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Formulation and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Domperidone hydrochloride

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Original Article
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ABSTRACT

A matrix dispersion type transdermal drug delivery system of domperidone was developed using different ratios of rosin with Eudragit RL and Eudragit RS. The effect of the polymers on the technological properties, i.e., drug release, water vapor transmission rate, percentage moisture loss and thickness were investigated. The patch containing Eudragit RL: Eudragit RS (8:2) showed a release of 87.10% in 12 h. Formulation D1 emerged as the most satisfactory formulation as far as the technological properties were concerned. Further skin permeation and skin irritation studies were carried out on rat skin and rabbit respectively. Therefore it can be concluded that the patch containing Eudragit RL: Eudragit RS in the ratio 8:2 achieved the desired objectives of transdermal drug delivery systems, such as overcoming of first pass effect, extended release and reduced frequency of administration.

KEY WORDS: Domperidone hydrochloride. Eudragit RL. Eudragit RS. Release studies. Transdermal patch.

RESUMEN

Se ha desarrollado un sistema de administración de fármaco transdérmico de matriz de dispersión de domperidona utilizando diferentes coeficientes de resina con Eudragit RL y Eudragit RS. Se ha investigado el efecto de los polímeros en las propiedades tecnológicas, es decir, liberación del fármaco, coeficiente de la transmisión del vapor del agua, porcentaje de pérdida de humedad y espesor. El parche con Eudragit RL: Eudragit RS (8:2) ha mostrado una liberación de 87,10% en 12 h. La formulación D1 ha resultado ser la formulación más satisfactoria, en la medida que afecta a las propiedades tecnológicas. Se han llevado a cabo otros estudios sobre permeabilidad e irritación cutánea en piel de ratones y de conejos respectivamente. Por lo tanto, se puede determinar que el parche que contiene RL: Eudragit RS en un coeficiente de 8:2 ha alcanzado los objetivos fijados de los sistemas de administración de fármaco transdérmico como una superación del efecto del primer pase, liberación prolongada y frecuencia reducida de administración.

PALABRAS CLAVE: Clorhidrato domperidona, Eudragit RL, Eudragit RS, estudio de liberación, parche transdérmico.

INTRODUCCIÓN

Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered[1]. Compared with oral and parental routes, drug delivery through skin can offer several advantages for example bypassing the hepatic "first pass" elimination[2], maintaining a constant, prolonged and therapeutically effective drug level in the blood stream or tissues[3], rapid termination of drug delivery[4], improved patient compliance[5]. However, transdermal delivery is limited to drugs having low doses, low melting points and molecular weights and a solubility of greater than 1 mg/ml in both water and mineral oil[6]. The disadvantage of this design is that it needs 6 to 8 h for a therapeutical plasma level to appear after application.

In the transdermal delivery systems, polymeric membrane is a key component and used to modulate the release rate of a therapeutic drug. A plasticizer is supposed to weaken the intermolecular forces between the polymer chains, resulting in a softened and flexible polymer matrix. Thus drug permeability through the membranes may also be affected by the addition of a plasticizer[7].

Domperidone Hydrochloride is a drug used to treat gastrointestinal disorders; it is contraindicated for individuals with hypersensitivity, gastrointestinal obstruction, perforation, or hemorrhage and prolactinoma. Caution should be used in patients with hepatic disease and with those taking anticholinergics, since they may antagonize the effect of domperidone in the gastrointestinal (GI) tract. The literature reveals that Domperidone Hydrochloride undergoes variable and extensive first pass metabolism before entering into systemic circulation.

MATERIALS AND METHODS

Materials

Eudragit RL and Eudragit RS were procured from Rohm Pharma, West Germany; Domperidone HCl was obtained as gift sample from Micro Labs, Hosur, India; Diethyl phthalate form Microfine chemicals, Mumbai, India, Chloroform from Qualigens Fine chemicals, Mumbai, India; Ethyl alcohol from Changshu Yangyuan Chemical, China and N,N Dimethyl formamide and Mercury were from Merck, India Ltd., Mumbai, India. Membrane for the permeability studies was the dorsal section of full thickness skin from Wistar rats weighing around 200 – 250 g, whose hair had been previously removed with an electronic clipper. Stratum corneum was prepared from the full thickness skin.

Methods

Preparation of film

Polymer matrix solution preparation

The composition of various film formulations is given in Table 1. The compositions were devised using polymers along with the drug. Chloroform, Ethanol and Dimethyl formamide were used as solvents for the film and the polymers were weighed accurately and dissolved in corresponding solvents. To this polymer solution 10.0% w/w plasticizer was added and mixed well. Calculated amount of the drug was added to the polymer solution and mixed using a cyclomixer; the uniform dispersion was poured on the mercury surface and dried at room temperature for 24 h. Controlled solvent evaporation was achieved by placing an inverted funnel over the petri dish. The dry films were removed and kept in a desiccator until used.

