeability of EC membrane. A significant increase in membrane permeability was observed. This could be explained by the change in the mechanism of transport. Addition of Eudragit RL 100 resulted in substantial increase in microporosity of the resultant membranes. Therefore, drug transport occurs principally by diffusion through the liquid filled membranes rather than by partitioning into the membranes.

In vitro permeation studies without rate-controlling membrane indicated that 1496.38 ± 3.92 $\mu g/cm^2$ drug permeated from PR1 patch at the end of 24 hour study. The pentazocine permeated from PR2 formulation was 1317.11 ± 4.57 $\mu g/cm^2$ at the end of 24 hours indicating less resistance offered by semipermeable membrane to pentazocine permeation. The permeation profile of PR3 and PR4 showed cumulative pentazocine permeated values of 879.11 ± 4.47 $\mu g/cm^2$ and 714.26 ± 3.36 $\mu g/cm^2$ respectively.

In these device drug reservoir existed as a saturate system with excess of particles, sandwiched between the backing layer and rate controlling membrane. Since the concentration of pentazocine in equilibrium with the inner surface of the enclosing membrane and the driving force for the diffusional drug release was constant. Hence, zero order permeation profile was observed, as long as excess drug is maintained in the reservoir. Once the device near exhaustion of drug concentration radiant falls and a deviation from zero order release occurs.

The permeation profile of pentazocine in presence of 20% DMSO showed increase in permeation flux value of PR9 to 63.06 $\mu g/cm^2hr$ in comparison to 62.34 $\mu g/cm^2hr$ for PR1. Similarly, cumulative amount of pentazocine permeated at the end of 24 hours also increased to 1513.45 ± 3.15 $\mu g/cm^2$ (Table 4)

The permeation flux for PR11 and PR12 were 38.01 and 31.77 $\mu g/cm^2h$ The statistical comparison using one way ANOVA followed by post hoc student t test at $P < 0.05$ showed that addition of 20% DMSO increased the permeability flux significantly. Statistical comparison of permeation flux of DMSO gel through CA and EC membrane shows the significant decrease in permeation flux at $P < 0.05$ (Table 7 and 8).

Permeation profile of Pentazocine in presence of 10% and 20% IPM showed similar results. Permeation rate and cumulative amount of Pentazocine permeated at 24 hours is shown in Table 6.

Statistical comparison of permeation flux of 10% IPM and 20% IPM reservoir system using one way ANOVA showed significant difference from each other at $P < 0.05$, Table 7 and 8.

Post hoc student 't' test was employed to access the significant difference between permeation flux through CA and EC membrane, showed the significant retardation by these membranes.

CONCLUSIONS

Ethyl cellulose and cellulose acetate membrane released the drug form reservoir in controlled manner over 24 hours. Permeation flux of drug depends on the presence of concentration of penetration enhancer and type of rate controlling membrane used. CA membrane was found to be less retarding compared to EC. Both showed formation of pores during dissolution studies.

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TABLE-2: FORMULATION OF PENTAZOCINE RESERVOIR SYSTEM WITH 20% ENHANCER

Formulation Code	Drug reservoir with 10 % enhancer	Rate controlling membrane
PR9	HPMC + DMSO	-
PR10	HPMC + DMSO	Semipermeable membrane
PR11	HPMC + DMSO	Cellulose acetate: PVP
PRl2	HPMC + DMSO	Ethyl cellulose + Eudragit RL 100
PR13	DMSO + IPM	-

PRl4	DMSO + IPM	Semipermeable membrane
PR5	DMSO + IPM	Cellulose acetate: PVP
PRl6	DMSO + IPM	Ethyl Cellulose + Eudragit RL100

TABLE-3 ;PERMEATION PARAMETER OF PENTAZOCINE HYDROCHLORIDE-DMSO RESERVOIR SYSTEM.

Formulation Code	Pentazocine permeated in 24 hours (µg/cm^2)	Permeation flux (µg/cm^2/h)	Percent retardation factor
PR1	1496.38±3.92	62.34	-
PR2	1317.1114.57	54.87	11.55
PR3	879.11±4.47	36.62*	38.35
PR4	714.26±3.36	29.76*	49.91
PR9	1513.45±3.15	63.06	-
PR10	1369.47±2.21	57.06	9.69
PR11	912.42±3.52	38.01*	39.71
PRl2	762.48±2.42	31.77*	50.35

n=3
*indicate statistically significant

TABLE- 4: ANOVA FOR PERMEATION FLUX DATA FOR 10% DMSO

Source of Variation	SS	df	MS	F	P-value	Fcrit
Between Groups	2092.057	3	697.3525	460.0785	2.71E-09	4.06618
Within Groups	12.1258	8	1.515725			
Total	2104.183	11				

TABLE- 5 :ANOVA FOR PERMEATION FLUX DATA FOR 20% DMSO

Source of Variation	SS	df	MS	F	P-value	Fcrit
Between Groups	2012.993	3	670.9977	582.0969	1.06E-09	4.06618
Within Groups	9.2218	8	1.152725			
Total	2022.215	11				

TABLE-6: PERMEATION PARAMETER OF PENTAZOCINE HYDROCHLORIDE - IPM RESERVOIR SYSTEM.

