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Research Article

Formulation development and evaluation of transdermal drug delivery system of a prokinetic agent - Itopride hydrochloride

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ABSTRACT

Transdermal patches of Itopride hydrochloride were prepared by solvent casting method using HPMC K 15, Carbopol 934 P and Eudragit L 100 in different ratios. Patches were evaluated for various physicochemical properties like thickness uniformity, weight variation, drug content, moisture uptake at 23%, 43%, 75% and 93 % RH, moisture content, folding endurance and water vapour transmission studies. The in-vitro permeation studies were carried out using modified Franz diffusion cell with cellophane as diffusion membrane. Effect of dibutyl phthalate as a plasticizer at concentration of 5% w/w and 10%w/w, on release kinetics of the drug was also studied. It was found that incorporation of dibutylphthalate as plasticizer decreases in-vitro permeation rate of drug. However, changes in concentration of dibutylpthalate from 5% to 10 % w/w do not affect the in-vitro permeation rate of drug significantly

Keywords: Transdermal patch; Itopride hydrochloride; in-vitro study; plasticizer.

INTRODUCTION

Transdermal drug delivery system is defined as self contained, discrete dosage form which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate, to the systemic circulation. (Jain NK, 2001)

Transdermal delivery can provide a number of advantages over conventional method of drug administration, including enhanced efficacy, increased safety, greater convenience and improved patient compliance. By delivering a steady flow of drug(s) in to the blood stream over an extended period of time, transdermal system can avoid the peak and valley effect of injectable therapy and can enable more controlled and effective treatment. By avoiding first pass metabolism through the gastrointestinal tract and the liver, the therapeutically equivalent dose(s) for the transdermal delivery of certain compounds can be significantly less than the corresponding oral dosage, potentially reducing dose related side effects. (Vyas SP,2002)

In this system (transdermal drug delivery) the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate-controlling polymeric membrane. In the drug reservoir compartment, the drug particles are either dispersed or suspended in solid polymer matrix. It is anticipated that transdermal drug delivery system can be designed to input drugs at appropriate rates to maintain a suitable plasma-drug level for therapeutic efficacy, without the periodic sojourns into the plasma concentration that would accompany toxicity or lack of efficacy. (Chien YW, 1987)

Itopride hydrochloride is a novel prokinetic agent. Itopride, by virtue of its Dopamine D2 receptor antagonism, removes the inhibitory effects on Acetylcholine release. It also inhibits the enzyme Acetylcholine esterase which degrades Acetylcholine. The net effect is an increase in Acetylcholine concentration, which in turn promotes gastric motility, increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastro-duodenal coordination.

It is used to treat patients suffering from gastrointestinal symptoms caused by reduced gastrointestinal motility such as non-ulcer dyspepsia (NUD), gastroesophageal reflux disease (GERD), diabetic gastroparesis, and functional dyspepsia. (Gupta S, 2005) These are chronic diseases for which treatment has to be taken for period of up to 8 weeks. Patient compliance is less with the available marketed conventional release products which are to be administered 2-3 times daily. Formulation of transdermal drug delivery system containing Itopride hydrochloride could be a better alternative to improve pharmaceutical formulation to optimize therapy and increase patient compliance. In view of the above facts, in the present investigation, an attempt is made to develop matrix type transdermal patches of Itopride hydrochloride using polymers like HPMC K 15, Carbopol 934 P and Eudragit L 100.

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MATERIALS AND METHODS

Itopride hydrochloride was gift sample from Inventia Healthcare Pvt. Ltd., Thane. Carbopol 934 P and Eudragit L 100 were gifted by Dr. Reddy's Laboratory, Hyderabad. HPMC K 15 was obtained from Central Drug House, New Delhi. The other chemicals used in the study were of analytical grade.

The FT-IR studies were performed to check the compatibility with excipients. Spectra of pure drug and drug along with polymer used were taken to ensure there is no incompatibility between drug and polymers.

