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FORMULATION AND EVALUATION OF CLOPIDOGREL BISULPHATE TRANSDERMAL PATCHES USING VEGETABLE OILS AS PERMEATION ENHANCER

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Keywords:

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ABSTRACT: Orally Clopidogrel bisulphate has a short elimination half-life (7-8 hrs.), low oral bioavailability (50%) undergoes extensive first pass metabolism (85%) and frequent high doses (75 mg) are required to maintain the therapeutic level as a result, dose development toxic effect. The purpose of this research work was formulation and evaluation of transdermal drug delivery system of Clopidogrel bisulphate using vegetable oils as permeation enhancer by using solvent evaporation technique for improvement of bioavailability of drug and reducing toxic effects. Matrix transdermal patches were prepared by using hydroxypropylmethylcellulose (HPMC) and ethyl cellulose (EC) polymers by incorporating glycerine and dibutylphthalate as plasticizers, respectively. Prepared formulations were evaluated for different physicochemical characteristics like thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss weight uniformity, etc.,. All the patches were uniform with respect to physicochemical evaluation. The *in vitro* drug release studies indicated that HPMC containing films have shown better release than that of EC containing films without any permeation enhancers. The result of diffusion study shows that formulation C7 showed maximum release of 88.7% in 24 h, whereas C2 showed minimum release of in 38.6% in 24h. The various permeation parameters were determined for all the formulations. The maximum flux was obtained with C7 formulation. All the films were found to be stable with respect to their physical parameters and drug content.

INTRODUCTION: A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application.

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Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. TDDS has gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably

avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance [1, 2].

Transdermal therapeutic systems are defined as a self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. An ideal drug to be formulated as transdermal drug delivery should possess several physicochemical properties, such as short half-life, small molecular size, low dose, low oral bioavailability, etc [3].

Clopidogrel bisulphate is an Anti-platelet drug, undergoes hepatic first pass metabolism and low oral bioavailability (50%) [4]. Hence, it is suitable for formulation as a transdermal patch. Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum [5].

Orally Clopidogrel bisulphate has a short elimination half-life (7-8 hrs.), low oral bioavailability (50%) undergoes extensive first pass metabolism (85%) and frequent high doses (75 mg) are required to maintain the therapeutic level as a result, dose development toxic effect. The purpose of this research work was to Formulation and evaluation of transdermal drug delivery system of Clopidogrel bisulphate using various polymers such as HPMC, PVP and Ethyl cellulose by solvent evaporation technique for improvement of bioavailability of drug and reducing toxic effects.

MATERIALS AND METHODS:

Materials: Clopidogrel Bisulphate was obtained from Dr. Reddy's laboratories limited, Hyderabad, India. HPMC and EC were purchased from Reliance cellulose products limited, Hyderabad, India. Other materials used in the study were of analytical grade.

Method of Preparation of Monolithic Transdermal Systems: The HPMC and EC films were prepared by solvent casting method using mercury substrate and evaluated for various parameters. Monolithic transdermal systems of HPMC and EC were prepared according to the formulae shown in **Table 1**. The drug: polymer ratio was used in all the formulations. The solutions were stirred for 20 min using a magnetic stirrer. Glycerine and Dibutyl phthalate were used as plasticizers for HPMC and EC films, respectively. A specific quantity of the drug was dissolved in alcohol and then added to respective polymer solution. The enhancer was added and solutions were stirred and poured in a petridish. The rate of evaporation of the solvent was controlled by inverting cut funnel over the petridish. After 24 h, the dried films were taken out and stored in a desiccator. Films F3, F4, F5, F6, F7 and F8 contained castor oil, coconut oil, cottonseed oil, linseed oil, olive oil and sunflower oil respectively. The films were prepared by incorporating them along with a plasticizer.[6]

Evaluation:

Physical appearance: All the transdermal films were visually inspected for colour, clarity, flexibility and smoothness.

Thickness of the patch: The thickness of the drug loaded patch was measured at five different points using a screw gauge and average thickness of five reading was calculated [7].

Folding endurance: The folding endurance was measured manually for the prepared films. A strip of film (2x2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance [8].

Tensile strength: In order to determine the elongation as a tensile strength, the prepared patch of size (4 x 1 cm^2) was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance travelled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg/cm^2 [8].

Tensile strength is expressed as follows;

$$Tensile\ strength = \frac{Tensile\ load\ at\ break}{cross\ sectional\ area}$$

Weight uniformity: The prepared patches were dried at 60°c for 4hrs before testing. A specified area of patch was cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weight [9, 10].

