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Formulation and evaluation of Clopidogrel bisulfate loaded transdermal patches for anti-platelet activity

Subramanian S and Senith SK*

Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore - 641 004, Tamil Nadu, India

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ABSTRACT

Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increases the bioavailability. Orally clopidogrel bisulfate has a short elimination half-life (7-8 h), 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. The purpose of this research was formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate using various polymers such as HPMC and EC by solvent casting technique for improvement of bioavailability of drug and reducing toxic effects. The developed transdermal patches may increase the therapeutic efficacy and reduce toxic effect of clopidogrel bisulfate. The prepared transdermal drug delivery system of clopidogrel bisulfate using different polymers such as HPMC and EC had shown good & promising results for all the evaluated parameters. Based on the *in vitro* drug release, drug content, weight variation, tensile strength, thickness and folding endurance results formulation F2 was concluded as an optimized formulation which shows its higher percentage of drug release.

* Corresponding Author

Name: Senith SK
Phone: +91-8807721228
Email: sksenith@gmail.com

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INTRODUCTION

Transdermal drug delivery is a topic of current interest in pharmaceutical technology and industry. In recent years, considerable attention has been focused on the development of new drug delivery system known as controlled release drug delivery system. Transdermal drug delivery system (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 first pass metabolism, less frequency of dosage form administration (Subramanian S *et al.,* 2012) reduction in gastrointestinal side effects and improves patient compliance. A recent approach to drug delivery is to deliver the drug in to the systemic circulation at a predetermined rate using skin as a site of application.

Clopidogrel bisulfate is a potent oral antiplatelet agent often used in the treatment of coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel bisulfite is an antiplatelet drug, undergoes hepatic first pass metabolism and low oral bioavailability (50%). Hence, it is suitable for formulation as a transdermal patch (Anupam patyal *et al.,* 2015). Drug molecules in contact with the skin surface penetrate by three potential pathways: Through the sweat ducts, via the hair follicules and sebaceous glands, or directly across the stratum corneum.

The objective of the present research work was to design, development and characterization of clopidogrel bisulfite transdermal drug delivery system by using various polymers such as hydroxyl

propyl methyl cellulose(HPMC), ethyl cellulose(EC) and dibutyl phthalate as plasticizer by solvent evaporation technique (Darwhekar *et al.,* 2011)

MATERIALS AND METHODS

Preformulation studies

Melting point

A small amount of Clopidogrel bisulfate is placed in a thin capillary tube 10-15 cm long, above 1mm in inside diameter and closed at one end. The capillary is filled by pressing the open end in to a small heap of the sample and vibrating it by drawing a file across the side to rattle the crystals down in to the bottom. The capillary tube is placed in a melting point viewer. The temperature range over which the sample is observed to melt is taken as a melting point. (Jain NK., 1997)

Calibration curve of clopidogrel bisulfate

A calibration curve was prepared by dissolving 100 mg of drug in 100 ml in methanol. The stock solution was diluted to get solutions in the range of 5 to 25 mcg/ml and analyzed in UV-Visible spectrophotometer at 220 nm.

Partition co-efficient

A 200 mg of clopidogrel bisulfate was dissolved in 100 ml of H_2O. From this 10 ml of solution was transferred to separating funnel and then 10 ml 1-octanol was added and shaken for 1h, kept aside for separation and then separated in to two layers. After proper dilution both aqueous and organic solution was analyzed by UV-Visible spectrophotometer at 220 nm.

$$\text{Partition Coefficient} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}}$$

Fourier transform infrared (FT-IR) studies

FT-IR technique was used to study the physical and chemical interaction between drug and excipients. The FTIR study revealed no physical or chemical interactions between clopidogrel and polymer.

Preparation of transdermal patch

Clopidogrel bisulfate was obtained as a gift sample from Saimirra Innopharm Pvt Ltd, Chennai. Transdermal patches of clopidogrel bisulfate were prepared by solvent casting technique (Rajesh N *et al.,*2010). Methanolic solution of polymer such as hydroxyl methyl cellulose, ethyl cellulose and drug along with dibutyl phthalate as plasticizer was prepared. The mixture was poured in to glass mold. The drying was carried out at room temperature for the duration of 24 h. After 24 h the dry films were removed from plastic mold and stored in dessicator until use.

