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In-Vivo and Ex-Vivo Comparative Studyof Transdermal Patch of Ramosetron Hydrochloride

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Abstract: Ramosetron hydrochloride has the half-life 5.8 hrs. and bioavailability in the body is 50% because of first-pass effect. The dose of Ramosetron hydrochloride is 5 mcg once daily depends on weight and gender that's why it required repeated dose. The transdermal patch of Ramosetron hydrochloride was formulated to assist the release and enhanced bioavailability of drug and patient conformance. The several formulations were fabricated by using different polymer concentration ratio. The prepared formulation was studied for several variables such as thickness, weight variation, drug content, moisture content, moisture uptake, folding endurance, tensile strength, in-vitro & In- Vivo drug release and Ex- vivo permeation study, etc. The comparative study has been done for ex-vivo and in-vivo studies for getting results with patches.

Keywords: Ramosetron hydrochloride, Transdermal patch, In-vitro release study, Ex-vivo permeation study etc.

Introduction

In comparison with traditional dosage forms specifically, enhanced conformance of patients on enduring treatment, assert an extend and persistent plasma proportion of drug (accordingly decline the adverse effects related among the oral route), avoiding biotransformation, decreasing inter- and intra-patient inconstancy and assembling it potential to situate an extremity to drug treatment wherever required the topical drug delivery contributes several conveniences [1]. Transdermal drug delivery system means the delivery of drug above the epidermis to accomplished systemic outcomes. The success of transdermal patches lies in their consumerism. Transdermal patches influence the delivery of drugs at controlled rate by contraption an appropriate coalescence of hydrophilic and lipophilic polymers [2-4].

Transdermal patches could extend the pharmacological outcomes and detach undulate of oral administered drug amount for several drugs [5]. Transdermal patches used recently are either reservoir or matrix patches. Matrix-type patches are extremely often used essence thinner, slighter costly to assemble, further pliable, consistent, and agreeable than reservoir-type [6,7].

Although, an insemination of transdermal drug delivery system is not substantial now a day advanced even in the delivery of antiemetic drug the use of this delivery system is a contemporary insemination [8]. As vomiting is an unexpected indication of gastrointestinal tract that essential an influential medical perception. The oral route of medicament is essentially not relevant and parentral therapy has numerous conditions and defects. Accordingly, an essential appear to explore a prospective alternative route across a skin distinctively, transdermal[9]. Nevertheless, the conventional treatment i.e., an antiemetic therapy has narrow adverse results. That's why, it essential to spin concerning safe, beneficial and time appraise system of delivery system. Accordingly, it is preferable to offer a productive and reliable transdermal drug delivery system over the treatment of vomiting and nausea.

Ramosetron hydrochloride is a newly selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist that allegedly has additional dominant antiemetic outcome differentiate among more 5-HT3 receptor antagonists [10].

Examining this recommendation, the supreme intent of this research is to progress the transdermal drug delivery system of Ramosetron hydrochloride to decrease the probability of notable oral adverse effects across alongside the indigent patient adherence. Additionally, topical patch imparts assist delivery of drug, consequently decreasing the dosing prevalence and therefore facilitates

the caregivers by bringing down the hurdles as associated with the oral route.

Materials and Method

Materials

Ramosetron Hydrochloride was obtained from the Zydus Cadila. Polyvinyl alcohol was obtained from Himedia, Mumbai. Eudragit S100 were obtained from Research-Lab Industries Mumbai, HPMC K4M and Dibasic sodium phosphate were obtained from Loba Chemie Pvt. Mumbai, India.

Methods

EX -VIVO SKIN PERMEATION STUDIES

By using Franz diffusion cell an ex-vitro permeation study was performed. The skin samples were detached from gastric site and using a flaking formulation hair was removed. The skin samples were clean among phosphate buffer (pH 7.4). The prepared skin was initiate throughout the donor and recipient division of diffusion cell. Then the prepared patches were situated above the skin by depositing the patch on the stratum corneum side of the skin with regard to the donor division and dermis side was facing with regard to receptor division. The receptor division of the diffusion cell was permeated among phosphate buffer (pH 7.4) and every 1 hrs. 5 ml of sample was withdraw and restore the similar among receptor fluid, and the sample was examined using the double beam UV-visible spectrophotometer. [13]