TABLE 1: COMPOSITION OF DIFFERENT TRANSDERMAL PATCHES CONTAINING CLOPIDOGREL

Formulation code	Permeation enhancer
C1	-
C2	-
C3	Castor oil
C4	Coconut oil
C5	Cotton seed oil
C6	Linseed oil
C7	Olive oil
C8	Sunflower oil

Percentage of Moisture Content: The prepared films were weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula [9-11];

Percentage Moisture Content=

$$\frac{\text{Initial Weight - Final Weight}}{\text{Final Weight}} \times 100$$

Percentage moisture absorption: The weighed films were kept in desiccators at room temperature for 24hrs containing saturated solutions of potassium chloride in order to maintain 84% RH. After 24hrs the films are to be reweighed and determine the percentage moisture absorption from the below mentioned formula [9-11];

Percentage Moisture Content=

$$\frac{\text{Final Weight - Initial Weight}}{\text{Initial Weight}} \times 100$$

Drug Content: A specified area of patch was dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique) [12].

Water vapour absorption (WVA) rate: The films of 3.14 cm^2 were weighed accurately and placed on the wire gauge, which was kept in a desiccator containing 200 mL of saturated solution of potassium chloride, which maintains 80-90% RH. The films were taken out and weighed after 1, 2, 3, 4, 5, 6, and 7days of storage. The study was performed at room temperature [13]. The percentage moisture absorption was calculated using the formula:

Water Vapor Absorption Rate=

$$\frac{\text{Final Weight – Initial Weight}}{\text{Time x Area}} \times 100$$

Water vapour transmission (WVT) rate: Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials & the polymer films of 3.14 cm^2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 7days. The vials were removed and weighed at time interval of 24 h for 7 consecutive days to note down the weight gain.[14]

Water Vapor Transmission Rate=

$$\frac{\text{Final Weight – Initial Weight}}{\text{Time x Area}} \times 100$$

***In-vitro* Permeation across the rat abdominal skin:**

1. **Preparation of the rat skin**: The Swiss albino rats with a weight range of 170-190gm were decapitated the abdominal skin of excised hairless rat skin was separated along the epidermal junction, and it was kept in the water bath, which was maintained at 60°C for 50 s. the heat-treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution for flattening and smoothening [15].

2. **Permeation studies:** Vertically assembled Franz diffusion cells having a downstream volume of 50ml, was used. The obtained skin was mounted on the diffusion cell, and the receiver compartment was filled with 50ml phosphate buffer of pH 7.4 and the temperature was maintained at 37°C. The samples were withdrawn every hour (replaced with 1ml of fresh buffer to maintain sink condition) and their concentrations were measured [14]. The cumulative percentages of drug permeated per square centimetre of patches were plotted against time.

3. **Permeation Data Analysis:** The flux (µg cm^{-2} hr^{-1}) of ACF was calculated from the slope of the plot of the cumulative amount of ACF permeated per cm 2 of skin at steady state against the time using linear regression analysis [8]. The steady state permeability coefficient (K_P) of the drug through rat epidermis was calculated by using the following equation: [8]

$$K_p = \frac{J}{C}$$

Where J is the flux and C is the concentration of ACF in the patch.

The penetration enhancing effect of penetration enhancer was calculated in terms of enhancement ratio (ER), and was calculated by using the following equation: [8]

$$ER = \frac{K_p \text{ with penetration enhancer}}{K_p \text{ without penetration enhancer}}$$

Kinetic modelling of drug release: To analyse the mechanism of drug release from the patches, the release data were fitted to the following equations:

Zero-order equation:

$$Q = k_0 t$$

Where Q is the amount of drug released at time t, and k_0 is the release rate.

First-order equation:

$$ln\ (100 - Q) = ln\ 100 - k_1 t$$

Where Q is the percent of drug release at time t, and k_1 is the release rate constant.

Higuchi's equation:

$$Q = k_2 \sqrt{t}$$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant.

Stability studies: All the films were exposed to two selected temperatures of 37°C and 45°C in two different hot air ovens Transdermal films with an area of 19.63 cm^2 were kept in the oven for a period of 4 weeks. The film sample with an area of 1cm^2 was cut from each formulation, and it was analysed for the drug content at the end of every week. The average of triplicate reading was taken.[16]

RESULTS AND DISCUSSION:

Investigation of Physicochemical Compatibility of Drug and Polymer: Drug-excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. Infrared (IR) spectra of Clopidogrel Bisulphate (A), Hydroxypropyl methyl cellulose (B), Ethyl cellulose EC (C), and physical mixture of Clopidogrel bisulphate with HPMC (D) and physical mixture of Clopidogrel bisulphate with EC (E) are shown in **Fig. 1, Fig. 2, Fig. 3, Fig. 4 and Fig. 5** respectively.

Physicochemical properties of prepared formulations: A total of 8 formulations were prepared using HPMC and EC polymers as per formulae given in Table 1. All the films were evaluated for their physical parameters and they were found to be flexible, smooth and transparent. The thickness of the patches varied from 0.1138 to 0.1258 mm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible result [**Table 2**]. The weight uniformity of the patches varied from 288.54 to 303.92 mg and the values were tabulated in table 2. The folding endurance was measured manually; films were folded 121 times maximum in formulation C7 [Table 2].