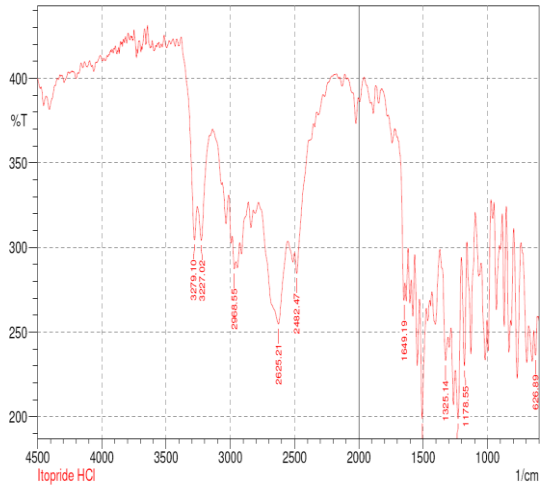

Figure 1: IR spectrum of Itopride hydrochloride

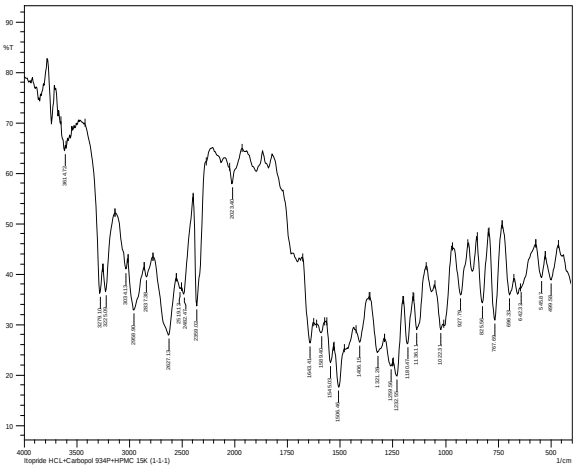

Figure 2: IR spectrum of Itopride hydrochloride, HPMC K 15 and Carbopol 934 P (1:1:1)

PREPARATION OF PATCHES

Solvent casting technique was used to prepare transdermal patches. Various composition of transdermal film containing Itopride hydrochloride along with polymers such as Carbopol 934 P, HPMC 15 K and Eudragit L 100 in different ratios was prepared.

Total polymer weight was fixed at 500mg and total solvent to prepare a formulation was 15 ml. Carbopol 934 P and HPMC 15 K were dissolved in mixture of methanol and dichloromethane 3:2 ratio for preparation of Carbopol-HPMC films and Eudragit L 100 and Carbopol 934P were dissolved in methanol for preparation of Carbopol-Eudragit films with the help of magnetic stirrer. Drug was separately dissolved in solvent system and mixed with the help of magnetic stirrer for 30 minutes. The solution containing drug was added to polymer solution and stirred for about 30 minutes using magnetic stirrer. The prepared solution was poured in petridish and dried at room temperature by covering petridish with inverted funnel for 48 hours. (Khannum A., 2008).

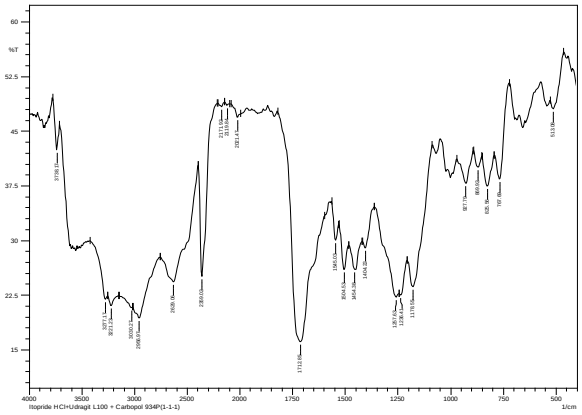

Figure 3: IR spectrum of Itopride hydrochloride, Eudragit L 100 and Carbopol 934 P (1:1:1)

Table 1: Composition of Formulations

Code	Carbopol 934 P	HPMC K 15	Eudragit L 100	Drug (mg)
HC1	1	1		100
HC2	1	2		100
HC3	1	3		100
HC4	1	4		100
CE1	4		6	100
CE2	3		7	100
CE3	2		8	100
CE4	1		9	100

