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Research Article

FABRICATION AND EVALUATION OF DOMPERIDONE TRANSDERMAL FILMS

ANISREE G S*, RAMASAMY C, JOHN WESLEY I

***Karpagam University, Coimbatore, Dept.of Pharmaceutics, Jamia Salafiya Pharmacy College, Malappuram, Kerala, India.**
Email: anisreegs@gmail.com

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ABSTRACT

The aim of the work was to develop a sustained release transdermal film of Domperidone. The oral bioavailability of Domperidone is very poor due to its rapid first pass metabolism. The formulation proceeded by using a natural and synthetic polymers. Transdermal drug delivery can be efficiently used for the active agents which causes severe gastric irritation and undergo rapid first pass metabolism, hence the transdermal films of domperidone were prepared by using HPMC as the main polymer and the combinations of Ethyl cellulose and Eudragit RS-100 in different ratios were attempted using Poly ethylene glycol 400 as the plasticizer. The prepared formulations were evaluated for the various physico chemical parameters, *in vitro* permeation studies and stability studies. The drug-excipients compatibility studies were done by Fourier Transform Infrared spectrophotometer (FTIR). The films showed satisfactory folding endurance and tensile strength. *In vitro* diffusion study was carried for 24 hours and formulation A4 showed 99.13% drug release at the end of 24 hours. It was observed that the system with HPMC:EC in the ratio 7:3 along with plasticizer was very promising in controlling release of domperidone via transdermal drug delivery system. The stability studies revealed all the films have good shelf life.

Keywords: Domperidone, Transdermal films, *In vitro* permeation.

INTRODUCTION

Transdermal therapeutic system[1] is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication through the skin. It provides controlled release of the drug to the patient, and enables a steady blood level profile leading to reduced systemic side effects and some times improved efficacy over other conventional dosage forms. This therapeutic system is used for non-ionized drugs required in small dosage[2] .It provides several benefits, including the avoidance of hepatic first-pass metabolism, which provides a constant drug delivery for a long period. It improves patient compliance and efficacy of the drug.

Vomiting is a forceful action accomplished by a fierece, downward contraction of the diaphragm. Nausea and vomiting are not diseases, but symptoms of many different physiological conditions of the body. In addition to this, nausea and vomiting are prominent with many cytotoxic drugs due to the direct stimulation of CTZ.

Domperidone[3, 4] (DOM), is a dopamine-receptor (D2) antagonist, widely used for the treatment of motion sickness, treatment of nausea and vomiting. Domperidone, a versatile drug with a proven efficacy in all type of patients that is commonly available in the form of tablet. It undergoes extensive first pass metabolism, leads to its poor availability in the systemic circulation. The conventional dosage forms of domperidone needs to be administered 2-3 times daily, which leads to patient noncompliance.

The above shortcomings associated with conventional administration of domperidone would be overcome by modifying the dosage form. Among the various drug delivery systems available, transdermal dug delivery provides many benefits like ease of application, extended period of action, increased bioavailability and increased patient compliance.

The two parameters such as low molecular weight and dose satisfy for Domperidone and thus the present study was undertaken in formulating transdermal films. Natural as well as synthetic polymers singly as well as in combinations were used for the fabrication. The polymers used are Hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose (EC), Eudragit RS 100(ERS-100). The polymers selected were non-toxic and non-absorbable and they did not lose their film forming properties when they formulated with drug. The formulated films were evaluated for their folding endurance, thickness, weight variation, drug content and *in-vitro* release parameters.

MATERIALS AND METHODS

Materials

Domperidone obtained as a gift sample from Themis labs, Thane. Hydroxy propyl methyl cellulose and EC were purchased from S.D fine chemicals. Eudragit RS-100 was procured from Evonic deggussa, mumbai. All other chemicals and reagents used in the study were of analytical grade.

Preparation of Transdermal Films [5,18,19,20]

Matrix type transdermal film containing DOM were prepared using different ratios of HPMC, EC,ERS-100.Solvent casting technique employed here for the fabrication of films. Formulation chart of the polymeric composition is presented in Table No: 1.

Accurately weighed polymers were dissolved in suitable solvent. DOM was added slowly to the polymer solution and mixed thoroughly to obtain a homogeneous mixture. Polyethylene glycol-400 (PEG-400) and Dimethylsulfoxide (DMSO) act as the plasticizer and permeation enhancer respectively. The polymeric solution was poured onto the locally fabricated mould having the surface area of 100 cm^2 and dried at room temperature in dust free environment. After 24h,the films were cut into 2cm^2 piece, packed in aluminium foil and stored over fused calcium chloride in a desiccator at room temperature for evaluation studies.

Evaluation of Transdermal films

Drug polymer interaction studies[6,7]

The compatibility study was carried out using Fourier transform infrared spectral analysis by KBr disc method. The spectra obtained for domperidone, polymers and the mixture were compared.