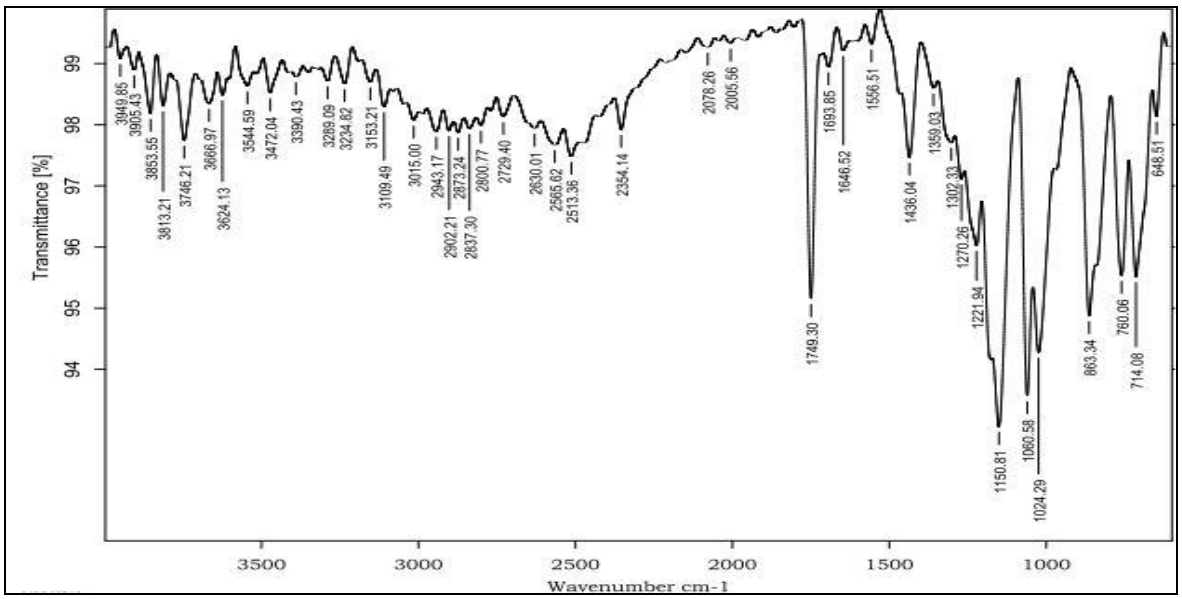

FIG. 1: FTIR OF CLOPIDOGREL BISULPHATE

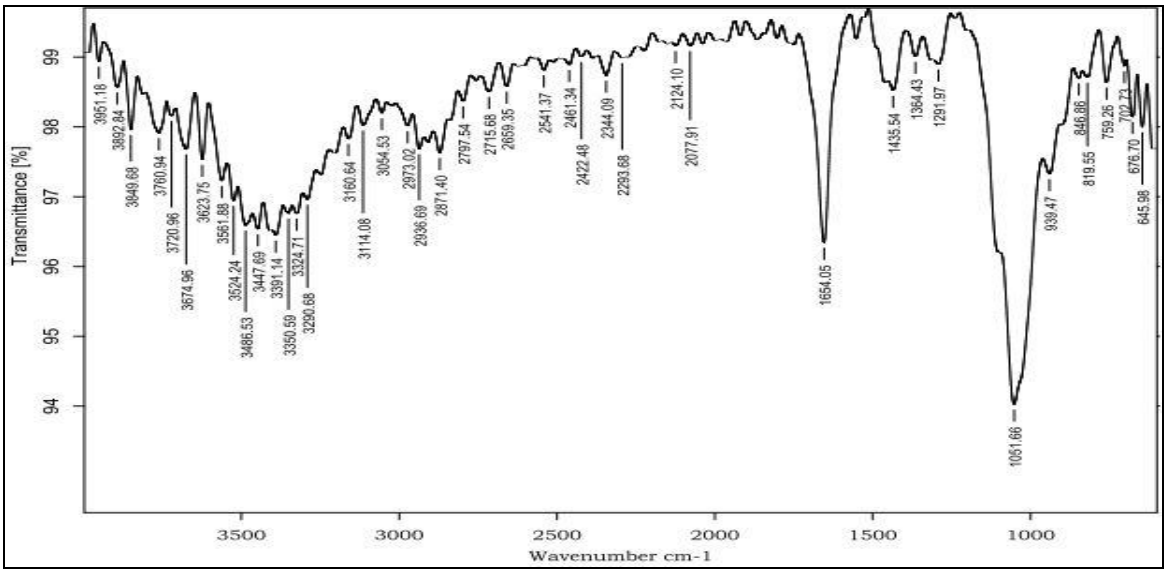

FIG. 2: FTIR OF HYDROXYPROPYL METHYL CELLULOSE (HPMC)