EVALUATION OF PATCHES

Thickness Uniformity

Thickness of films is measured using digital vernier caliper. The thickness was measured at three different points on the film and average of the reading was taken to ascertain thickness uniformity in patch. (Mutalik S., 2005)

Weight Variation

This test provides a mean for measuring uniformity in term of weight within the batch as well as from batch to batch. Three discs of defined area were cut and weight of each disc was determined using single pan balance. (Gattani SG, 2008)

Drug Content

Accurately weighed patches were individually placed in minimum quantity of methanol and volume was made up to 10 ml using 0.1 N Hydrochloric acid. From this

Table 2: Evaluation of physico-chemical properties of transdermal patches

CODE	Thickness Uniformity(mm)	Weight variation(mg)	Drug content Mcg/patch	Folding endurance	WVTR (mg/cm^2 hr)
HC1	0.076±0.005	5.93±0.9451	1434.05±3.53	642±14.79	6.0
HC2	0.063±0.011	7.03±0.7637	1408.96±2.55	217±14.93	5.3
HC3	0.086±0.005	6.96±0.6658	1415.103±7.13	181±22.27	5.1
HC4	0.06±0.01	5.70±0.4582	1408.74±1.59	197±7.81	6.0
CE1	0.146±0.005	8.10±0.7000	1413.70±4.75	189±13.74	6.6
CE2	0.143±0.015	7.0±0.7549	1406.92±0.743	33.66±7.76	6.6
CE3	0.173±0.005	8.93±0.4163	1413.48±2.86	41.33±1.52	6.1
CE4	0.176±0.005	7.93±0.9539	1414.49±4.30	6.33±2.08	6.9

Table 3: Evaluation of moisture absorption at different %RH and moisture content

CODE	%moisture up-take(23%RH)	%moisture uptake (43% RH)	% moisture up-take (75% RH)	%moisture uptake (93% RH)	% moisture content
HC1	0.71±0.4582	1.05 ± 1.252	2.5 ± 1.7058	12.62 ± 0.2000	5.45±0.45
HC2	0.82±0.2211	1.82 ± 0.3511	3.3 ± 0.5196	8.91 ± 0.2000	8.40±0.20
HC3	1.01±0.5513	0.90± 0.3214	0.44 ± 0.7575	5.71 ± 0.8544	6.86±0.65
HC4	1.19±1.106	2.13 ± 0.4509	3.59 ± 0.4509	17.21± 0.5000	0
CE1	1.01±0.3312	2.09 ± 0.8962	8.21 ± 0.4618	11.16 ± 0.8080	16.66±0.52
CE2	0.79±0.7503	1.80 ± 1.1503	2.22 ± 0.3785	7.36 ± 0.7810	10.66±0.28
CE3	0.31±0.6661	0.48 ± 0.057	0.58 ± 0.1154	7.50 ± 0.4041	6.57±0.43
CE4	0.22±0.8852	0.38 ± 0.4932	2.05 ± 1.4570	2.43 ± 0.6658	7.9±0.54

solution, 1ml was transferred to 10 ml volumetric flask and volume was made up with methanol. The absorbance was taken at 257.6 nm. The blank solution was prepared in similar way. Corresponding concentration was then obtained from calibration curve and the actual drug content in each film was calculated. (Mutalik S., 2005).

Moisture Absorption Studies

The capacity of film to uptake moisture is an important parameter of the polymeric films, since it may affect release rate of drug. Moisture absorption studies were carried out at 23, 43, 75, and 93% RH, RT by using saturated solutions of potassium acetate, potassium carbonate, sodium chloride and potassium nitrate respectively. The pre-weighed samples of patches were kept under the humidity conditions and weighed after 24 hours. Increase or decrease in weight, changes in physical appearances were observed. (Sanap GS, 2008)

Moisture Content

The films were weighed and kept in desiccators containing fused calcium chloride for at least 24 hrs or more until it showed constant weight.

Folding Endurance

It was determined by repeatedly folding the 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. (Jamakandi VG, 2009).

Water Vapour Transmission Rate (WVTR)

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1g anhydrous calcium chloride was placed in the cells and the respective polymer film was fixed over the brim.

The cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after 48 hours of storage. (Shivhare UD, 2009).

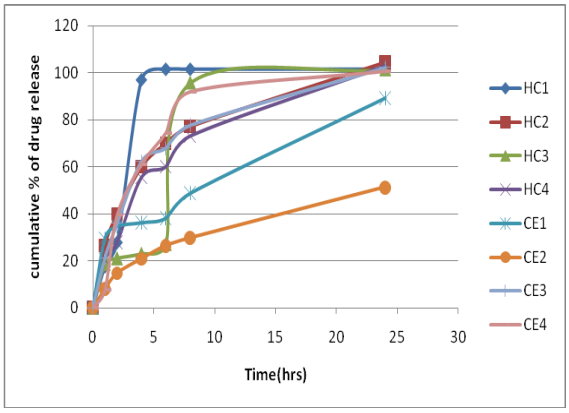

Figure 4: Comparative diffusion studies of all patches

In vitro Permeation Studies

Cellophane membrane was mounted between the donor and receptor compartment of modified Franz diffusion cell. The patch was kept in contact with cellophane membrane. The receptor compartment contained phosphate buffer (pH 7.4). The assembly was kept on a magnetic stirrer and stirred at a speed of 200 rpm. The temperature of the assembly was kept 37 ± 0.5 ºC. After various time intervals 1ml of sample was withdrawn from sampling port and replaced with fresh

medium up to 24 hours to study. The samples withdrawn were analyzed spectrophotometrically at 257.2 nm. (Aquil M., 2002).

Study of Drug Release Kinetics

The in vitro permeation data was further treated with kinetic equations such as zero order, first order, Kosemeyer Peppas model and Hixon Crowell to understand the release kinetics and mechanism of release from the formulated patches.(Jose CP, 2001) Software used for this purpose were BITSOFT and PCP Disso-V2.08.

Effect of plasticizer on film

Plasticizer can affect release kinetics of the film. A plasticizer, dibutyl phthalate was added in 5 % w/w and 10 % w/w concentration of polymer weight. The films were then evaluated for in-vitro drug permeation. (Shinde AJ, 2008)

RESULTS AND DISCUSSION

Formulation of transdermal patches

Transdermal patches of Itopride hydrochloride were prepared by solvent casting method on glass moulds, using polymers like HPMC K 15, Carbopol 934 P and Eudragit L 100. In all these formulations amount of drug per cm^2 of patch was maintained at 1410 mcg.

Evaluation of Transdermal Patches

Transdermal patches of Itopride hydrochloride were formulated and evaluated for various parameters. In the present study, total eight formulations were prepared by varying polymer ratio, using different polymers. These patches were subjected for evaluation of various physico-chemical characteristics and drug release studies.

After carrying out initial preformulation studies, drug-excipients compatibility was carried out by FT-IR analysis. Initially the IR spectrum of pure drug was obtained. The results of this observation concluded that there is no interaction between the drug (Itopride hydrochloride) and other excipients.

Prepared patches were evaluated for various physico-chemical properties like thickness uniformity, weight variation, drug content, moisture uptake at 23%, 43%,75% and 93 % RH, moisture content, folding endurance, water vapour transmission studies and in-vitro permeation studies.

Thickness Uniformity

The thickness of patches varied from 0.06-0.086 mm for HPMC-Carbopol patches and 0.143-0.176 mm for Carbopol-Eudragit patches with low values of standard deviation. Eudragit L 100-Carbopol 934 P patches were found to be thicker than HPMC K-15- Carbopol 943 P patches. Therefore it can be said that inclusion of Eudragit increases thickness of the film. It could be attributed to higher density of Eudragit L 100 than HPMC K 15.

Weight Variation

The weight of patches varies from 5.70-7.03mg for HPMC-Carbopol patches and 7.0-8.93mg for Carbopol-Eudragit patches with low values of standard deviation. Eudragit L 100-Carbopol 934 P patches weighed more than HPMC K-15- Carbopol 943 P patches. This is in conformity to the thicker patches of Eudragit-Carbopol as compared to HPMC- Carbopol patches.