Drug compatibility studies

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. The drug and the excipients must be compatible with one another to produce a product that is stable, efficacious, attractive and easy to administer and safe. FT-IR and X-ray diffraction studies were used to investigate any physicochemical interactions between drug and excipients used in the formulation.

Physicochemical properties of the films

The films were evaluated for the following physicochemical properties.

Film thickness

The thickness of the patches was determined using screw

Tabla 1. Composition of patches.

Ingredients in mg	D1	D2	D3
Domperidone	20	20	20
Eudragit RL	200	150	125
Eudragit RS	50	100	125
Diethyl phthalate (%w/w) of the polymer	10	10	10
Chloroform	1.5	1.5	1.5
Ethanol	0.5	0.5	0.5
Dimethylformamide	0.5	0.5	0.5

gauge, recording a mean of three determinations.

Weight Variation

Four films from each batch were weighed individually and the average weight was calculated.

Drug content

Films of a specified area were cut and weighed accurately. Pieces were taken into a 100 ml volumetric flask and 50 ml of phosphate buffer solution (pH 7.4) was added and stirred vigorously for 4 hr to extract drug. Finally the solution was suitably diluted with pH 7.4 buffer, and samples were analyzed spectrophotometrically at 205 nm for drug content.

Moisture content

The prepared patches were cut into 20 X 50 mm strips, were weighed individually and kept in a desiccator containing calcium chloride at 37°C for 24 h. The films were reweighed individually until a constant weight was obtained. Percentage of moisture content was then calculated based on the change in the weight with respect to the initial weight of the film.

Moisture absorption studies

The water absorption capacities of various films were determined at 75% relative humidity (RH). Films were cut into 20 X 50 mm strips, were weighed, kept in a desiccator at 40°C for 24 h, removed and exposed to RH conditions of 75% (containing saturated solution of sodium chloride) in different desiccators at room temperature. Weight was taken periodically until a constant weight was obtained. The water absorption capacity of the films (in weight %) was calculated in terms of percentage increase in the weight of film over the initial weight of the strip.

Flatness and elongation brake

Longitudinal strips were cut from the prepared medicated films. The flatness was determined at various points by using vernier calipers. The percentage elongation brake was determined by noting the length just before the break point and determined.

Folding endurance

Folding endurance 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 was the folding endurance.

Scanning electron microscopy

In order to know general morphology and drug releasing pores of the formulation SEM was taken using a Philips XL 30 scanning electron microscope at an excitation voltage of 20 kV.

In vitro Permeation Studies

An in vitro permeation study was carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 150 to170g was used. Hair from the abdominal region was carefully removed by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in pH 7.4 buffer before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 37 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of 1 ml was removed from the receptor compartment at regular intervals and an equal volume of fresh medium was added. Samples were filtered through Whatman filter paper No: 41 and analyzed spectrophotometrically at 205 nm. The study was performed for twenty four hours, and amount of drug release was calculated.

Skin irritation and sensitization testing

Skin irritation and sensitization testing were performed on healthy rat (average weight: 150 to 170 g). The dorsal surface (25cm2) of the rat was cleaned, and the hair was removed by shaving after the skin was cleaned using rectified spirit and the representative formulations were applied over the skin. These were removed after 24 h and the skin was examined for any untoward reaction.

Stability studies

Stability testing has become an integral part of formulation development. It generates information on which proposal for shelf life of drug or dosage form along with their recommended storage conditions are provided as per ICH guidelines for stability study for new drug development. The formulation was stored at 25oC and 65% RH for 12 months for long term stability study. The samples were taken and analyzed for their physicochemical parameters at the end of 3rd month.

RESULTS AND DISCUSSION

Three different compositions of patches containing varying proportions of Eudragit RL and Eudragit RS were prepared. The composition is shown in Table 1.