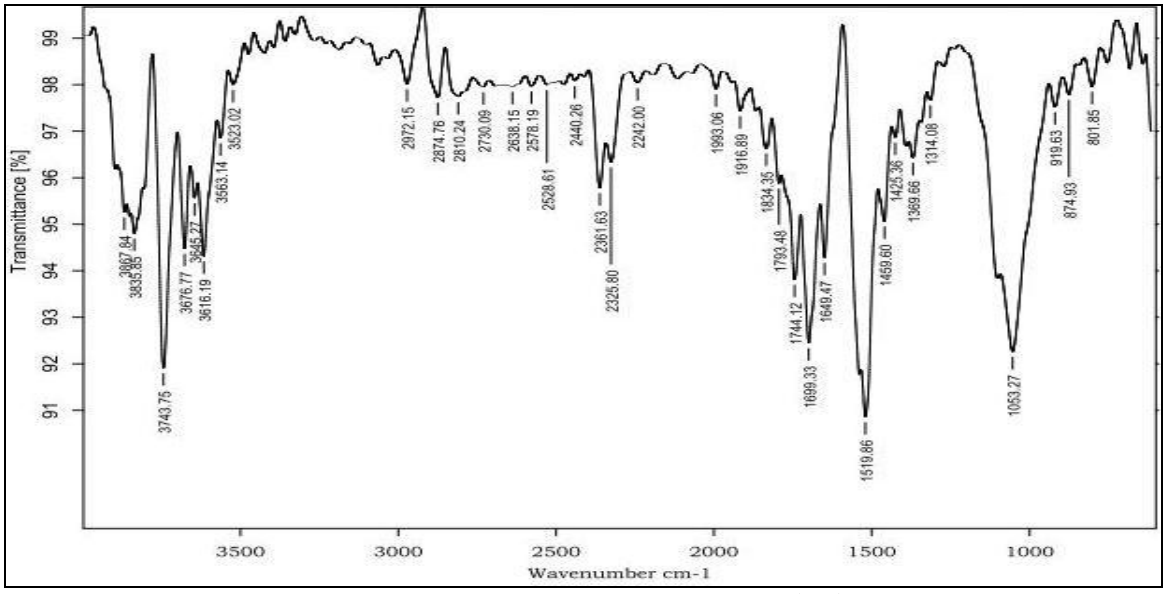

FIG. 3: FTIR OF ETHYL CELLULOSE (EC)

