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DESIGN, DEVELOPMENT AND EVALUATION OF SUMATRIPTAN SUCCINATE TRANSDERMAL PATCHES

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ABSTRACT

Most of the therapeutic agents are recommended through an oral route, but oral route has disadvantages like first pass metabolism, liver toxicity, etc, due to gastrointestinal pH. This leads poor bioavailability of drugs, which are not stable in G.I pH. To overcome this problem, increase the bioiavailibility, reduce the dose and dose dumping Transdermal delivery system is better option as novel drug delivery system, which bypass the hepatic first pass metabolism, and avoid drug degradation due to systemic absorption of the drug. Minimize plasma level fluctuations and extend the drug activity besides improving patient compliance. Sumatriptan succinate is a selective 5-hydroxytryptamine receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate. Sumatriptan succinate is a white to off-white powder that is readily soluble in water. Oral administration of Sumatriptan succinate suffers from poorbioavailability, partly due to presystemic metabolism- some of it gets broken down in the stomach and bloodstream before it reaches the target arteries. Sumatriptan is metabolized primarily by monoamine oxidase A into an indole acetic acid analogue, part of which is further conjugated with glucuronic acid. These metabolites excreted in the urine and bile. Only about 3% of the active drug may be recovered unchanged. Because of this the bioavailability is only 15% with half life is 2.5 hrs. In this work, the effort has done to improve bioavailability of the sumatriptan succinate by transdermal patches dosage form by using polymers HPMCK4M, carbopol934 and Dibutylpthalate as used as plasticizers.

INTRODUCTION: Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. 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.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively [1]. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into

systemic circulation, which often causes undesirable side effects.

Thus, various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc, emerged. Several important advantages of trans-dermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea.

The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.

MATERIAL AND METHODS:

Materials: Sumatriptan succinate was obtained as gift sample by sun pharmaceuticals Ltd, Ahmadabad. Polymers carbopol 934, HPMCK4M were obtained as gift sample from Micro Labs Ltd, Bangalore. Remaining reagents are used from S.D Fine chemicals Mumbai.

Preparation of Transdermal Films of Sumatriptan succinate: Transdermal films containing Sumatriptan succinate were prepared by the solvent evaporation technique[5] for the formulations shown in **Table 1**. Solution of HPMCK4M and carbopol934p were prepared in purified water. The polymeric solution was mixed with weighed amount of Sumatriptan succinate slowly. To the mixture, 4 drop of glycerin (117.6 mg), 1 drop dibutyl phthalate (27.4 mg), and 0.25 ml of surfactant (PEG 400 / Tween 80) and permeation enhancer (DMF / DMSO) were added and mixed. The drug-polymer solution was casted in a glass mould of 40 cm^2 (4 × 10 cm^2). The mould was kept in hot air oven at 40^oC for drying for 24 h. Inverted plastic funnel was placed over the mould to prevent the current of air. After drying the films were peeled from glass mould, wrapped in aluminum foil, and preserved in desiccator for further studies**.**

TABLE 1: FORMULATION OF SUMATRIPTAN SUCCINATE TRANSDERMAL PATCHES

Formulation	Sumatriptan succinate (mg)	HPMC K4M (mg)	Carbopol934P (mg)	Glycerin (mg)	Dibutyl phthalate (mg)
F1	25	500	**	117.6	27.4
F2	25	400	100	117.6	27.4
F3	25	300	200	117.6	27.4
F4	25	200	300	117.6	27.4
F5	25	100	400	117.6	27.4
F6	25	*	500	117.6	27.4

Viscosity: Aqueous solutions containing both polymer and plasticizer were prepared in the same concentration as that used for preparation of patches [12]. A Brookefield viscometer (LVDV-E, Brookfield Engineering Labs. Inc, USA) attached to the helipath spindle number 18 and small sample adaptor was used. The viscosity was measured at 20 rpm at room temperature. The recorded values were the mean of three determinations.

Drug- excipient Compatibility Studies: In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Sumatriptan succinate and the selected polymers.

The pure drug and drug with excipient were scanned separately.

Evaluation of the Patches: Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies (**table 2**).

Thickness Uniformity: The thickness of each film was measured by using screw gauze. The thickness was measured at six different places on each film and the average thickness of the film was taken as the thickness of the film.

Folding Endurance: Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which is considered satisfactory to reveal good patch properties [8].

The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the patches for three times.