Plasticizer is often incorporated in transdermal therapeutic system to give flexibility to the polymer matrix, thereby improving their contact with the skin; plasticizers lower the temperature of the second order phase transition of

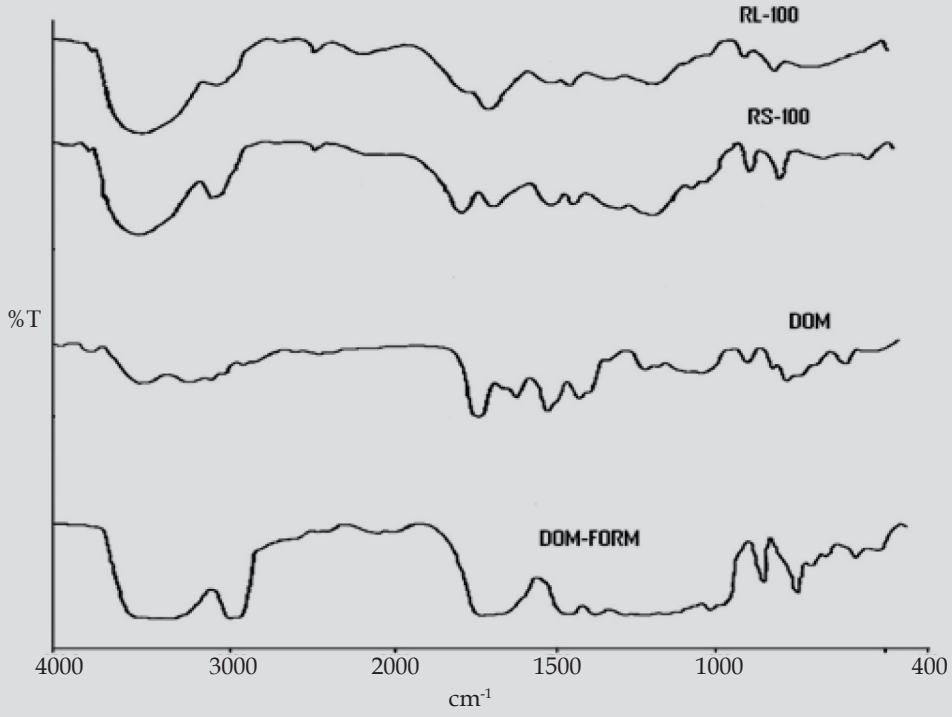
the polymer and increase the workability, flexibility and permeability of the drug, in the present study, 10% w/w was added to the polymer solution.

FTIR and X-ray diffraction studies were performed to investigate chemical interactions between drug and the excipients. Domperidone Hydrochloride shows characteristic absorption at 3442.80 (NH stretch), 2830.32 (methyl frequencies), 1619.61 (NH bonds), 1698 (aromatic combination bonds) and 706.13 (aliphatic chloro compound) these characteristic bands were present in all spectra, no new bands or shift in characteristic peaks appeared. IR spectra are shown in Fig 1. XRD of Domperidone shows at 15.2, 22.9, 23.8 and 44.3 degrees these characteristic peaks were present in XRD, no new peaks or shift in characteristic peaks appeared. XRD are shown in Fig 2. From FTIR and XRD results reveal that there is no interaction between the drug and the excipients used in the formulation.

The formulated films were characterized for various parameters such as thickness, uniformity of weight, flatness and elongation brake (%), folding endurance, moisture content, moisture absorption and drug content. These are essential parameters for the evaluation of the dosage form in order to achieve a formulation with uniformity and consistency within a batch. The results are shown in Table 2. The drug content analysis of the prepared formulations show that the processes used to prepare the patches in this investigation gives uniform drug content, minimum batch variability and exhibit uniform thickness and uniformity of weight. The uniformity in drug content, uniformity of weight and thickness indicates that the polymeric solution of the drug is well dispersed. However little variations were observed in different formulations, which may be due to the variation in polymeric content.