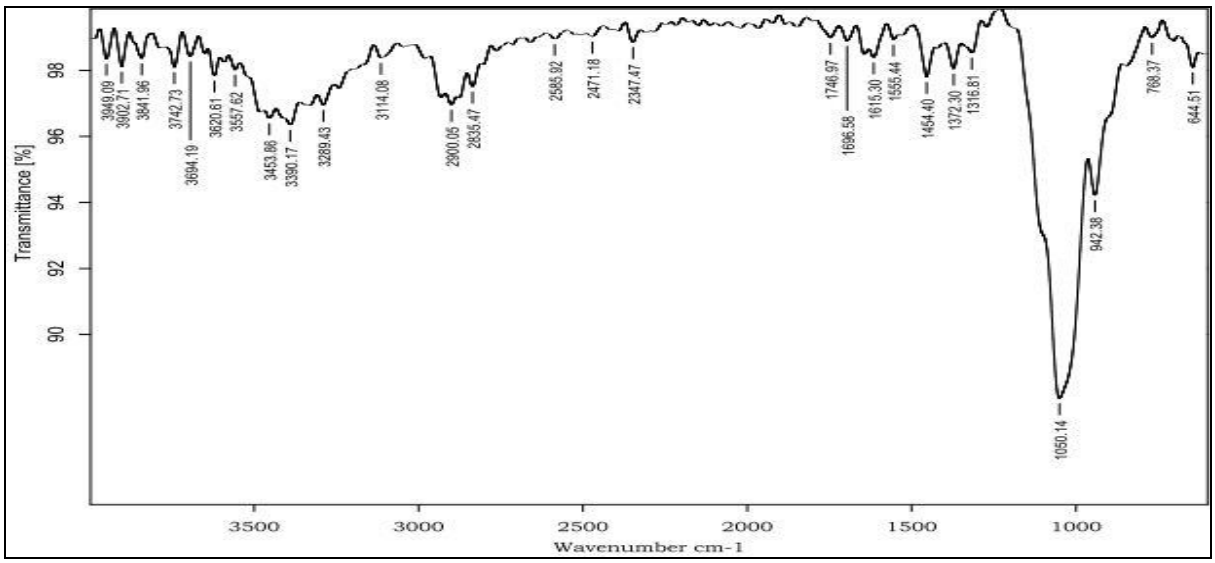

FIG. 4: FTIR OF PHYSICAL MIXTURE OF CLOPIDOGREL BISULPHATE AND HPMC

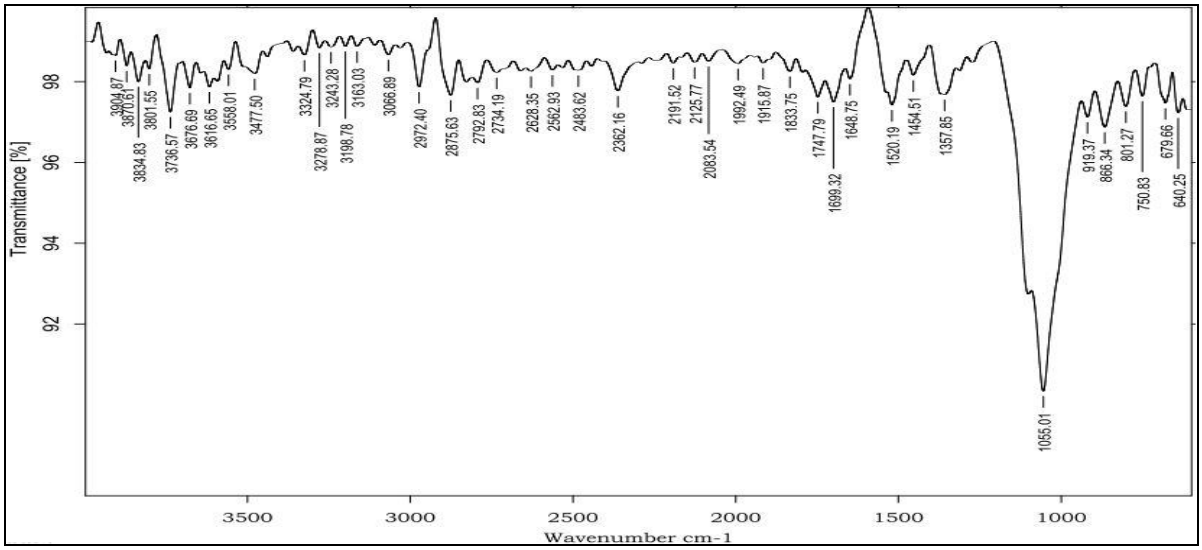

FIG. 5: FTIR OF PHYSICAL MIXTURE OF CLOPIDOGREL BISULPHATE AND EC

Formulation C3 showed highest tensile strength and the formulation C6 showed least tensile strength [Table 2].

Formulation C1 absorbed highest amount of moisture which also revealed its high hydro-philicity and formulation C2 absorb least amount of moisture [**Table 3**]. Moisture absorption values varied from 2.53 to 1.35 % and the values of moisture content were noted in table 3.The rate of WVA from all monolithic systems was determined and they followed the order: $C_7 < C_1 < C_8 < C_2 < C_5 < C_4 < C_6 < C_3$ and the values were noted in table 3. The WVT studies for all monolithic formulations were conducted, which indicates that all the formulations from C1 to C8 were permeable to water vapour.

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF PREPARED FORMULATIONS

Batch code	Thickness (mm) ± S.D	Weight uniformity (mg)	Folding endurance ± S. D	Flatness ±S.D	Tensile strength (kg/cm^2)
C1	0.119 ±0.0037	288.54 ±0.462	80 ± 4	98.30 ±0.200	3.52 ±0.004
C2	0.116 ±0.0044	302.92 ±0.507	96 ± 2	97.23 ±0.153	2.96 ±0.110
C3	0.117 ±0.0059	303.74 ±0.434	51 ± 3	97.96 ±0.041	3.66 ±0.006
C4	0.114 ±0.0024	302.46 ±0.219	85 ± 1.5	98.17 ±0.305	3.33 ±0.006
C5	0.119 ±0.0061	289.54 ±0.241	91 ± 2.5	97.37 ±0.252	3.42 ±0.006
C6	0.126 ±0.0044	293.76 ±0.513	102 ± 4.7	98.37 ±0.153	3.24 ±0.006
C7	0.117 ±0.0034	291.84 ±0.416	121 ± 2.1	98.57 ±0.208	3.41 ±0.007
C8	0.120 ±0.0053	293.20 ±0.612	120 ± 2.5	95.61 ±0.539	3.32 ±0.006

The order of rate of WVT from all monolithic systems was as follows: $C_7 < C_8 < C_4 < C_6 < C_5 < C_3 < C_1 < C_2$.The results revealed that the drug content was almost uniform in all the films with low SD values shown in the table 3. The *in vitro* release profile of Clopidogrel bisulphate from two different polymers and then permeation enhancers were added to the polymeric system, which showed better release. The *in vitro* release of drug across rat skin from HPMC and EC films showed only 53.8% (C_1) and 38.3% (C_2) at the end of 24h, respectively [**table 4, Fig. 6**]. The flux was calculated from the slope of linear graph, and it was found to be 1.663 and 1.153 µg/cm^2.h respectively. It was evident from the above result that there was a lower flux through the rat skin. Hence, a permeation enhancer must be incorporated in the system. The HPMC film gave better results than EC film. Therefore, the HPMC film was selected for incorporation of various vegetable oils as permeation enhancers. In later studies, the effect of permeation enhancer on the release of drug from different monolithic systems was conducted. Different oils were selected as used in various concentrations, 30% w/w concentration was used in the subsequent experiments.