Formulation Code	Pentazocine permeated at 24 hours (µg/cm^2)	Permeation flux (µg/cm^2/h)	Percent retardation factor
PR5	1438.24±6.87	59.92	-
PR6	1225.89t3.93	51.01	13.38
PR7	870.26±4.18	36.26*	38.60
PR8	652.53±4.68	27.18*	50.19
PRl3	1478.84±4.61	61.61	-
PR|4	1345.36±5.36	56.05	4.71
PRl5	891.30±3.34	37.13*	37.27
PRl6	685.46±2.25	28.56*	50.43

n=3
*Significant difference

TABLE-7: ANOVA FOR PERMEATION FLUX DATA FOR 10% IPM

Source of Variation	SS	Df	MS	F	P-value	Fcrit
Between Groups	1936.905	3	645.6351	252.6799	2.91E-08	4.06618
Within Groups	20.4412	8	2.55515			
Total	1957.346	11				

TABLE-8: ANOVA FOR PERMEATION FLUX DATA FOR 20% IPM

Source of Variation	SS	df	MS	F	P-value	Fcrit
Between Groups	2183.016	3	727.6719	671.2944	6.02E-10	4.06618
Within Groups	8.671867	8	1.083983			
Total	2191.688	11				

TABLE- :9 IN VITRO PENTAZOCINE PERMEATION MG/CM^2 FROM DSMO RESERVOIR DEVICE

Formulation Code	Time (hr)								
	1	2	3	4	5	8	12	18	24
PR1	196.15 ±2.30	325.29 ±1.98	400.36 ±2.42	435.19 ±3.36	616.25 ±2.37	715.42 ±3.74	975.46 ±3.71	1310.24±4.17	1496.38±3.92
PR2	152.24 ±10.26	264.45 ± 1.97	312.53 ± 2.31	354.60 ± 2.17	542.42 ± 3.45	622.39 ± 324	880.24 ± 4.31	1096.43±4.63	1317.11±4.57
PR3	122.35 ±1.18	192.36 ±2.30	232.26 ±1.94	264.39 ±2.35	326.42 ±2.26	395.10 ±2.47	560.25 ±2.69	768.19 ±3.68	879.11 ±4.47
PR4	69.82± 0.84	101.24 ±1.31	174.45 ±1.78	194.24 ±2.27	254.21 ±1.87	315.94 ±2.63	498.45 ±2.63	684.19 ±3.28	714.26 ±3.36
PR9	201.54 ±2.64	341.84 ±2.31	422.47 ±3.51	451.15 ±2.24	610.62 ±2.54	725.94 ±4.61	984.63 ±2.25	1356.74±2.26	1513.45±3.15
PR10	168.78 ±2.35	275.63 ±2.14	336.53 ±3.15	368.51 ±4.51	571.89 ±5.03	635.47 ±5.39	891.26 ±4.62	1102.51 ±4.31	1369.47±2.21
PR11	136.51 ±1.69	228.84 ±3.24	264.48 ±4.62	356.30 ±2.28	346.30 ±2.51	421.52 ±2.98	584.24 ±3.10	785.36 ±3.31	912.42 ±3.52
PRl2	78.32 ±2.21	145.61 ±4.31	189.95 ±3.87	225.51 ±3.30	276.41 ±2.28	381.31 ±2.21	542.54 ±2.54	715.61 ±3.30	762.48 ±2.42

n=3

TABLE-10: IN VITRO PENTAZOCINE PERMEATION (MG/CM^2) FROM IPM RESERVOIR DEVICE

n=3

Formulation code	Time in hours								
	1	2	3	4	5	8	12	18	24
PR5	213.46 ±2.24	310.65 ±3.24	358.16 ±4.18	410.24 ±3.65	523.14 ±3.41	681.38 ±4.51	945.60 ±5.26	1290.18 ±6.45	1438.24 ±6.87
PR6	150.38 ±1.78	254.35 ±1.94	294.23 ±2.34	334.45 ±3.38	437.26 ±2.64	563.40 ±4.15	837.26 ±3.23	1054.83 ±4.12	1225.89 ±3.93
PR7	115.25 ± 1.68	186.45 ±4.51	209.84 ±3.21	246.39 ±3.46	307.54 ±3.78	371.45 ±2.75	535.25 ±4.30	734.18 ±5.15	870.26 ±4.18
PR8	75.14± 1.26	124.16 ±2.81	150.25 ±2.36	210.13 ±2.18	235.68 ±2.61	251.43 ±4.68	448.39 ±3.96	594.34 ±3.74	652.53 ±4.68
PR13	225.89 ±3.21	325.84 ±6.36	374.15 ±3.70	425.20 ±4.51	548.36 ±2.98	697.21 ±4.03	975.26 ±2.53	1310.43 ±2.46	1478.84 ±4.61
PR14	165.85 ±2.90	266.53 ±2.36	312.51 ±3.34	354.51 ±2.29	468.14 ±3.87	589.84 ±3.47	863.59 ±2.26	1096.36 ±2.47	1345.36 ±5.36
PR15	125.38 ±2.25	195.94 ±3.54	239.41 ±4.63	267.42 ±2.63	354.42 ±3.24	391.51 ±3.35	548.16 ±4.36	763.32 ±2.31	891.30 ±3.34
PR16	81.62± 2.26	615.36 ±2.25	185.41 ±3.54	257.45 ±2.26	271.14 ±3.61	310.69 ±4.32	471.15 ±3.35	632.61 ±3.36	685.46 ±2.25

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