Evaluation of clopidogrel bisulfate transdermal patches

Physical appearance

Formulation patches were evaluated for their physical appearance, uniformity, entrapment of any air bubble or precipitation of bubble or precipitation of drug, which on a large part determines patient acceptability of the patch and also therapeutic efficacy.

Thickness

The thickness of the drug loaded patch was measured in different points by using a digital micrometer and the average thickness and standard deviation for the thickness of the prepared patch was determined.

Weight variation

Weight variation was studied by individually weighing 10 randomly selected patches and average weight was calculated. The individual weight should not deviate significantly from the average weight.

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the patches. Folding endurance is determined by repeatedly folding the patch at the same place without break. The number of times the patch could be folded at the same place without breaking a folding endurance value

Drug content uniformity

Amount of drug entrapped in a patch was determined by completely dissolving a patch of size 2 X 2 cm^2 in 100 ml phosphate buffer solution (pH 7.4). Complete dissolution was achieved by placing the solution containing patch on shaker for about 24 h. Solution was then filtered and drug content was estimated spectrophotometer at 220 nm after suitable dilution (Subramanian S *et al., 2016*).

In vitro drug release studies

The *in-vitro* release was carried out with the semi-permeable membrane using open ended cylinder. The top of the cylinder exposed to atmosphere was considered as the donor compartment. The beaker containing diffusion medium which was phosphate buffer (pH7.4) is the receptor compartment. The drug containing patch was kept in the donor compartment and it was separated from the receptor compartment by a semi permeable membrane. The beaker was maintained at 37°C and stirred at 50 rpm with magnetic beads operated by magnetic stirrer. A sample of 1ml was withdrawn at every one hour time interval and replaced with fresh buffer. The concentration was determined by UV

Table 1: Formulation of Clopidogrel Transdermal Patch

Formulation code	Drug (mg)	HPMC (mg)	EC (mg)	Methanol (ml)	Dibutyl Phthalate (Drops)
F1	75	25	50	5	1
F2	75	50	25	5	1
F3	75	25	25	5	1
F4	75	50	50	5	1

Table 2: Physicochemical properties of prepared formulations

Formulation Code	Thickness(mm) {Mean±SEM}	Weight uniformity(mg) {Mean±SEM}	Folding endurance {Mean±SEM}	Drug content (%) {Mean±SEM}
F1	0.13 ± 0.0	155 ± 3.7	189 ± 2.0	88 ± 0.98
F2	0.13 ± 0.0	148 ± 2.9	199 ± 2.0	95 ± 0.20
F3	0.11 ± 0.0	130 ± 3.9	211 ± 8.0	89 ± 0.14
F4	0.16 ± 0.0	169 ± 8.0	169 ± 7.0	86 ± 0.84

* All are average, standard error from mean of six values

spectrophotometer at 220 nm after appropriate dilution with buffer (Gnanaprakash K *et al.,* 2012).

Tensile strength

Tensile strength of prepared patch was determined by using texture analyzer (Subramanian S *et al.,*2012). Then film was cut into 10 × 10 mm strips. Each test strip was placed in tensile grips on the texture analyzer. Tensile strength was computed using load required to break the film. Tensile strength was the maximum stress applied to a point at which the film was broken. (Subramanian S *et al.,* 2011).

