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Research Article

DESIGN, DEVELOPMENT AND CHARACTERIZATION OF CLOPIDOGREL BISULFATE TRANSDERMAL DRUG DELIVERY SYSTEM

DWARAKANADHA REDDY P*, SWARNALATHA D, SIDDA RAMANJULU B, KARTHIK SAI KUMAR P, SARDAR USSAIN M

Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Kadapa, Andhra Pradesh, India.
Email: dwarakanadha.reddy25@gmail.com

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ABSTRACT

Transdermal drug delivery is an alternative route for systemic drug delivery, which minimizes the absorption and increase the bioavailability. Orally clopidogrel bisulfate 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 bisulfate using various polymers such as sodium carboxymethylcellulose (SCMC), guar gum and tragacanth with different proportions by solvent evaporation technique. The Fourier transform infrared study revealed no physical or chemical interactions between clopidogrel bisulfate and excipients. Partition co-efficient present in between 2 and 6 for this drug so it is suitable for the transdermal patches. The prepared formulations were evaluated for different physicochemical characteristics such as thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, percentage elongation break test and weight uniformity. The diffusion studies were performed by using modified Franz diffusion cells. The result of dissolution studies shows that formulation, F6 (SCMC and tragacanth) showed maximum release of 98.6% in 24 hrs, whereas F1 (SCMC and guar gum) showed minimum release of 42.9% in 24 hrs. Based on the drug release and physicochemical values obtained the formulation F6 is considered as an optimized formulation, which shows higher percentage of drug release of 98.6% in 24 hrs. The developed transdermal patches increase the therapeutic efficacy and reduced toxic effect of clopidogrel bisulfate.

Keywords: Clopidogrel bisulfate, Transdermal patch, Solvent casting techniques.

INTRODUCTION

Controlled 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 [1]. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS), which can deliver medicines via the skin portal to the systemic circulation at a predetermined rate over a prolonged period. 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 [2,3]. A recent approach to drug delivery is to deliver the drug into the systemic circulation at a predetermined rate using skin as a site of application.

Clopidogrel bisulfate, methyl (+)-(S)-(2-chlorophenyl)-6,7dihydrothie no[3,2-c] dihydrothieno[3,2] pyridine5(4H)- acetate sulfate (1:1), is a potent oral antiplatelet agent often used in the treatment of coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel bisulfate is an antiplatelet 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].

The objective of the present research work was to design, development and characterization of clopidogrel bisulfate transdermal drug delivery system by using various polymers such as sodium carboxymethylcellulose (SCMC), guar gum and tragacanth by solvent evaporation technique.

METHODS

Clopidogrel bisulfate was obtained as a gift samples from MSN Pharma Pvt. Ltd., Hyderabad. Sodium carboxy methyl cellulose, tragacanth was purchased from Universal Lab Pvt. Limited, Mumbai (India). Guargum and ethanol were purchased from Himedia Pvt. Limited, Mumbai. PEG 400 was purchased from Fischer Inorganic and Aromatic Ltd. All other laboratory chemicals used in the research work were analytical grade.

Partition coefficient determination

The partition coefficient studies were performed by using n-octanol as non-aqueous phase and water as an aqueous phase. The two phases were mixed in equal quantities and kept for saturation with each other in separating the funnel. After mixing the system remain undisturbed for ½ hr. About 10 mg of drug added to this solution and was occasionally shaken in separating the funnel. After shaken the resulting solution was kept a site for 24 hrs. After 24 hrs, two phases were separated in a separating funnel. The aqueous phase was filtered. Suitably diluted and amount of clopidogrel bisulfate in an aqueous phase was determined by measuring absorbance at 220 nm using ultraviolet (UV) spectrophotometer. The partition coefficient of clopidogrel bisulfate was calculated from the ratio between the concentration of clopidogrel bisulfate in organic and aqueous phases from the below mentioned formula [6].

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

Fourier transform infrared (FTIR) studies

FTIR 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 bisulfate and polymer.

Preparation of a transdermal patch

Transdermal patches of clopidogrel bisulfate were prepared by solvent casting technique. Ethanolic solution of polymer and drug along with

polyethylene glycol (plasticizer) was prepared. The homogenous mixture was poured into plastic mold. The solvent was allowed to evaporate at a controlled rate by placing an inverted funnel over the plastic mold. The drying was carried out at room temperature for the duration of 24 hrs. After 24 hrs the dry films was removed from plastic mold and stored in desiccators until used [7].

Evaluation of patches

Thickness of the patch

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

Weight uniformity

The prepared patches were dried at 60°C for 4 hrs before testing. A specified area of the 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.

Folding endurance

A strip of a specific area 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 value of the folding endurance.