TABLE 3: PHYSICOCHEMICAL PROPERTIES OF PREPARED FORMULATIONS

Batch code	Moisture uptake (%) ± S.D*	Moisture content (%) ± S.D*	WVA rate constant (g/24 h/cm^2)	WVT rate constant (g/24 h/cm^2)	% Drug Content ± S.D*
C1	2.5 ± 0.06	1.9 ± 0.04	1.81 x 10^{-4}	4.814 x 10^{-3}	96.86 ± 0.06
C2	1.4 ± 0.04	3.2 ± 0.05	2.02 x 10^{-4}	4.883 x 10^{-3}	98.84 ± 0.05
C3	1.8 ± 0.04	2.9 ± 0.04	2.18 x 10^{-4}	4.638 x 10^{-3}	97.03 ± 0.14
C4	2.3 ± 0.04	1.6 ± 0.04	2.05 x 10^{-4}	4.311 x 10^{-3}	98.20 ± 0.23
C5	2.2 ± 0.01	1.8 ± 0.02	2.03 x 10^{-4}	4.631 x 10^{-3}	97.01 ± 0.15
C6	2.0 ± 0.03	2.2 ± 0.07	2.14 x 10^{-4}	4.612 x 10^{-3}	97.62 ± 0.15
C7	1.7 ± 0.02	2.7 ± 0.05	1.12 x 10^{-4}	2.521 x 10^{-3}	97.37 ± 0.46
C8	1.5 ± 0.03	2.6 ± 0.06	1.97 x 10^{-4}	4.212 x 10^{-3}	97.68 ± 0.22

To know the mechanism of drug release, the data was subjected to various kinetic studies.

(1) Percentage cumulative of drug permeated versus time according to zero order [**Fig. 7**].

(2) log percentage cumulative drug retained vs time according to first order [**Fig. 8**]

(3) percentage cumulative of drug permeated versus square root of time [**Fig. 9**].

(4) log percentage cumulative drug permeated vs log time. [**Fig. 10**].

***In-vitro* Drug release from monolithic systems:** The drug release from HPMC and EC films without any permeation enhancer are found to be 53.5% and 38.41%, respectively. The results indicated that HPMC film has shown better release than that of EC film, which may attributed to high water vapour permeability of HPMC film and hydrophobic nature of EC. The flux, permeability coefficient, permeability rate and diffusion rate were high for HPMC film than that of EC film. Hence, it was dedicated to incorporate permeation enhancers in the HPMC monolithic system for better release.

The drug release profiles of the formulations were given in the **table 5** at the end of 24h among the systems; film containing 30% w/w olive oil in HPMC polymer (C7) has shown maximum release than that of systems containing other oils as permeation enhancers. The flux, diffusion rate, permeability coefficient and permeability rate were compared.

The results indicated that C3 exhibited good flux and permeation than that of other systems, which may be due to high percentage of oleic acid (83.5%) present in olive oil. The enhancement ratio was calculated by dividing the flux of formulation with permeation enhancer by the flux of formulation without permeation enhancer. The order of enhancement was found to be: C3 < C4 < C5 < C8 < C6 < C7.

TABLE 4: PHYSICOCHEMICAL PROPERTIES OF PREPARED FORMULATIONS

Formulation code	Q_{24} Release %	Flux (µg/cm^2.h)	Enhancement ratio (ER)
C1	53.5	166.3	-
C2	38.41	115.3	-
C3	62.53	193.4	1.163
C4	73.27	223.4	1.343
C5	77.43	238.0	1.431
C6	83.73	258.4	1.554
C7	88.7	279.9	1.683
C8	80.4	246.0	1.479

TABLE 5: REGRESSION CO-EFFICIENT (R^2) VALUES OF DIFFERENT KINETIC MODELS AND DIFFUSION EXPONENT (n) OF PEPPAS MODEL FOR CLOPIDOGREL BISULPHATE TDDS

Batch code	Zero order R^2 Mean ± S.D	First order R^2 Mean ± S.D	Higuchi R^2 Mean ± S.D	Peppas plot	
				R^2 Mean ± S.D	n value Mean ± S.D
C1	0.9933 ±0.003	0.9688 ±0.0012	0.8684 ±0.0016	0.9412 ±0.0068	1.0267 ±0.0125
C2	0.9956 ±0.002	0.9931 ±0.0012	0.9218 ±0.0026	0.9406 ±0.0053	0.9485 ±0.0078
C3	0.9805 ±0.008	0.9975 ±0.003	0.9638 ±0.0083	0.8727 ±0.0026	1.0208 ±0.0043
C4	0.9805 ±0.008	0.9852 ±0.005	0.962 ±0.0013	0.8653 ±0.0045	1.0499 ±0.0086
C5	0.9833 ±0.0076	0.9793 ±0.007	0.954 ±0.007	0.8704 ±0.0059	1.0637 ±0.0095
C6	0.9955 ±0.002	0.9484 ±0.003	0.9344 ±0.0049	0.8785 ±0.0037	1.0793 ±0.0055
C7	0.9936 ±0.0015	0.9457 ±0.0046	0.9351 ±0.0011	0.9039 ±0.0044	1.1463 ±0.0096
C8	0.9869 ±0.003	0.9689 ±0.0016	0.9503 ±0.0013	0.8615 ±0.0029	1.0624 ±0.0058

The drug release profiles of all monolithic systems were fairly linear with their correlation coefficients values were from 0.9805 to 0.9956 and were given in table 5. To know the mechanism of drug release from all the monolithic systems, the data was plotted according to Higuchi's equation given in fig. 9. The plots were linear with their correlation coefficients between 0.8684 and 0.962. The results confirmed that, the mechanism of drug release for all the monolithic systems was diffusion controlled.