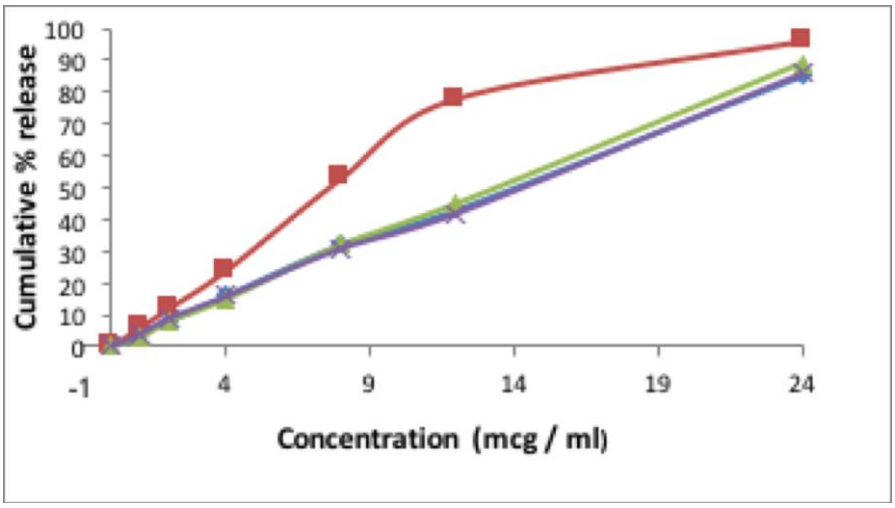

Figure 1: *In vitro* drug release

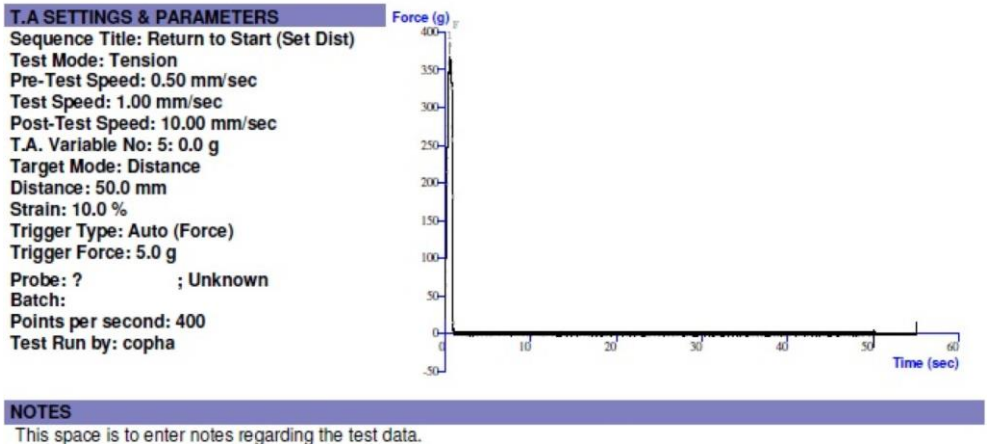

Figure 2: Texture analysis of formulation 1

RESULTS AND DISCUSSION

In the present work efforts, have been made to prepare transdermal drug delivery system of clopidogrel bisulphate using the polymers HPMC, EC using dibutyl phthalate as a plasticizer by solvent casting technique. The selection of polymer combinations produces clear, smooth, uniform, substantive flexible and desired thickness film for the transdermal drug delivery system of clopidogrel bisulphate. Melting point confirms the drug, FTIR proves that there was no interaction between polymers and drug, partition co-efficient value of 2.3 proves the lipophilicity of drug. Calibration curve with regression value of 0.998 also gave straight line.

The prepared formulations were evaluated for different physicochemical characteristics such as thickness of patches vary from 0.11 mm to 0.16 mm minimum standard values assumed that the process used for preparing the drug delivery system is capable of giving reproducible result and proportionate increase in polymer increases thickness of patch. The folding endurance was measured manually and films were folded several times and if the film shows any cracks it was taken as end point. The folding endurance was better in F2 & F3