Uniformity of Weight: Patches of size 1x1 cm^2 were cut. The weights of three patches were taken using Shimadzu balance of sensitivity 0.0001 g (Shimadzu, Tokyo, Japan) and the weight variation was calculated [8].

Drug content Uniformity: The films were tested for the content uniformity [9]. A film of size 2x2 cm^2 was cut and placed in a volumetric flask. Ten ml of methanol was added and the contents were stirred in a shaker bath for 24 h to dissolve the film. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 241 nm using UV- VIS spectrophotometer (UV-1601, Shimadzu Corporation, Tokyo, Japan).

Swelling Studies: Weight and area increase due to swelling were measured [10].

Weight increase due to Swelling: The drug-loaded patch of size 1 x 1 cm^2 was weighed on a pre-weighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer (pH 7.4) solution was added. After every five min, the cover slip was removed, wiped with tissue paper, and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Area increase due to Swelling: A drug loaded patch of size 1x1 cm^2 was cut and placed in a petridish containing 50 ml of phosphate buffer (pH 7.4) solution. A graph paper was placed beneath the petridish and was clearly visible, which facilitated the measurement of increase in the area. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, %S was calculated using the following equation;

$$\%S = \frac{X_t - X_o}{X_o} \times 100$$

Where X_t is the weight or area of the swollen patch after time t and X_o is the original patch weight or area at zero time.

Tensile Strength: Tensile strength of the film was determined [11] with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K). The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4x1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the patch was taken directly from the dial reading in kg.

Water vapor Transmission Rate: For this study, vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven, about 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 63 % RH. The cells were taken out and weighed after 72 h.[13] The amount and rate of water vapor transmitted was calculated by the difference in weight using the formula.

$$\text{WVT rate} = WL/S$$

Where, W is the water vapor transmitted in grams, L is the thickness of the film in cm, and S is the exposed surface area in square cm.

***In vitro* release studies of Sumatriptan succinate patches in phosphate buffer (pH 7.4):** The drug release was determined using U.S.P. dissolution tester (TDT-08L, Electrolab, Bombay, India) thermostatic at 37±1°C and stirred at a rate of 50 rpm [14, 15]. Sink condition was maintained throughout the study.

Each film was fixed on a glass slide with the help of cyanoacrylate adhesive, so that the drug could be released only from upper face. The slide was immersed in the vessel containing 900 ml of phosphate buffer (pH 7.4) solutions. Aliquots of 5 ml of samples were withdrawn with graduated pipette at every one hour time intervals up to 10 h replacing with equal volume

of phosphate buffer (pH 7.4) solutions. The sample was analyzed spectrophotometrically at 227 nm and the cumulative amount of drug released at various time intervals was calculated. The test was carried out in triplicate (**table 3 figure 1**).

TABLE 2: PHYSICOCHEMICAL CHARACTERISTICS OF SUMATRIPTAN SUCCINATE TRANSDERMAL PATCHES

PC	TN (mm)	WU (mg)	Swelling		TS (kg)		CU	FE	WVTR (mg cm^{-2} h^{-1})
			% weight increase after 30 min	% area increase after 60 min	Dummy patches	Drug loaded patches			
F_1	0.199	19.63	431.31	61.60	2.333	2.830	91.58	> 300	0.151
F_2	0.262	21.80	406.11	59.39	1.793	2.460	94.65	> 300	0.167
F_3	0.190	17.40	291.93	51.09	1.233	1.306	95.43	> 300	0.093
F_4	0.186	18.80	386.07	35.23	1.306	1.816	96.78	> 300	0.104
F_5	0.263	22.33	312.667	52.11	1.400	1.856	93.91	> 300	0.136
F_6	0.177	14.56	380.23	51.09	1.406	1.876	89.10	> 300	0.104