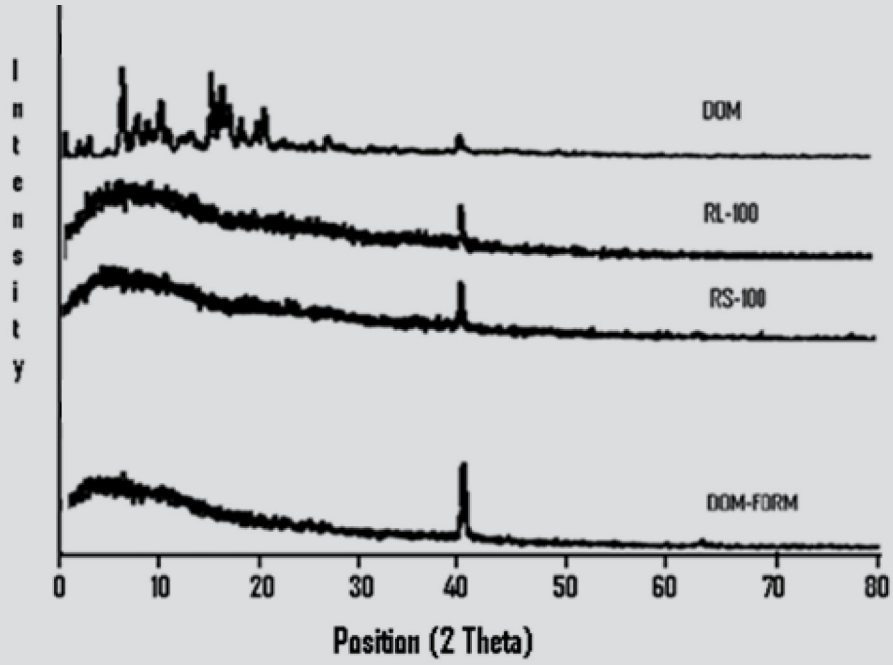
Release studies are required to predict the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices is essential for ensuring sustained release performance. Drug release from a transdermal therapeutic system can be characterized in terms of the rate and extent to which the drug is released from the device by in vitro diffusion studies. The in vitro diffusion studies are predictive of in vivo performance of a drug. Release of drug from transdermal patches is controlled by the chemical properties of drug, form of delivery as well as the physiological and physicochemical properties of the biological membrane (Rao et al. 2000). Rate controlling factors include, drug concentration in the matrix, chemical nature of matrix material and device geometry. The cumulative amount of Domperidone hydrochloride permeated through the rat abdominal skin, into a receptor solution, as a function of time. The mean cumulative amounts of drug permeated from the formulations were found to be 87.10%, 67.13% and 54.25% for D1, D2 and D3 respectively after 12 h; the results are shown in Fig 3. From the results it reveals that formulation D1 showed the better release when compared to others. The drug release data obtained for formulation

Tabla 1. FT-IR spectra of drug, excipients and physical mixture.



RL-100: Eudragit RL-100
RS-100: Eudragit RS-100
DOM: Domperidone hydrochloride
DOM-FORM: Domperidone hydrochloride formulation

Tabla 1. X-RD pattern of pure drug, excipients and physical mixture .



DOM: Domperidone hydrochloride
RL-100: Eudragit RL-100
RS-100: Eudragit RS-100
DOM-FORM: Domperidone hydrochloride formulation

Tabla 2. Physical characteristics of Domperidone patches.

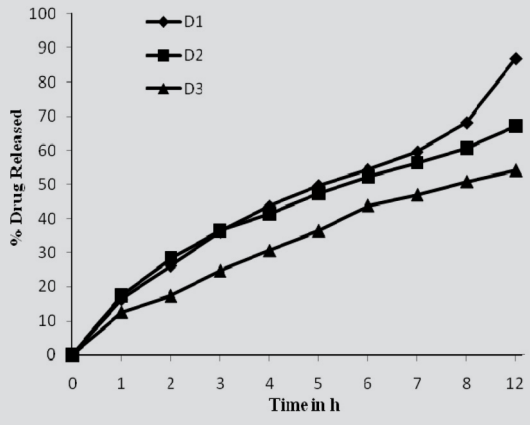
Physical characteristics	D1	D2	D3
Thickness	0.16±0.014	0.14±0.014	0.15±0.014
Uniformity of weight (g)	0.265 ±0.013	0.249 ±0.001	0.264±0.001
Flatness and elongation brake (%)	99.6 ±1.26	102.0 ±1.26	96.0 ±1.67
Folding endurance (no's)	124.0 ±1.67	119.0 ±2.19	127.0 ±1.54
Moisture content (%)	4.49 ±0.017	3. 95±0.018	4.04 ±0.023
Moisture absorption (%)	2.45 ±0.009	1.27 ±0.008	2.94 ±0.009
Drug content (mg)	19.37 ±0.93	19.02 ±0.74	18.03 ±0.75

D1 was plotted according to Zero order, first order, Higuchi, Korsemeyer-Peppas equation and Hixson Crowell equation. The above results were verified with respect to the linear regression coefficient (r^2) and the results are shown in Table 3. From the above kinetic studies, it was observed and inferred that the release of the drug from the formulation D1 follows the first order release kinetic and Higuchi diffusion equation. Hixon Crowell equation also found to be linear, these indicates that the release from the patch was both diffusion and erosion method.

Results of SEM analysis, performed to investigate the surface morphologies and pore size of before and after diffusion of patches and the SEM photographs are shown in Fig 4 and 5. The results of skin irritation studies show no signs of erythema when compared to that of the control; the absence of edema indicates that the polymeric patches are compatible with the skin.