IN-VIVO STUDY

The animal protocol to performed in-vivo study and skin penetration study was assessed and accepted by Institutional Animal Ethics Committee and for the studies their guidelines were followed. Male albino rats 7-9 weeks old and weighing 225–250 gm was used during the study. The animals were retaining below standard laboratory situation. In polypropylene cages the animals were housed among free approach to standard laboratory diet and water. Two groups each accommodating eight rats were formed for in-vivo permeation study. To control group one mL of 0.5 % ramosetron hydrochloride suspension prepared by 10mg tablet in aqueous media was administered orally. For transdermal application of test group, the rats were anesthetized by i.v. injection of a combination of ketamine hydrochloride and xylazine. The hair on abdominal skin was clear and the abdomen was cleaned smoothly among distilled water. By a silicon rubber the patch was then applied to the skin surface (2.0 cm^2) in open

containers glued to the skin. The blood samples of both control and test groups were composed at pre-decided time period between the tail vein of rat in vacutainer tubes, mixed and centrifuged at 5000 rpm for 20 min. The plasma was isolated and stored at 21 °C upto the drug examination was performed.

Pharmacokinetic variables were determined by non-compartmental examination also known as model independent investigation using WinNonLin version. Peak plasma concentration (Cmax) and time of its occurrence (Tmax) were read immediately from the separate plasma concentration–time profiles. Area under concentration time curve (AUC_{ot}) was in accordance with linear trapezoidal technique though mean residence time (MRT) was determined by dividing the AUMC0t by AUC0t. [14]

Result and Discussion

Vomiting is an emerging condition during the oral route of medicament is basically not contented, particularly in motion sickness situation where oral or parenteral route of administration is not allowable. Although, the several antiemetic preparations are accessible throughout oral route yet eventually be unusable throughout incessant vomiting. Accordingly, a pharmaceutical method was predicted to create notable scientific information by conspiring and expanding a novel, secure, intra-operative and patient-friendly dosage form particularly, transdermal drug delivery dosage form. For the delineation and expansion of antiemetic drug toward novel dosage form. Among decreased dose the hypothesis beyond preparation is to impart good patient compliance.

In- vitro drug release studies

In Figure 1 and Table 1 the drug liberating account of formulated transdermal films is constituted. Compared to the other batches the effect of liberated studies manifest that F3batch preparation has greater drug release 89.43 % in 8 hrs. Along with an outcome and graphs it is explicit that the drug liberation was depending on different polymer ratio and permeation enhancer content.

Table 1: In-vitro drug release study

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	28.50 %	33.62 %	36.45 %	31.56 %	29.96 %
1	31.65 %	44.89 %	47.98 %	42.51 %	33.56 %
2	34.89 %	59.61 %	60.56 %	54.69 %	38.45 %
4	38.34 %	66.54 %	68.23 %	63.93 %	47.32 %
6	40.54 %	71.24 %	73.87 %	68.42 %	59.45 %
8	43.59 %	83.12 %	**89.43 %**	81.34 %	68.39 %