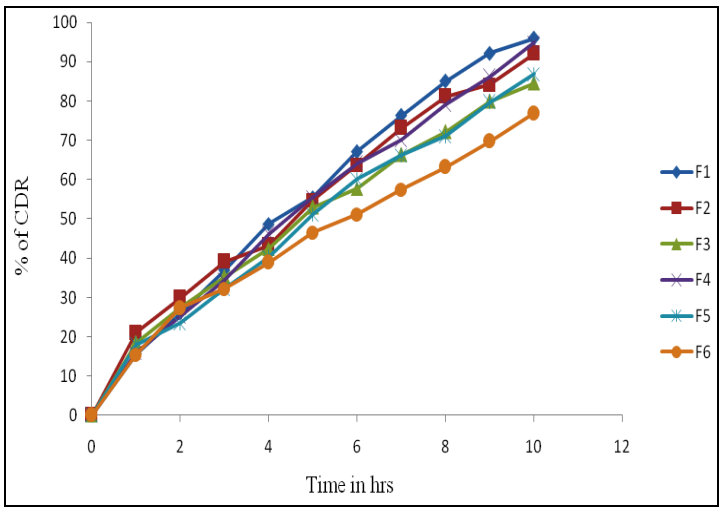

FIGURE 3: *IN-VITRO* DRUG RELEASE FORMULATION F1 TO F6

***In vitro* skin Permeation Studies:** Male Wistar rats (140±20 g) free from any visible signs of disease were selected for the *in vitro* skin permeation studies [11, 16]. The hair on abdominal region was removed using a depilatory preparation one day prior to experiment. On the day of experiment, the animals were sacrificed by cervical dislocation and the abdominal skin was excised. The fatty material adhered to the dermis was carefully peeled off. Freshly excised rat skin was mounted on donor compartment. Transdermal film containing DMSO as permeation enhancer was placed. A modified diffusion cell was used for drug release from the transdermal patches. The transdermal film of area 4 cm^2 was placed on the rat skin, which was then tied to the diffusion cell.

This diffusion cell was immersed in a beaker (receptor compartment) containing 100 ml phosphate buffer (pH 7.4) solution, which was used as the receptor fluid. The receptor compartment was stirred by using a magnetic stirrer at 100 rpm and the whole assembly was maintained at 37±1°C. The amount of the drug released was determined by withdrawing 5 ml of samples at specific time intervals up to 10 h. The volume withdrawn was replaced with equal volume of fresh phosphate buffer solution. The absorbance of the withdrawn sample was measured after suitable dilution at λ_{max} 227 nm to estimate Sumatriptan succinate. The experiment was carried out in triplicate and average values were reported.

Stability Studies: Optimized medicated films were subjected to short term stability testing. Films were placed in a glass beaker lined with aluminum foil and kept in a humidity chamber maintained at 40±2°C and 75±5% RH for 1 month as per ICH guidelines [18]. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week. The data presented were the mean of three determinations. The study was conducted on three films to validate the results.

RESULTS AND DISCUSSION:

Drug Estimation: A calibration curve of sumatriptan succinate in phosphate buffer (pH 7.4) solution was constructed at λ_{max} 227 nm with a UV-VIS spectro-photometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve in the concentration range of 1-10 µg/ml. Analyses were done in triplicate.

Drug-Polymer Compatibility: FT-IR spectra of Sumatriptan alone and its combination with polymers are shown in **Figure 2 & 3**. FT-IR spectra of the pure Sumatriptan and the drug-polymer mixture showed characteristic bands at 3364cm $^{-1}$ (N-H stretching), 1298 cm^{-1} (S-O stretching), 1702 (C=O stretching), and 3119 cm $^{-1}$ (C-H stretching), due to functional groups,

indicating the chemical stability of Sumatriptan in the chosen polymeric mixture. This also indicates that Sumatriptan is not involved in any chemical reactions with the polymer used. Further, the interference was also verified using UV-spectrophotometry method.