Stability testing of the prepared formulation was carried out

Figure 3. In-vitro release profile of formulations D1 to D3



at 25oC and 65% RH for 3 months. The samples were taken and analyzed for their physicochemical parameters for 3 months. The physicochemical parameters like appearance, thickness, unformity of weight, moisture content, moisture

Tabla 3. Drug release kinetic of Domperidone hydrochloride transdermal patch

Formulation code	Zero order equation (r^2)	First order equation (r^2)	Higuchi mode (r^2)	Hixson Crowell model (r^2)	Korsemeyer Peppas model (r^2)
D1	0.959	0.969	0.928	0.767	0.992

absoption and drug content were found to be satisfacotry, and there is no change with respected to the initial analysis results.

CONCLUSION

The present study shows that Domperidone Hydrochloride patch containing Eudragit RL and Eudragit RS in the ratio 4:1 with 10%w/v of diethyl phthalate achieved the desired objectives of transdermal drug delivery systems, such as overcoming of first pass effect, extended release and reduced frequency of administration may serve as a better system for transdermal delivery. It also satisfies the requirements of modern drug delivery systems in delivering the drug in predetermined manner.

Figure 4. SEM photographs of domperidone transdermal patch before diffusion

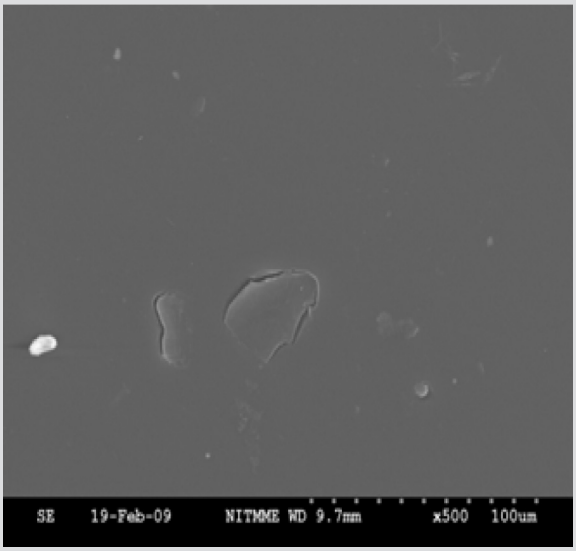
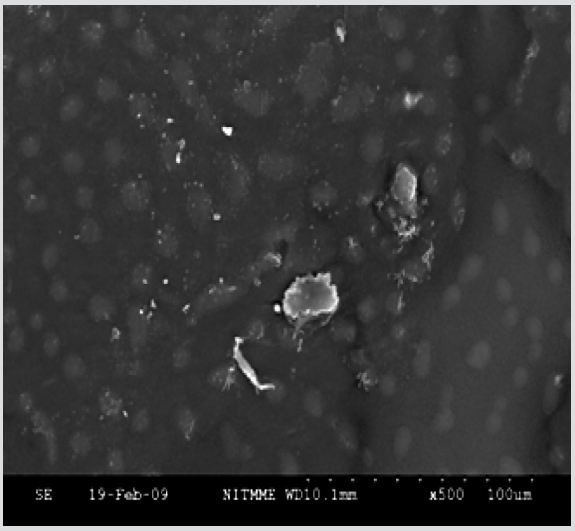


Figure 5. SEM photographs of domperidone transdermal patch after diffusion



REFERENCE

1. Ghosh TK, Pfister WF. Transdermal and Topical Delivery Systems: An overview and future trends. In: Ghosh TK, Pfister WF (ed.) Transdermal and Topical Drug Delivery Systems, CRC Press, Boca Raton, FL, 1997; pp. 1-32.

2. Chandrasekaran SK. Controlled release of scopolamine for the prophylaxis of motion sickness. Drug Dev Ind Pharm. 1983; 9: 627-646.

3. Clissold SP, Heel RC. Transdermal hyocine (Scopolamine): a preliminary review of pharmacodynamic properties and therapeutic efficacy. Drugs. 1985; 29: 189-207.

4. Nachum Z, Shahal B, Shupak A, Spitzer O, Gonen A, Beiran I, et al. Scopolamine bioavailability in combined oral and transdermal delivery. J Pharmacol Exp Ther. 2001; 296: 121-123.

5. Chien YK. Advances in transdermal systemic medium. In: Transdermal Controlled Systemic Medications, Marcel Dekker Inc., New York, 1987, pp. 1-22.

6. Devi VK, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm. 2003; 29(5): 495-503.

7. Wang FJ, Yang YY, Zhang XZ, Zhu X, Chung TS, Moochhala S. Cellulose acetate membranes for transdermal delivery of scopolamine base. Mat Sci Engg C. 2002: 20: 93-100.