In order to get linear plots, the data was subjected to the regression analysis and the values were given in table 5. The patches were observed for changes in colour, appearance, flexibility and drug content at regular interval of one week for one month.

All the films were stable at 37°C and at 45°C with respect to their physical parameters and drug content [**Figs. 11 and 12**].

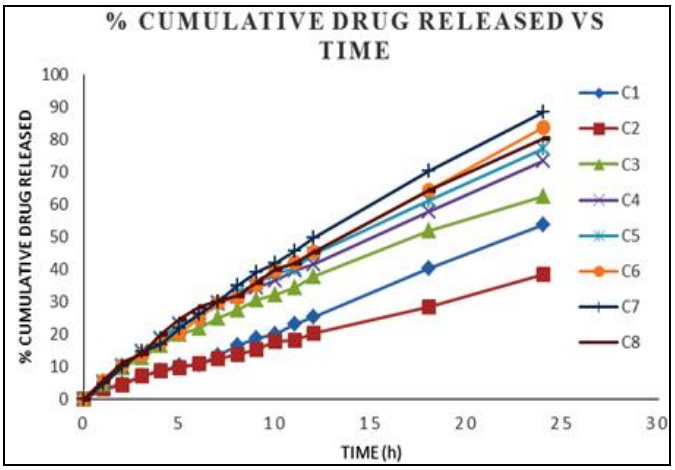

FIG. 6: COMPARATIVE *IN VITRO* RELEASE PROFILE OF CLOPIDOGREL BISULPHATE TDDS

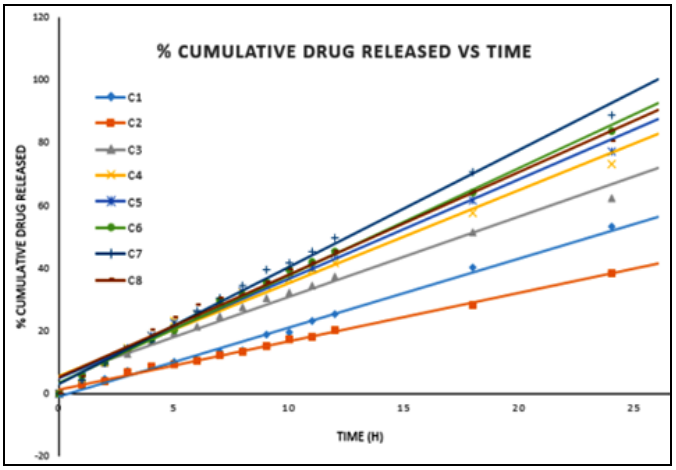

FIG. 7: COMPARATIVE *IN VITRO* RELEASE PROFILE OF CLOPIDOGREL BISULPHATE TDDS ACCORDING TO ZERO ORDER KINETICS

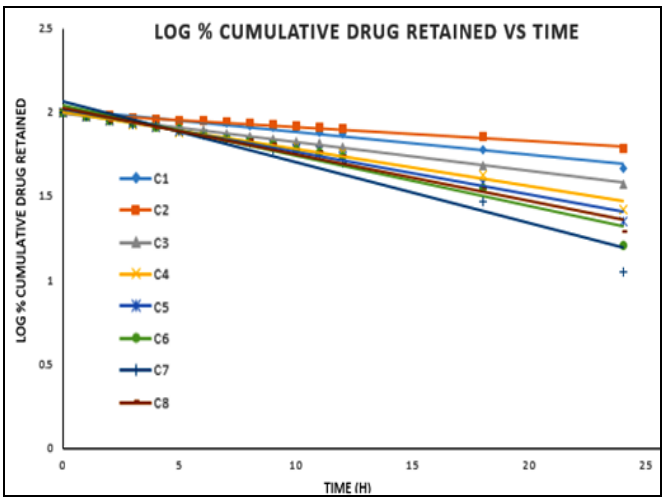

FIG.8: COMPARATIVE *IN VITRO* RELEASE PROFILE OF CLOPIDOGREL BISULPHATE TDDS ACCORDING TO FIRST ORDER KINETICS

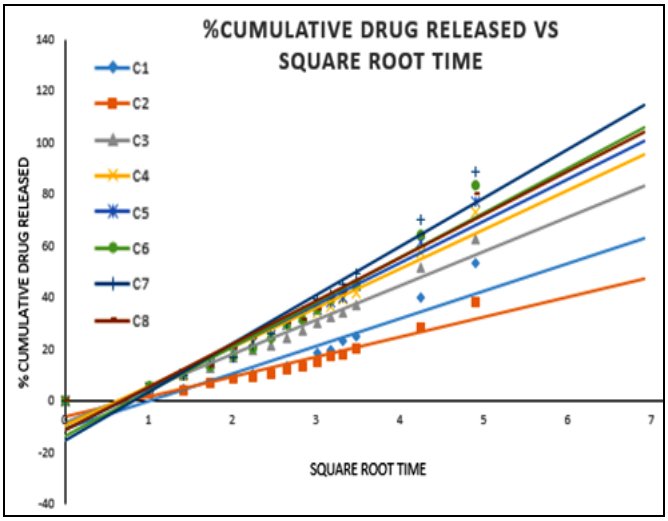

FIG. 9: COMPARATIVE *IN VITRO* RELEASE PROFILE OF CLOPIDOGREL BISULPHATE TDDS ACCORDING TO HIGUCHI PLOT

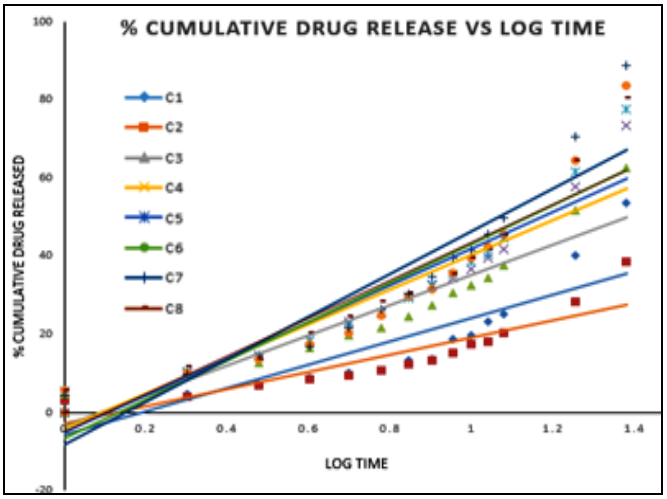