Percentage moisture content

The prepared films were weighed individually and to be kept in desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture content=Initial weight – final weight/ final weight ×100

Percentage moisture uptake

The weighed films were kept in desiccators at room temperature for 24 hrs containing a saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture uptake=Final weight – initial weight/initial weight ×100

Water vapor permeability

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 and the polymer films were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber at 85% RH condition for a period of 24 hrs. The vials were removed and weighed at various time intervals like 3, 6, 12, 18 and 24 hrs to note down the weight gain.

Drug content

A specified area of the patch was dissolved in a suitable solvent in a specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or high-performance liquid chromatography technique).

Percentage elongation break test

The percentage elongation break was determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula:

Elongation percentage=L1-L2/L2×100

Where, L1 is the final length of each strip and L2 is the initial length of each strip.

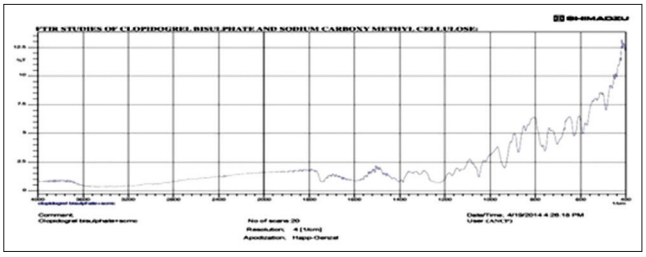

Fig. 1: Fourier transform infrared spectra of clopidogrel bisulphate

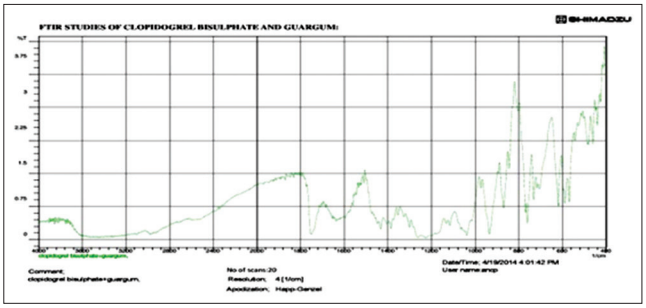

Fig. 2: Fourier transform infrared spectra of clopidogrel bisulphate and sodium carboxymethylcellulose

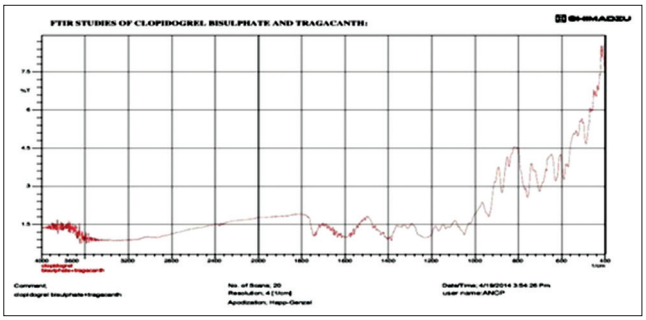

Fig. 3: Fourier transform infrared studies of clopidogrel bisulphate and tragacanth

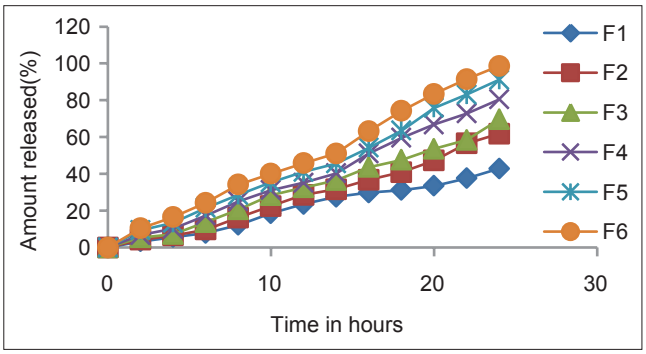

Fig. 4: *In-vitro* drug release studies of clopidogrel bisulfate transdermal patch

***In-vitro* drug diffusion studies**

The *in-vitro* diffusion study was carried out with the abdominal rate skin using Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The temperature was maintained at 37±0.5°C and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4) [8-10]. *In-vitro* studies are also done for TDDS was two types of diffusion cells are used as horizontal and vertical. The mice abdominal skin was

placed on receptor compartment and both compartments held tight by clamps. Phosphate buffer pH 7.4 was used as receptor solution. The volume of the diffusion cell was 15 ml and stirred with bent stainless steel pin. The temperature was maintained at 37±2°C with the help of the magnetic stirrer. The diffusion was carried out for 24 hrs and 1 ml sample was withdrawn at an interval of 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hrs. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 220 nm in UV spectrophotometer.