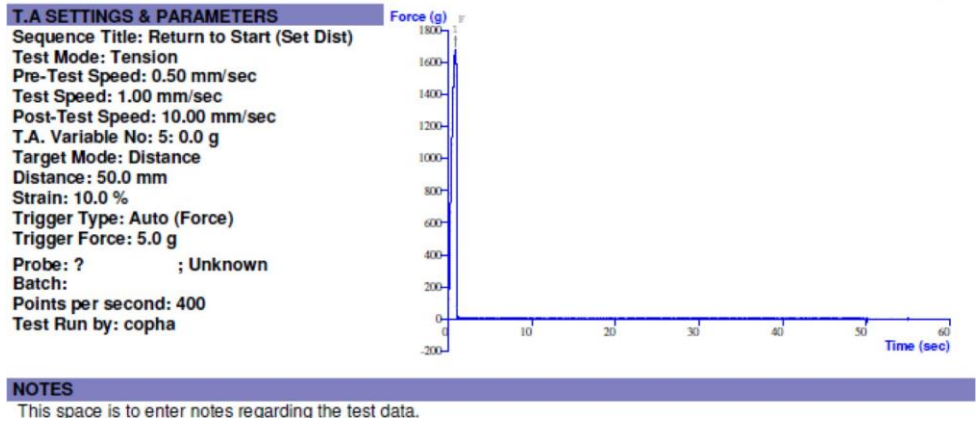

Figure 3: Texture analysis of formulation 2

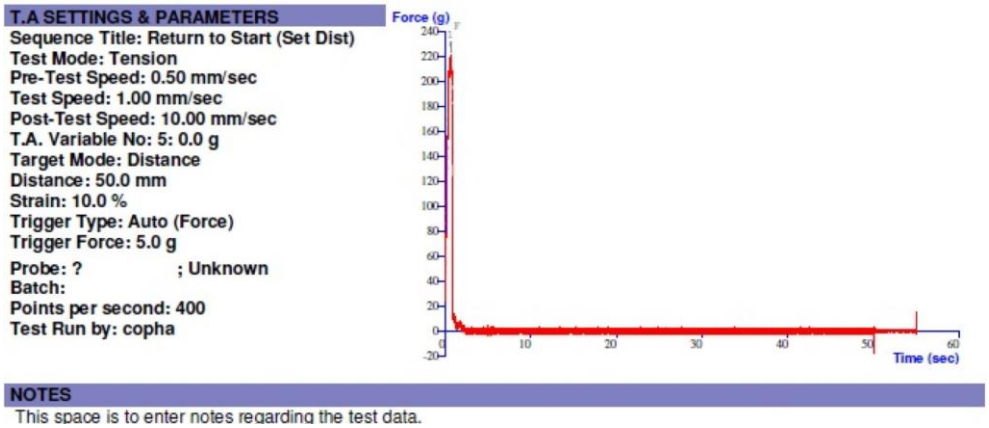

Figure 4: Texture analysis of formulation 3

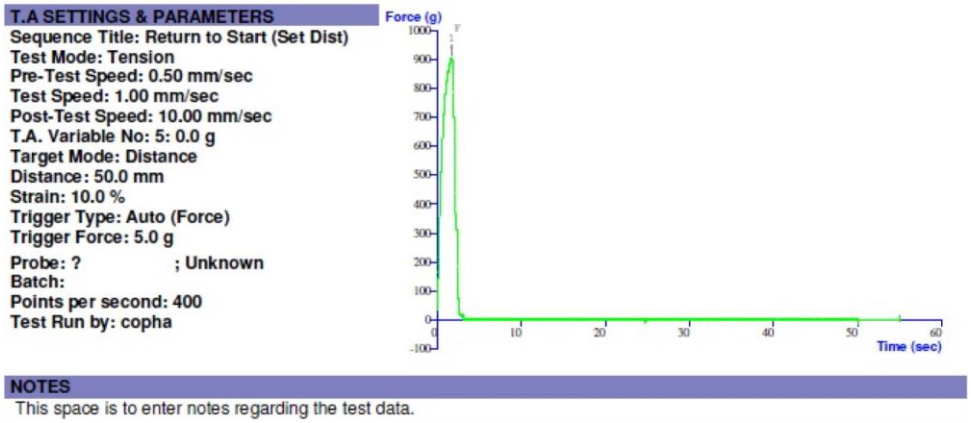

Figure 5: Texture analysis of formulation 4

formulation. Drug content uniformity & weight variation of the prepared formulation has shown that the process used to prepare the transdermal film in this study was capable of giving film with uniformity. The result of drug content indicates that the drug is uniformly dispersed in formulation.

In vitro drug release studies were carried out for the different formulations with semi permeable membrane using open ended cylinder. The relationship can be established as F2 > F3>F1>F4. Thus, by varying amount of polymer in film, percent release can be varied. Drug Polymer affinity can be major factor that control release of drug from formulation. Maximum amount of drug release (i.e, 95%) was observed with formulation F2 and the minimum (i.e., 86 %) in formulation F4. Comparison of all formulations of clopidogrel bisulfate patches revealed the fact that the developed formulation F2 showed comparable release characteristics. Thus, it may have fair clinical efficacy hence the formulation F2 has met the objective of the present study, which may hold promise for further *in vivo* studies.

CONCLUSION

The prepared transdermal drug delivery system of clopidogrel bisulfate using different polymers such as HPMC and EC has shown good promising results for all the evaluated parameters. Based on the *in vitro* drug release and drug content result, formulation F2 shows its higher percentage of drug release with 95 % of drug content.

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