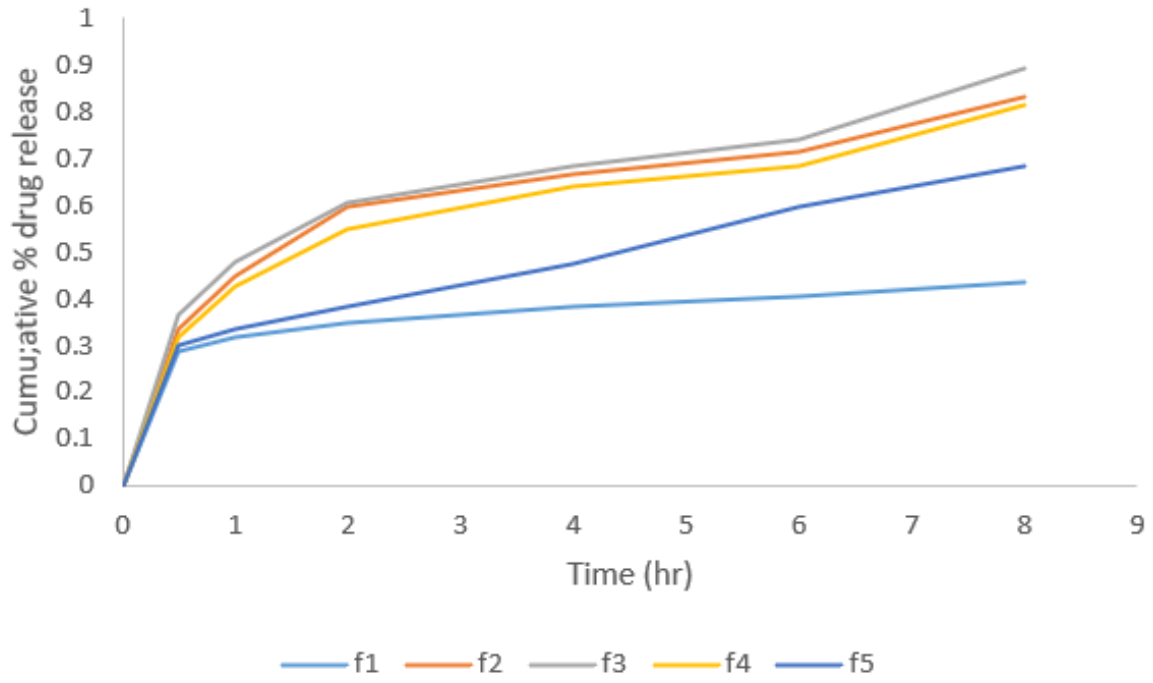

Fig.1: In-vitro drug release studies of transdermal patches

Ex- vivo permeation studies

Table 2: *Ex-vivo* skin permeation study

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	1.146487	1.187654	1.290475	1.164675	1.153758
1	2.657898	2.893456	2.963487	2.838674	2.745632
2	4.764578	4.913465	4.984567	4.863463	4.793683
4	7.409832	7.794576	7.932657	7.759844	7.589473
6	9.348756	9.883467	9.957489	9.828573	9.374953
8	12.94575	12.99046	**13.05674**	12.98364	12.96847

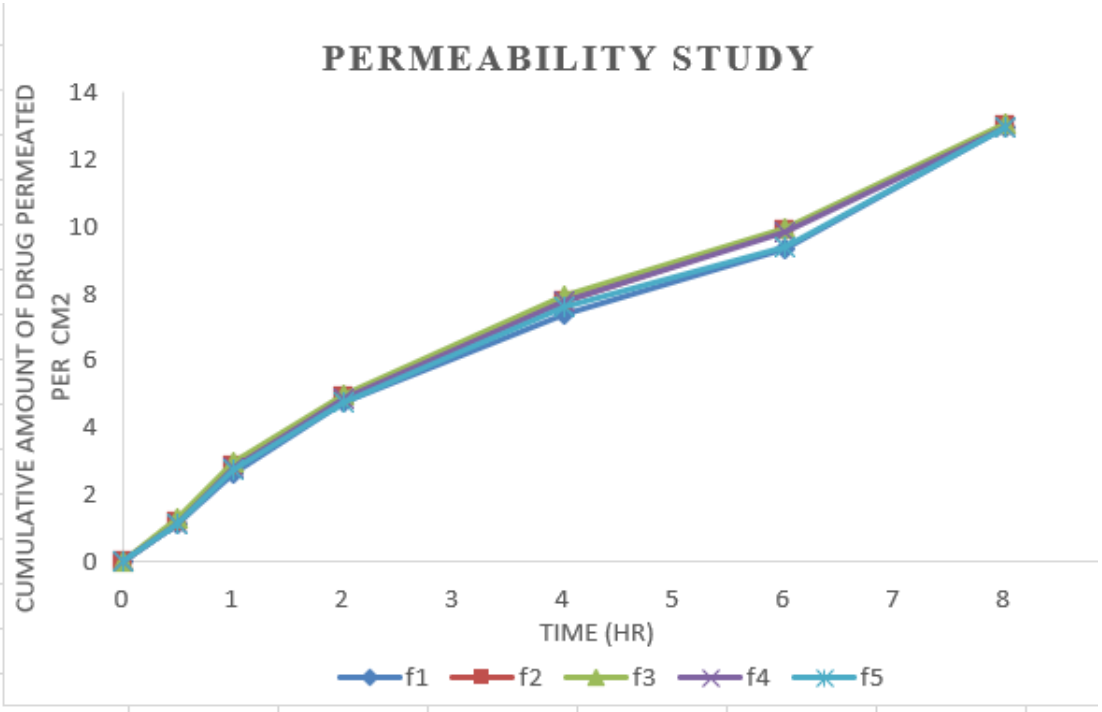

Fig.2: Ex-vivo permeation studies of transdermal patches.

For F1, F2, F3, F4 and F5 formulation an ex- vivo permeation studies were

accomplished. The effective outcome indicates in Figure 2 and Table 2 disclosed that F3 formulation has drug permeation 13.05674 µg/cm² in 8 hrs. Therefore, among the use of permeation enhancer manifest superior effect in enhanced drug permeation. Plotting the progressive quantity of drug permeated per square centimeter of the patches between the rat stomach skin opposed to time in minutes.