Table 1: Composition of clopidogrel bisulfate transdermal patches

Ingredients	F1	F2	F3	F4	F5	F6
Clopidogrel bisulfate	37	37	37	37	37	37
SCMC	300	300	300	300	300	300
Guar gum	100	150	200	-	-	-
Tragacanth	-	-	-	100	150	200
Ethanol	5	5	5	5	5	5
PEG 400	0.4	0.4	0.4	0.4	0.4	0.4

SCMC: Sodium carboxymethylcellulose

Table 2: Partition coefficient of drug in PBS in 7.4

Partition coefficient of drug	Solvent system	Log D values
Clopidogrel bisulfate	Phosphate buffer: N-octanol	2.2±0.04

PBS: Phosphate-buffered saline

Table 3: Partition coefficient of drug in skin

Partition coefficient of drug	Solvent system	Log D values
Clopidogrel bisulfate	Phosphate buffer: n-octanol	2.4±0.06

Table 4: Permeation study of clopidogrel bisulfate in phosphate buffer 7.4

S.No	Time (hrs)	% Amount of permeation
1	0	0
2	1	7.65
3	2	14.15
4	3	20.27
5	4	26.17
6	5	35.07
7	6	40.16
8	8	46.11
9	10	55.60
10	12	60.02
11	24	69.08

RESULT AND DISCUSSION

In the present work efforts have been made to prepare transdermal drug delivery system of clopidogrel bisulfate using as SCMC, guar gum and tragacanth with different proportions (3:1, 3:1.5 and 3:2) by solvent casting technique. The selection of polymer combinations produces clear, smooth, uniform, substantive, flexible and desired thickness film for the TDDS of clopidogrel bisulfate. The prepared formulation was evaluated for different physico-chemical properties. The thickness of the patches varied from 0.120 mm to 0.235 mm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible result.

The folding endurance was measured manually, films were folded 72 times maximum in formulation F3 and if the film shows any cracks it was taken as end point. The folding endurance was better in F3 formulation. As the concentration of SCMC and tragacanth increase, moisture uptake of patches was also increase.

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

Water vapor transmission study determines the permeability characteristics of the patches. The result of water vapor transmission study reviled that all the formulation are permeable to water vapor [11-15].

In-vitro drug release studies were carried out for the different formulations using Franz diffusion cell. The result of dissolution studies shows that formulation, F6 (SCMC and tragacanth) showed maximum release of 98.6% in 24 hrs, whereas F1 (SCMC and guar gum) showed minimum release of 42.9% in 24 hrs. Based on the drug release and physicochemical values obtained the formulation F6 is considered as an optimized formulation. No visible changes were observed in transdermal patches after storage in stability testing as per ICH guidelines for 3 months.

Comparison of all formulations of clopidogrel bisulfate patches revealed the fact the developed formulation F6 showed comparable release characteristics. Thus it may have fair clinical efficacy. Hence, the formulation F6 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 grades of SCMC, tragacanth and guar gum had shown good promising results for all the evaluated parameters. It was concluded that SCMC and tragacanth of moderate level useful for preparation of sustained release matrix transdermal patch formulation. The developed transdermal patches increase the therapeutic efficacy and reduced toxic effect of clopidogrel bisulfate.

Table 5: *In-vitro* drug release studies of clopidogrel bisulfate transdermal patches

S.No	Time (hrs)	F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	2	3.3±0.25	4.2±0.45	5.4±0.78	6.8±28	9.4±0.27	10.4±0.29
3.	4	5.6±0.59	6.5±0.28	7.2±0.26	10.2±0.39	13.4±0.95	16.5±0.67
4.	6	7.8±0.34	9.7±0.56	13.7±0.95	17.4±0.57	21.5±0.56	24.3±0.58
5.	8	12.2±0.98	16.2±0.99	20.6±0.77	25.1±0.48	28.6±0.20	34.2±0.87
6.	10	18.6±0.96	22.5±0.45	28.4±0.97	31.2±0.90	35.4±0.38	40.1±0.37
7.	12	23.6±0.93	28.6±0.69	32.6±0.34	35.2±0.98	41.1±0.46	45.8±0.96
8.	14	27.5±0.74	31.6±0.97	36.5±0.45	40.3±0.95	45.6±0.37	51.1±0.97
9.	16	29.8±0.09	36.8±0.95	43.7±0.97	51±0.35	54.2±0.47	63.2±0.96
10.	18	31.2±0.37	40.9±0.89	47.6±0.68	59.6±0.97	63.5±0.46	74.2±0.85
11.	20	33.5±0.34	47.2±0.86	53.6±0.75	66.8±0.35	75.8±0.89	83.4±0.97
12.	22	37.6±0.86	56.5±0.9	58.4±0.97	72.8±0.85	83.1±0.96	91.5±0.35
13.	24	42.9±0.96	61.8±0.9	69.6±0.27	80.5±0.96	91.1±0.64	98.6±0.98

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