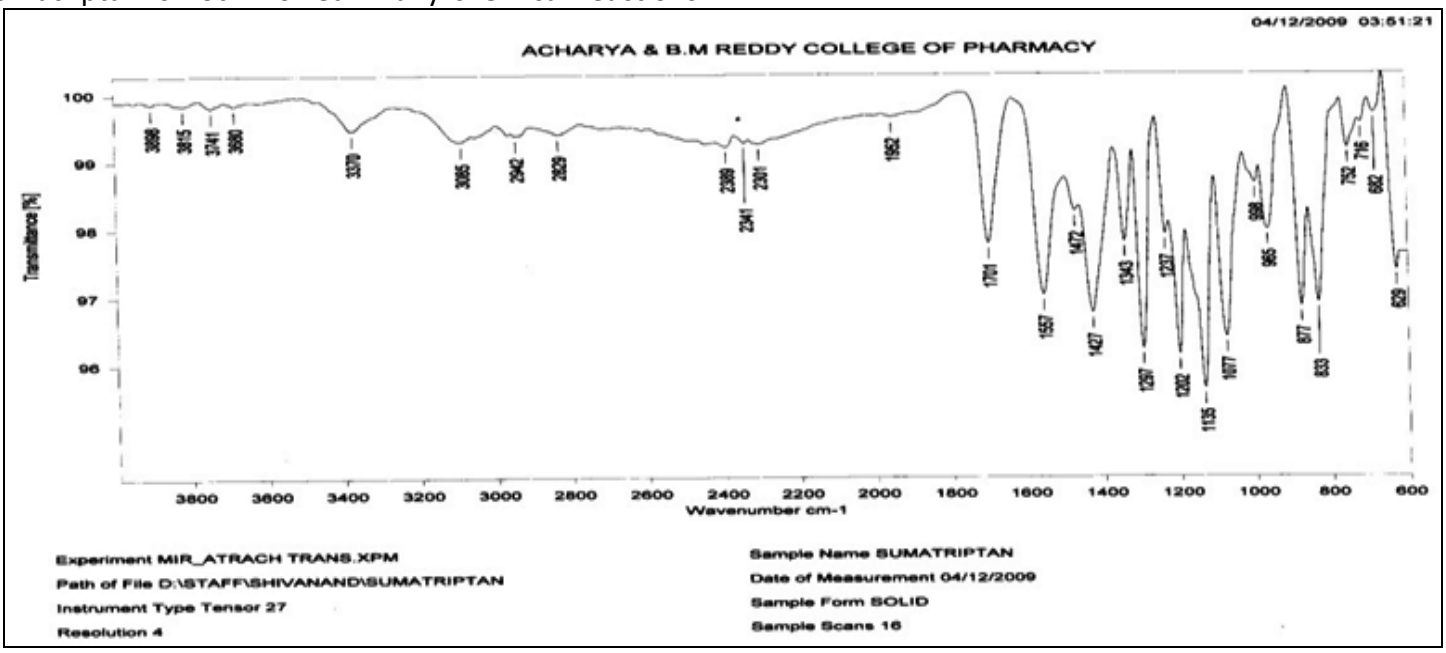

FIGURE 1: FTIR SPECTRUM OF PURE SUMATRIPTAN SUCCINATE

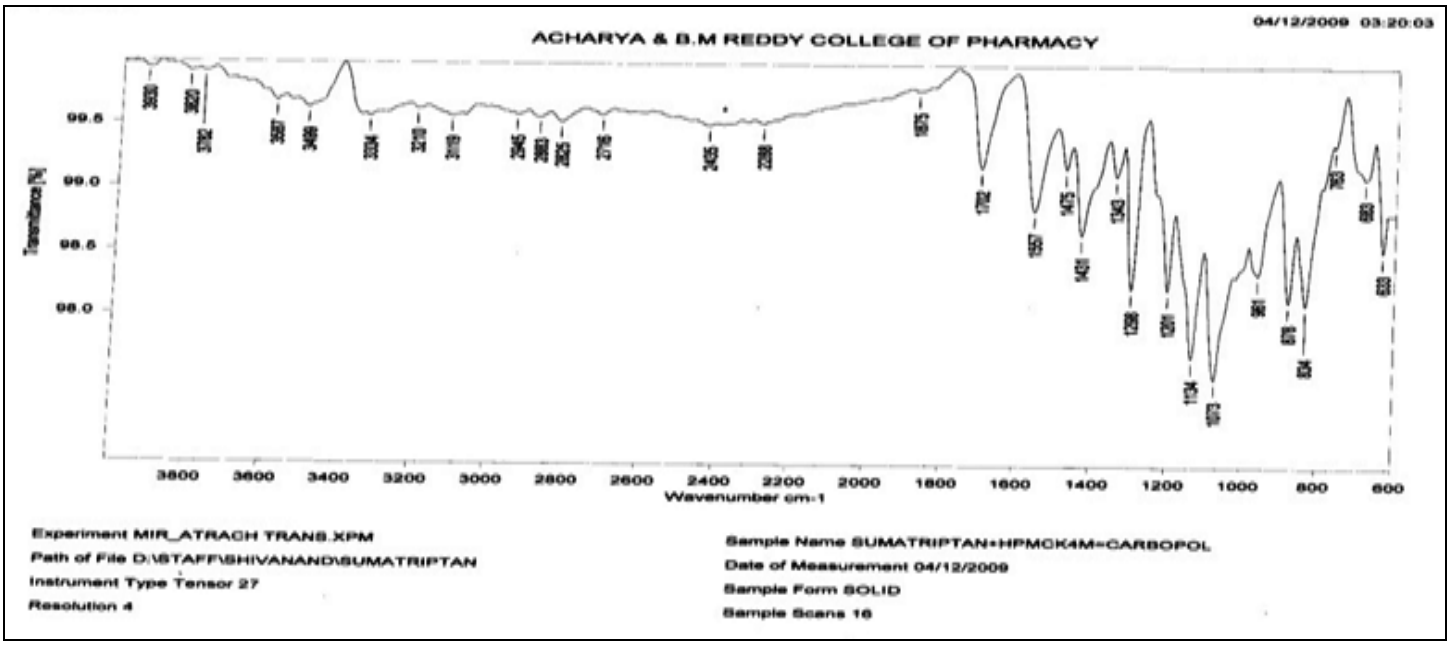

FIGURE 2: FTIR SPECTRUM OF PHYSICAL MIXTURE OF SUMATRIPTAN SUCCINATE WITH HPMC K4M AND CARBOPOL 934P

Content Uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 89.1 to 96.78% for formulations F1 to F6. The drug content analysis of the prepared formulations had shown that the process employed to prepare films in this study was capable of giving films with a uniform drug content and minimum batch variability.

Water vapor Transmission Rate: The patch formulated with HPMCK4M alone showed WVTR of 0.147±0.039 mg cm^{-2} h^{-1}, which can be attributed to the hydrophilic nature of the polymer. The casting of the HPMCK4M with polymer of Carbopol934M maximum the values of the water vapor transmission rate.

***In vitro* skin Permeation Studies:** The *in vitro* permeation study was performed across hairless rat

abdominal skin using modified diffusion cell. It was found that about 89.16% of the drug permeated through hairless skin from film F6. The permeation kinetics was studied by regression analysis (R^2 =0.935). The permeation of sumatriptan followed first order.

TABLE 2: CUMULATIVE PERCENTAGE OF DRUG RELEASED, IN VITRO STUDIES.

	% Cumulative drug released					
Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	15.54 ± 1.25	21.00 ± 1.00	18.48 ± 1.50	15.96 ± 1.35	18.06 ± 1.05	12.45 ± 1.45