FIG. 10: COMPARATIVE *IN VITRO* RELEASE PROFILE OF CLOPIDOGREL BISULPHATE TDDS ACCORDING TO PEPPAS PLOT

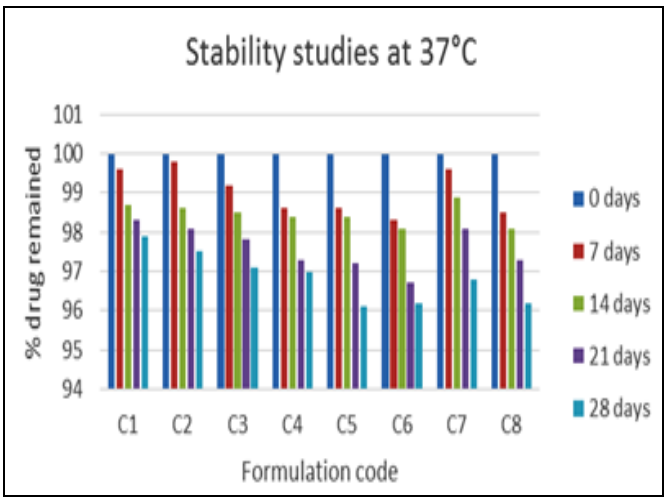

FIG. 11: STABILITY STUDIES OF TRANSDERMAL PATCHES AT 37 °C

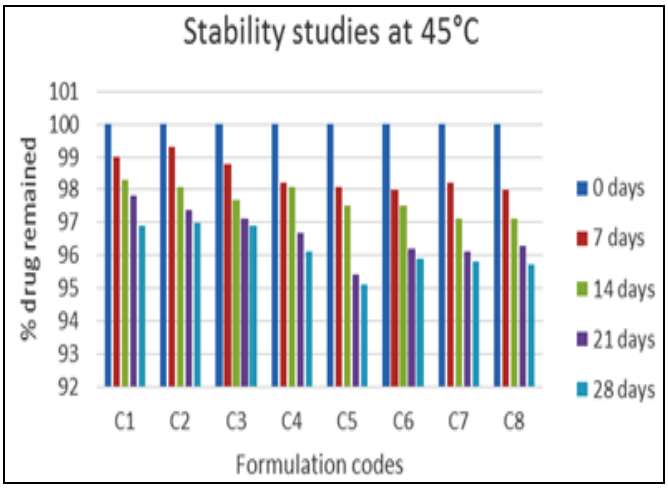

FIG. 12: STABILITY STUDIES OF TRANSDERMAL PATCHES AT 45°C

CONCLUSION: Thin flexible, smooth and transparent films were obtained with HPMC and EC polymers using glycerine and Dibutyl phthalate as plasticizers. Thickness, weight and drug contents of all the formulations remained uniform with low SD values.

All the systems were permeable to water vapour at 84% RH and followed zero-order kinetics. All the monolithic systems containing HPMC polymer showed good release than that if EC systems. The monolithic systems were found to be stable at 37°C and 45°C. Studies have shown promising results; hence there is a scope for further pharmaco-dynamics and pharmacokinetic evaluation.

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