Folding Endurance [8,9]

Folding endurance reveals the flexibility of the films. This was determined by repeatedly folding the film at the same place until it broke. The maximum number of times the films could be folded at the same place without breaking or cracking gives the value of folding endurance.

Thickness and Weight variation[10,11]

The thickness was assessed at six different parts of the films using digital thickness gauge. For each formulation, three randomly selected films were used. For weight variation test, three films from

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

Drug Content [12,13]

A film was cut in to small pieces and put in to 100mL buffer solution (pH-6.8). This was then shaken in a mechanical stirrer at 37^{0}C for 24h to get a homogeneous solution. The obtained solution was filtered and the drug content was determined spectroscopically at 272 nm after suitable dilution.

In- vitro permeation studies [14,15]

The studies were performed with the help of a modified Franz diffusion cell of capacity 15mL using cellophane membrane, activated in phosphate buffer pH 6.8(by boiling and followed by keeping in it for over night). A section of the membrane was cut, measured and placed on the dermal side of the membrane in the donor compartment facing the drug matrix side of the film to the membrane. The holder containing the membrane and formulation was then placed on the receiver compartment of the modified diffusion cell, containing phosphate buffer pH 6.8.The temperature of the diffusion cell was maintained at 32±2^{0}C.

The whole unit was kept on a magnetic stirrer and solution in the receiver compartment was constantly and continuously stirred. The samples were withdrawn at predetermined and stipulated time intervals. An equal quantity of the phosphate buffer was replaced. Absorbances were measured at 272nm spectroscopically, taking phosphate buffer as blank. The amount of drug permeated per square centimeter at each interval was recorded. It was taken for calculating the cumulative drug release. The permeation study was carried out for 24h.

Stability studies [16,17]

The prepared films were placed in USP type-I amber coloured vials. The vials are closed with bromobutyl rubber plugs and then sealed with aluminium cap. Bottles were placed in stability chamber at 40±2^{0}C and 75%RH for three months. Each time three films were withdrawn and evaluated for their physical appearance and drug content.

Table 1: Table shows Formulation chart of Transdermal films

Formulation Identity	Drug (in mg)	Polymer (In Ratio)			PEG-400(%)
		HPMC	EC	ERS100	
A1	10	10	0	---	10
A2	10	9	1	---	10
A3	10	8	2	---	10
A4	10	7	3	---	10
A5	10	6	4	---	10
A6	10	5	5	---	10
A7	10	4	6	---	10
A8	10	3	7	---	10
A9	10	2	8	---	10
A10	10	1	9	---	10
A11	10	0	10	---	10
B1	10	9	---	1	10
B2	10	8	---	2	10
B3	10	7	---	3	10
B4	10	6	---	4	10
B5	10	5	---	5	10
B6	10	4	---	6	10
B7	10	3	---	7	10
B8	10	2	---	8	10
B9	10	1	---	9	10
B10	10	0	---	10	10

Table 2: Table shows Evaluation parameters of Transdermal films

Formulation Identity	Folding Endurance*	Thickness(µm) *	Weight Variation (mg/ cm^2) *	Drug Content(%)*
A1	508±0.013	0.04±0.002	14.1 ± 0.18	98.021±0.256
A2	468±0.016	0.05±0.012	18.65± 0.09	98.424±0.512
A3	495±0.04	0.07±0.013	19.3± 0.12	98.687±0.348
A4	513±0.092	0.09±0.02	17.47± 0.08	99.68±0.098
A5	498±0.095	0.11±0.016	19.8+ .0.20	98.812±0.179
A6	512±0.063	0.09±0.018	18.56± 0.15	98.23±0.189
A7	400±0.98	0.17±0.19	19.67± 0.09	99.15±0.098
A8	468±0.025	0.16±0.019	19.97 ± 0.06	98.89±0.139
A9	406±0.097	0.21±0.090	21.03± 0.13	98.86±0.095
A10	511±0.052	0.20±0.12	21.06± 0.19	99.08±0.21
A11	518±0.056	0.05±0.011	21.2± 0.23	98.38±0.193
B1	498±0.052	0.06±0.016	22.9±0.018	99.036±0.211
B2	489±0.091	0.05±0.12	21.7±0.21	98.07±0.188
B3	511±0.07	0.07±0.013	20.0±0.19	98.23±0.185
B4	502±0.044	0.05±0.018	21.12±0.24	98.86±0.176
B5	516±0.07	0.16±0.015	19.7±0.18	98.245±0.192
B6	498±0.124	0.19±0.021	18.16±0.21	98.13±0.169
B7	513±0.02	0.06±0.018	16.09±0.18	98.168±0.186
B8	518±0.063	0.16±0.015	15.9±0.19	101.836±0.213
B9	508±0.16	0.08±0.016	23.11±0.31	99.16±0.195
B10	512±0.186	0.12±0.019	17.9±0.26	98.361±0.256

Average of three observations ±SD

RESULTS

Natural as well as synthetic polymers were used for the fabrication of Domperidone transdermal films. Infrared spectroscopic studies were performed to assess the interaction between the drug and selected polymers. The interpreted data showed that there were no interactions between drug and polymers because the principle peaks of the drug and mixture were nearly similar to that of pure substances.