2	26.04 ±1.20	29.91 ± 1.13	27.34 ±1.45	25.19 ± 1.36	23.52 ± 1.10	27.31 ± 1.46
3	36.90 ± 1.23	39.12 ± 1.18	35.25 ± 1.25	34.35 ± 1.52	32.23 ± 1.13	30.25 ± 1.40
4	48.72 ± 1.21	43.32 ± 1.20	42.38 ± 1.36	46.15 ± 1.42	40.19 ± 1.24	38.93 ± 1.30
5	55.56 ± 1.23	54.77 ± 1.15	52.98 ± 1.35	55.51 ± 1.26	51.19 ± 1.09	46.52 ± 1.36
6	67.13 ± 1.30	63.79 ±1.18	57.73 ± 1.38	64.11 ± 1.39	60.17 ± 1.10	51.22 ± 1.38
7	76.25 ± 1.28	73.12 ± 1.23	66.29 ± 1.09	70.11 ± 1.31	66.19 ± 1.19	57.52 ± 1.15
8	85.09 ±1.11	81.17 ± 1.14	72.11 ± 1.25	79.11 ± 1.31	71.11 ± 1.10	63.14 ± 1.17
9	92.15 ± 1.38	84.21 ± 1.19	79.89 ± 1.27	86.25 ± 1.09	79.65 ± 1.32	69.68 ± 1.27
10	95.98 ± 1.24	92.12 ± 1.15	84.58 ± 1.19	94.85 ± 1.25	86.85 ± 1.25	76.85 ± 1.21

Correlation between *in vitro release* and *in vitro* permeation: *In vitro* release studies and their correlation with *in vitro* skin permeation studies will be helpful to predict therapeutic efficiency of the dosage form. So correlation between *in vitro* release behavior of a drug and its *in vitro* permeation in rat skin is demonstrated experimentally to reproduce therapeutic response. The data of *in vitro* release and *in vitro* skin permeation of sumatriptan from film F6 was regressed using MS-Excel statistical program to understand *in vitro* release and *in vitro* permeation correlation. A good correlation was observed (since R^2 value was 0.810) for patch F6.