Drug Content

Formulated patches in each group were found to have uniform drug distribution with values ranging from 1408.96- 1434.05mcg/ patch in case of HPMC-Carbopol patches and 1406.92-1414.49 mcg/patch for Carbopol-Eudragit patches.

Moisture Absorption Studies

Moisture uptake was found to be dependent on the relative humidity (RH). As relative humidity increased, percent moisture uptake by the patches also increased. Moisture uptake was found to be high in patches containing higher concentration of HPMC K 15 on account of its hydrophilic nature. Moisture uptake was also found to be high in patches containing higher concentration of Carbopol 934 P on account of its hygroscopic nature.

In case of HPMC-Carbopol patches, maximum % of moisture uptake was 1.19%, 2.13%, 3.59%, and 17.21% at 23%RH, 43% RH, 75%RH, 93% RH respectively. Among HPMC-Carbopol patches, HC4 patches showed maximum % of moisture uptake because of higher proportion of hydrophilic polymer.

In case of Carbopol-Eudragit patches, maximum % moisture uptake was 1.01%, 2.09%,8.21%,11.16% at 23% RH, 43% RH, 75%RH, 93% RH respectively. Among Carbopol-Eudragit patches, CE1 patches showed maximum moisture absorption because of higher proportion of Carbopol which shows hygroscopic properties.

Moisture Content

The result of moisture content study showed that patches contained specific amount of moisture in them. Moisture content in HPMC-Carbopol patches ranged from 0% to 8.40% whereas moisture content in Carbopol-Eudragit patches ranged from 6.57%-16.66%. Small moisture content in the formulation helps it to remain stable and prevents from being a completely dried and brittle film. The results of moisture content study clearly show the higher moisture uptake by films containing higher proportion of Carbopol. This could be attributed to hygroscopic nature of Carbopol.

Folding Endurance

Folding endurance measures the ability of patch to withstand stress resulting in rupture. Folding endurance was in range of 197-642 times in case of HPMC-Carbopol patches and 6-189 times in case of Carbopol-Eudragit patches. HPMC-Carbopol patches showed

remarkable superiority in comparison to Carbopol-Eudragit patches in case of folding endurance. So, it can be inferred that HPMC-Carbopol combination was better than Carbopol-Eudragit combination. This gives an indication of the former combination to be more significant.

Water Vapour Transmission Rate (WVTR)

Water vapour transmission (WVT) studies showed that all patches were permeable to water vapour. WVT for HPMC-Carbopol patches ranged from 5.1-6.0 mg/cm^2hr whereas for Eudragit-Carbopol patches it ranged from 6.1-6.9 mg/cm^2hr. From the studies, it can be concluded that Eudragit-Carbopol patches were more permeable to water vapour than HPMC-Carbopol patches. This may be due to higher affinity of HPMC for water vapours than Eudragit.

In vitro Permeation Studies

From in-vitro permeation studies, it is imperative that patches HC1 and HC3 were releasing almost full dose within 6 and 8 hours respectively following burst release whereas release from HC2 and HC4 patch were 77.12% and 73.12% respectively, up to 8 hours. From this result, HC2 and HC4 were chosen for further studies. In case of Carbopol-Eudragit patches, patches CE2 and CE4 were releasing 29.74% and 95.95% of drug in 8 hours whereas release from CE1 and CE3 was 48.75% and 77.59% upto 8 hours respectively.

Study of Drug Release Kinetics

To know the mechanism of release from these formulations, the data were treated according to zero order, first order, Higuchi diffusion kinetics and korsnmeyer-peppas model. Studies showed that all the four formulations followed first order showing that rate of release to be dependent on initial concentration of drug present in the patch formulation.

Effect of plasticizer on film

According to the dissolution profile of the formulations, 4 formulations were chosen to see the effect of plasticizer on the release profile of the formulation. Plasticizer chosen for the purpose was dibutyl phthalate and was used in concentration of 5 % and 10% w/w.