The films obtained were transparent, smooth and flexible. The result of folding endurance, thickness, weight variation, drug content are represented in Table No:2 and are acceptable. Films exhibited uniform weight and thickness, which indicates that the polymeric solution of drug is completely and uniformly dispersed. Stability studies also performed and the results obtained were acceptable.All the films exhibited fairly uniform drug content ranging from 98.778 ± 0.264 to 101.836 ± 0.096.The results of *In-vitro* diffusion studies are represented in Table No: 3 and the corresponding expressions for ideal films are shown in Fig No:1-1 and 1-2 .

DISCUSSIONS

From the findings, selected polymers have better film forming capacity in the formulation of transdermal films. The tensile strength of HPMC:EC films found to be better as compared with HPMC,EC,ERS-100,and HPMC-ERS100.In drug content studies and *In-vitro studies* the formulations fabricated by single polymers showed some deviation from the expected values. But in combination, showed similar values.

In-vitro permeation studies through cellophane membrane showed the amount of drug that is available in receptor compartment. From the observations and results, the combination of polymers has the ability to extent the duration of absorption as compared with single polymer. Stability studies were also performed to identify the shelf life of the formulations. From the physical appearance and drug content evaluation, it was clear that the ideal film have adequate shelf life.

From the above findings, the formulation which have the polymeric combination HPMC:EC in the ratio of 7:3 met all the parameters and thus satisfies the aim of the study.

Table 3: Table shows *In-vitro* Drug release results of ideal films.

Time (Hrs)	Percentage Cumulative Drug Release*									
	A4	A7	A8	A9	A10	B1	B3	B4	B8	B9
0	0	0	0	0	0	0	0	0	0	0
0.5	9.51 ±0.03	8.08 ± 0.16	6.05 ± 0.62	7.13 ± 0.26	3.57 ± 0.20	12.56 ±0.024	7.83 ± 0.18	6.18 ±0.021	12.56 ±0.12	13.58 ±0.15
1	13.53 ±0.13	12.98 ± 0.23	19.22 ± 0.31	10.61 ± 0.31	7.45 ± 0.31	18.35 ±0.09	11.31 ± 0.16	10.48 ±0.097	18.35 ±0.94	16.93 ±0.91
2	22.91 ±1.08	21.44 ± 0.62	31.89 ± 1.38	14.29 ± 1.29	10.65 ± 1.04	21.86 ±1.13	15.95 ± 0.21	19.17 ±1.05	21.86 ±0.93	23.86 ±1.42
3	34.73 ±0.96	39.64 ± 0.38	42.95 ± 1.62	26.93 ± 0.21	23.65 ± 1.28	30.36 ±1.32	25.92 ± 0.31	23.16 ±0.95	30.36 ±1.87	32.564 ±1.07
4	45.48 ±0.98	47.92 ± 0.21	52.55 ± 1.18	48.47 ± 0.18	38.03 ± 0.32	39.85 ±1.22	31.28 ± 0.23	33.81 ±1.12	39.85 ±1.09	40.56 ±1.61
5	58.83 ±1.13	52.93 ± 0.81	62.54 ± 1.31	59.51 ± 1.09	49.93 ± 1.18	43.18 ±1.09	40.43 ± 0.28	40.84 ±0.16	43.18 ±0.96	49.35 ±1.91
6	76.66 ±0.95	68.28 ± 1.03	70.80 ± 0.28	68.91 ± 0.31	59.76 ± 1.31	46.84 ±0.98	53.45 ± 0.31	52.76 ±0.98	46.84 ±1.15	52.54 ±0.93
12	89.12 ±1.08	73.49 ± 1.32	76.14 ± 0.96	73.52 ± 0.80	68.07 ± 2.19	72.57 ±1.13	66.36 ± 0.19	74.51 ±0.95	61.57 ±1.06	69.82 ±1.18
18	97.68 ±1.12	76.78 ± 0.89	80.04 ± 1.13	76.52 ± 1.28	75.86 ± 1.10	83.87 ±1.19	70.13 ± 0.17	82.48 ±1.12	79.87 ±0.98	82.86 ±1.97
24	99.13 ±0.92	95.53 ±0.11	97.83 ±1.24	91.14 ±1.09	94.31 ±0.98	95.87 ±1.06	98.85 ±0.96	96.48 ±0.89	95.87 ±1.12	95.02 ±0.98