***In vitro* skin Irritation Studies:** No erythema was observed from a primary skin irritation test carried out on rabbits after the application of transdermal films. The absence of erythema indicated that these polymeric patches of sumatriptan were compatible with skin and hence can be used for the transdermal application.

Stability Studies: Films that were placed in humidity chamber for short time stability studies were withdrawn every week and analyzed for their drug content. Percentage drug present in the patches were determined spectrophotometrically. Decrease in the drug content from the films ranged from 1.25 to 2.3 %. It was found that the drug loss is less though the films were stored for one month. The films were also observed for their appearance and texture. These properties did not change in films during the period of study. Transdermal films containing sumatriptan using HPMCKM and Carbopol934 polymers showed satisfactory characteristics without being drastically influenced by ageing.

CONCLUSION: On the basis of the *in vitro* characterization, it was concluded that sumatriptan could be administered transdermally through TDDS. Transdermal patches consisting of the bioadhesive polymer HPMCK4M and Carbopol934P with DMSO as permeation enhancer demonstrated sustained and controlled release of the drug across rat abdominal skin during *in vitro* permeation studies. The drug remained intact and stable in the TDDS during storage, with no significant chemical interaction between the drug and the excipient. Further work is to establish the therapeutic utility of this system by pharmacokinetics and pharmacodynamic studies on human beings.

REFERENCES:

1. Tanwar YS: Formulation and evaluation of transdermal films of salbutamol sulphate. The Dhaka University J Pharm Sci 2005; 4:1816-20.
2. Kshiragar NA: Drug delivery systems. Ind J Pharmcol 2000; 32:554-61.
3. British Pharmacopoeia, 5th ed. 2005: 1745.
4. Martindale: The complete drug reference Great Britain. Pharmaceutical press, 34th edition 2004. 881.
5. Sankar V, Johnson DB, Sivanand V, Ravichandran V, Raghuraman S, Velrajan G, Palaniappan R, Rajasekar S, Chandrasekaran AK: Design and evaluation of nifedipine transdermal patches. Indian J Pharm Sci 2003; 65(5):510-5.
6. Aulton ME. Pharmaceutics: The science of dosage form design London. Chruchhill Livingstone. 2nd edition. 2002: 31-2.

7. Martin A, Swarbrick J, Cammarara A. Physical pharmacy New Delhi. B.I Vaverly Pvt Ltd. 4th edition. 1996:264-8.
8. Panigrahi L, Ghosal SK: Formulation and evaluation of pseudolatex transdermal drug delivery system of terbutaline sulphate. Indian J Pharm Sci 2002; 79-82.
9. Gupta SP, Jain SK: Effective and controlled transdermal delivery of metoprolol tartrate. Indian J Pharm Sci 2005; 67(3):346-50.
10. Gua JH, Cooklock KM: Bioadhesive polymer buccal patches for buprenorphine controlled delivery: Solubility consideration. Drug Dev Ind Pharm 1995; 21:2013-9.
11. Kulkarni RV, Mutalik S, Hiremath D: Effect of plasticizers on the permeability and mechanical properties of eudragit films for transdermal application. Indian J Pharm Sci 2002; 64(1):28-31.
12. Noha AN, Nabila AB, Fatima A, Ismail, Lobna MM: Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Pharm Acta helvetiae 2003; 53: 199-212.
13. Raghavendra K, Doddayya H, Marihal SC, Patil CC, Habbu PV: Comparative evaluation of polymeric films for transdermal application. The Eastern Pharmacist 2000 (Dec); 43(516): 109-111.
14. Ilango R, Kavimani S, Mullaicharam AR, Jayakar B: *In vitro* studies on buccal strips of Glibenclamide using chitosan. Ind J Pharm Sci 1997; 232-5.
15. Doijad RC, Manvi FV, Rao MVSN, and Patel PS: Buccoadhesive drug delivery system of isosorbide dinitrate: Formulation and evaluation. Ind J Pharm Sci 2006; 68(6):744-8.
16. Das MK, Bhattacharya A, Ghosal SK: Transdermal delivery of trazodone hydrochloride from acrylic films prepared from aqueous latex. Indian J Pharm Sci 2006; 68(1): 41-6.
17. Nagarajan M, Narmada S, Ganeshan M, Buchi N. Nalluri: Preparation and evaluation of transdermal patches of salbutamol sulphate. The Eastern Pharmacist 1996; 127-8.
18. David J M. International stability testing. USA: Interpharm Press Inc.

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