Finally progressive percentage of drug penetrate between the rat skin was corresponded opposed to increasing % of drug liberated utilizing in -vitro liberating test during optimized formulation F3, Fig.3 indicate that an association through the % of Ramosetron hydrochloride liberate in- vitro and percentage of drug permeated ex -vivo. Between in- vitro drug liberating and Ex- vivo drug permeation studies the linear and the elevated connection coefficient of 0.995 manifest the great association. Consequently, in transdermal drug delivery systems by cause the absolute distinction in the test situation of in- vitro and Ex -vivo liberate studies, an elevated association and providence of in-vitro and Ex -vivo release account, it may be deduced that like a transdermal patch must be a helpful transporter.

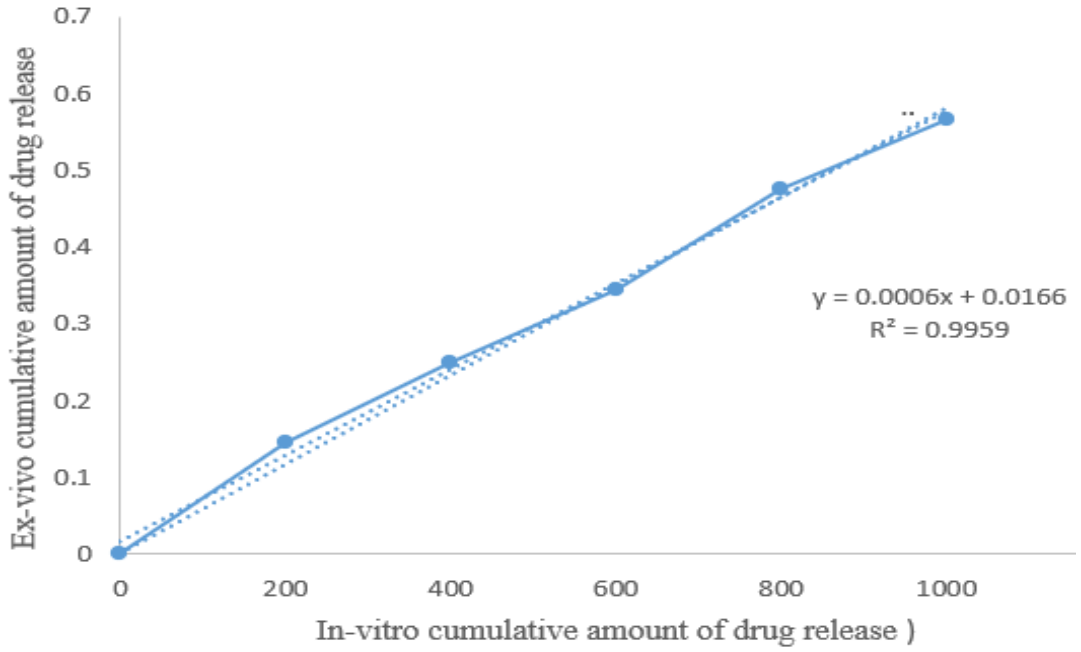

Figure 3: In-vitro and Ex- vivo connection through accumulative quantity drug released In-vitro and amount of drug permeated Ex-vivo of optimized Ramosetron hydrochloride transdermal patch (F3).

***In vivo* drug release studies**

In-vivo permeation study

The AUC of topically applied optimized preparation was 458.09 ± 28.8 ng/ml/h, while AUC of orally administered drug suspension was 123.98 ± 19.43 ng/ml/h. This emerges towards 3.5-fold enhanced relative bioavailability shown in fig.4. The peak plasma concentration (Cmax) of ramosetron hydrochloride behind oral administration was found to be 41.43 ± 2.9 ng/ml at 0.4 ±0.2 h, while behind transdermal administration of optimized preparation it was 29.98 ± 1.99 ng/ml at 3.0 ± 0.6 h shown in Fig. 5. Short Cmax and extended Tmax, might be because of the barricade properties of the skin and moderate partitioning of the drug towards the skin. The successful drug concentration (> 17 ng/mL in plasma) was sustained during at least 16 hrs. between transdermal administration. The in-vivo data exhibited notably greater bioavailability of ramosetron hydrochloride behind transdermal administration was because of prevention of considerable number of hepatic first pass metabolism related among oral administration. The greater MRT values of transdermal delivery (11.12 ± 1.2 h) versus the oral route (3.04 ± 0.3 h) might be because of sustained recovery of drug towards the systemic circulation by controlled release of drug.