Average of three observations ± SD

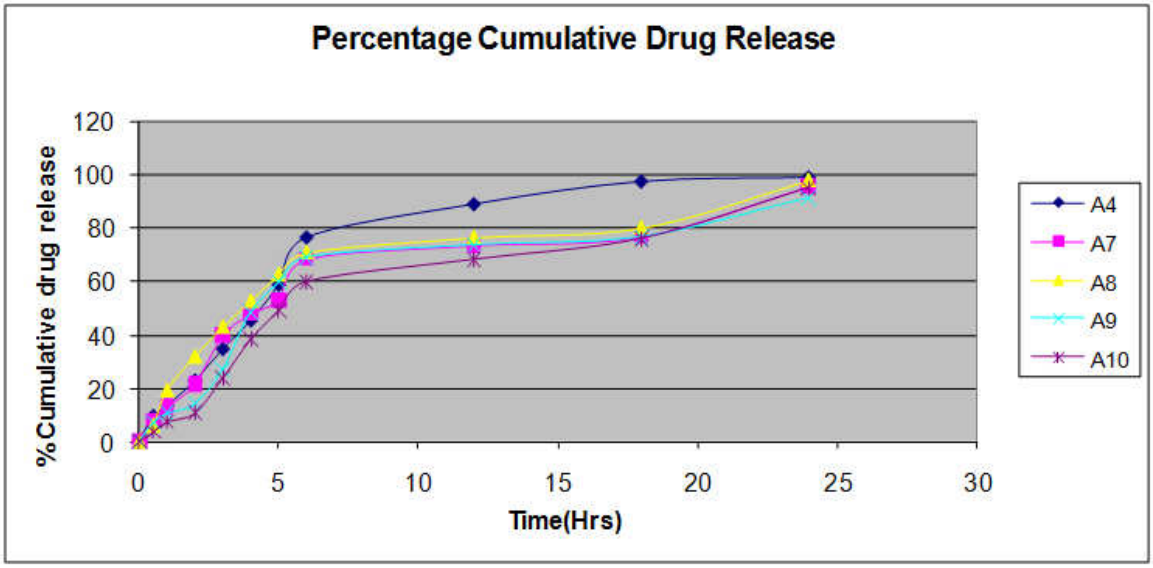

Fig. 1-1: Figure showing percentage cumulative drug release (Ideal Formulations)

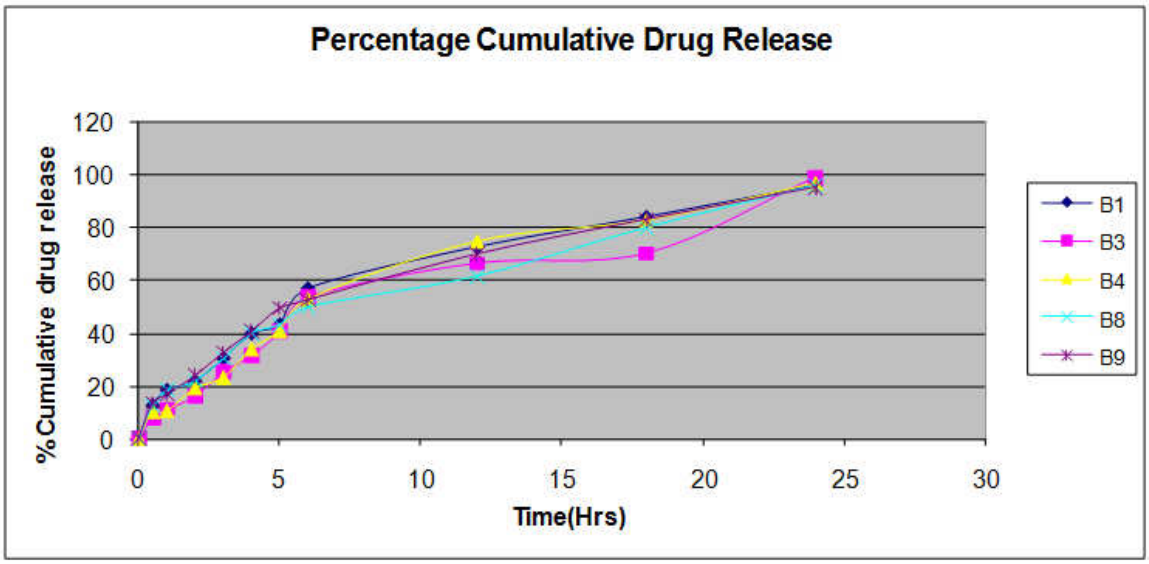

Fig. 1-2: Figure shows percentage cumulative drug release(Ideal formulation)

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