The in vitro permeation data was further treated with kinetic equations such as zero order, first order, Kosemeyer Peppas model and Hixon Crowell to understand the release kinetics and mechanism of release from the formulated patches. The in vitro permeation data of formulation HC2 (5% DBP) shows Peppas Korsmeyer as best fit model for drug release with correlation coefficient value of 0.9898. The in vitro permeation data of formulation HC2 (10% DBP) shows Hixon Crowell as best fit model for drug release with correlation coefficient value of 0.9890. The in vitro permeation data of formulation HC4 (5% DBP) shows first order as best fit model for drug release with correlation coefficient value of 0.9991.The in vitro permeation data of formulation HC4 (10% DBP) shows first order as best fit model for drug release with correlation coefficient value of 0.9985. Results show that incorporation of dibutylphthalate as plasticizer decreases in-vitro permeation rate of drug. However, change in concentration of dibutylpthalate from 5% to 10 % w/w do not affect the in-vitro permeation rate of drug significantly.

ACKNOWLEDGEMENT

Itopride hydrochloride was received as gift sample from Inventia Healthcare Pvt. Ltd., Thane. Carbopol 934 P and Eudragit L 100 were gifted by Dr. Reddy's Laboratory, Hyderabad. HPMC K 15 was obtained from Central Drug House, New Delhi. We gratefully acknowledge their contributions in completion of this work.

REFERENCES

Aquil M., Ali A. Monolithic matrix type transdermal drug delivery system of pinacidil monohydrate: in-vitro characterization, European Journal of Pharmaceutics and Biopharmaceutics, vol. 54, no. 2, 2002 pp. 161-64.

Chein, YW. 'Transdermal therapeutic systems', in Controlled drug delivery: Fundamentals and applications. New York: Marcel Dekker Inc.1987: pp.524-49.

Gattani S.G., Zawar L.R., Kakade K.N., Sharma S.J. 'Optimization of transdermal film of lovastatin, Ind. Drugs, vol. 45, no.1, 2008 pp. 79-91.

Gupta S., Kapoor V., Gupta B.M., kapoor B., Verma U., Gupta V. ' Effect of Itopride hydrochloride on QT interval in adult healthy volunteers', JK Practitioner, vol. 13, no. 4, 2005 pp. 207-210.

Jain S., Bhadra D., Jain SJ, 'Transferosomes-A novel carrier for effective transdermal drug delivery', in Jain, N.K., (ed.) Advances in controlled and novel drug delivery, New Delhi: CBS Publisher and Distributor, 2001: pp. 426-23.

Jamakandi V.G., Mulla J.S., Vinay B.L., Shivakumar H.N. ' Formulation, characterization, and evaluation of matrix type transdermal patches of a model antihypertensive drug', Asian Journal of Pharmaceutics, vol. 3, no.1, 2009 pp. 59-65.

Jose C.P., Loba M.S. 'Modelling and comparison of dissolution profiles', Eur. J. Pharm Sci, vol. 13, 2001 pp. 123-33.

Khannum, A., Pandit V., Bhaskaran S., Banu V. 'Preparation and evaluation of tolterodine tartarate transdermal films for the treatment of overactive bladder', Research J. Pharm and Tech, vol. 1, no.4, 2005 pp.516-521.

Mutalik S., Udupa N. 'Formulation, development, in vitro and invivo evaluation of membrane controlled

transdermal system of glibencamide', J.Pharm. Pharmacet. Sci., vol. 8, no. 1, 2005 pp.26-38

Sanap G.S., Dama G.Y., Hanade A.S., Karpe S.P., Malawade S.P., Kakade R.S., Jadhav U.Y. 'Preparation of transdermal monolithic system of indapamide by solvent casting method and the use of vegetable oil as permeation enhancer', Int. J. Green Pharm., vol. 2, no. 1, 2008 pp. 129-133.

Shivhare U.D., Dorlikar V.P., Mirani B.N., Bhusani K.P. 'Controlled release formulation and characterization of carvedilol transdermal film, Priory Lodge Journals, vol. 12, no.2, 2009 pp. 121-28

Vyas S.P., Khar R.K. 'Controlled drug delivery, concept and advances', Delhi: Vallabh Prakashan, 2002:pp.412-413.