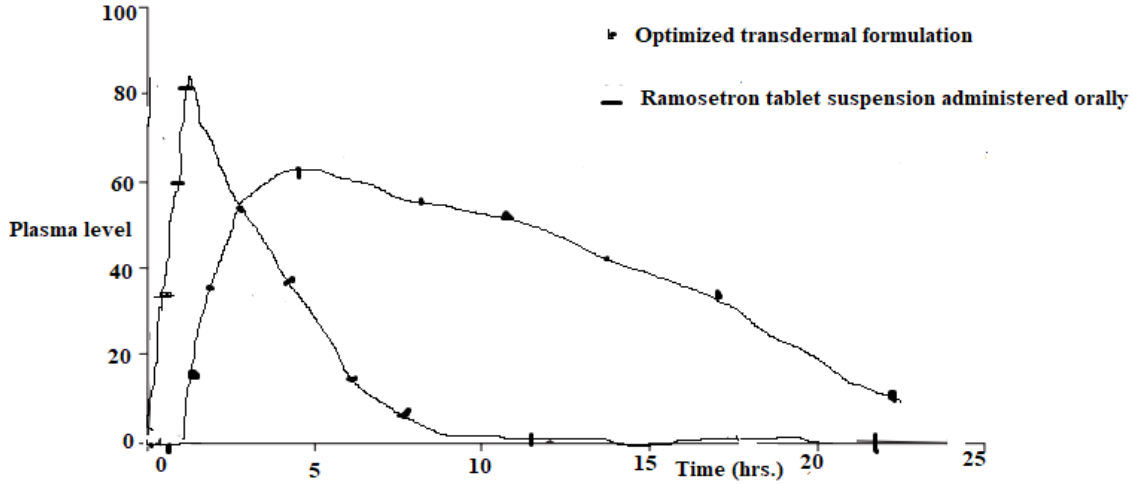

Fig. 4: AUC of optimized transdermal patch formulation and orally administration of tablet suspension.

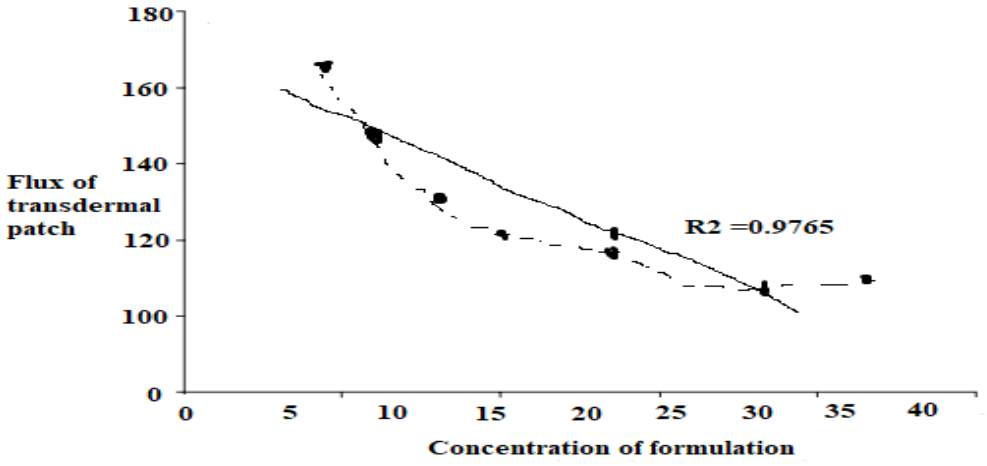

Fig.5: C max of optimized transdermal patch formulation and orally administration of tablet suspension.

Conclusion

Transdermal patches of Ramosetron hydrochloride were effectively fabricated by using several polymers concentrations in different ratio. Formulated patches were established to possess smooth and constant aspect once they are effective upon skin. The moisture content and moisture uptake in the preparation of transdermal patch was established to be F3 batch shows the limited outcomes of polymer concentration ratio. The thickness and flatness of the films were characterized and the outcome disclosed that the radiate mixer was evenly extended above the cast. The drug content characterization was ready during discrete preparation and the merit is in the admissible compass. The outcome of released studies indicates that F3 batch formulation has higher drug liberation 89.43% in 8 hrs and drug permeation 13.05674 µg/cm² in 8 hrs. It may be concluded that the Ex-vivo and In-vivo comparative data shows the best results with the F3batch.

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