FORMULATION DEVELOPMENT AND EVALUATION OF CLOPIDOGRELBISULFATE TRANSDERMAL PATCHES

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ABSTRACT: Clopidogrel bisulfate is a medication that is used for the treatment of cardiovascular problems and to suppress the aggregation of platelets.Almost entirely absorbed (98%) upon oral treatment, it exerts its effect via blocking theadenosine diphosphate.50% of drugs end up in urine and 40% in feces. Dosing is needed often since the plasma half-life of the medication is roughly 8 hours.to keep the drug's therapeutic blood levels steady for long-term treatment.Therefore, the medicine was administered directly to the systemic circulation via the skin using the transdermal patches.The transdermal patches were made using the solvent evaporation technique.It was determined what effect varied ratios of polymer concentrations have. The drug's physicochemical characteristics were unaffected by the polymers utilized in this investigation.The physical appearance, thickness, weight fluctuation, and drug content homogeneity of all the batches were assessed.We investigated the release mechanisms and conducted the in vitro drug dissolving investigation using the Franz diffusion device. One way to measure the efficacy of a polymer in slowing the release of a medicine from a transdermal patch is to look at its mean dissolving time. The optimal dose of PVP and ethyl cellulose was 200 mg, as it allowed for 92% drug release in 16 hours, compared to 85% drug release in 10 hours for all other formulations. This led to the discovery of F4 as the optimal formulation. The constructed patches all showed diffusion-governed zero-order release kinetics.

INTRODUCTION: There has been a rise in the use of transdermal drug delivery systems (TDDS), which are adhesives containing drug devices with a set surface area that transfer a predefined quantity of medicine to the intact skin at a preprogrammed pace. Protecting the body from harmful environmental elements, skin serves as the body's biggest organ. It is necessary to overcome the skin barriers 2 for a medicinal product administered via the skin to attain its therapeutic properties.

Transdermal medication delivery systems are characterized as "patches"—self-contained discrete dose forms that, when placed to healthy skin, slowly release their contents into the bloodstream. 3. When compared to traditional injectable and oral approaches, TDDS has several benefits. It lessens the strain on the digestive system and liver that is typical of the oral route.

It lessens the negative effects of a medicine due to a transient overdose and increases patient compliance. The ease of use is still another perk, particularly with patches that need to be applied no more than once a week. Adherence to pharmacological treatment may be improved with the use of a straightforward dose plan. Drugs must be taken for longer periods of time and more often for some chronic conditions, such as diabetes, hypertension, TB, and cancer. the patient may not take their medication as prescribed, which might result in an unstable plasma levels of the medicine. Poor absorption and gastrointestinal irritation are common side effects of many orally taken medications. 5.

The anti-platelet medication clopidogrel bisulfate has a poor oral bioavailability of 50% and is first-pass metabolized in the liver.So, it can be made into a transdermal patch.There are three possible entry points for drug molecules that come into touch with skin: the sweat ducts, the hair follicles and sebaceous glands, and the stratum corneum itself. Due to the medicine's short plasma half-life (about 8 hours), regular dosage is required to maintain therapeutic blood levels of the drug during therapy. Because of this, it may be effectively formulated as a transdermal patch.

Thus, clopidogrelbisulphate is a perfect candidate for transdermal medication administration. The development of clopidogrelbisulphate patches was accomplished by using solvents in equal quantities with ethyl cellulose, HPMC, PEG-400 as a plasticizer, and DMSO as a permeation enhancer. Assessment of the

patches that have been manufactured by in-vitro drug release tests using the Franz diffusion equipment, as well as the examination of drug release kinetics from each formulation.

MATERIALSANDMETHODS:

Materials: Clopidogrelbisulfatewas a giftsample from AurobindoPharma Ltd, Hyderabad. Poly vinylpyrrolidone,hydroxypropylmethylcellulose, ethyl cellulose were received from Loba Chemicals, Mumbai. Dimethyl sulfoxide, polyethylene glycol, chloroform were procured from S. D. Fine Chemicals, Mumbai.

Preparation of Clopidogrelbisulphate Trans- dermal patches: Clopidogrelbisulphate trans- dermal patches were prepared by solvent evaporation method. Weighed quantities of polymers like hydroxy propyl methyl cellulose, Poly vinyl pyrrolidone, and ethyl cellulose were dissolved in chloroform and ethanol solvent mixture. The drug was added to the above polymer solution alongwith polyethylene glycol as plasticizer anddimethylsulfoxide as permeation enhancer and thoroughly mixed to form a homogeneous mixture. The volume was made up to 10 ml withchloroform. Then the drug solution was added to thepolymericsolution,castedontopetriplatesofsurface area about 69.42 sq.cm, allowed for air drying overnight followed by vacuum drying for 8- 10 hr. The entire sheet was cut into small patches with an area of 5cm ^{2}*i.e.* with a diameter of 2.5 cm. About 10 patches were obtained from each sheet [7].

Evaluation of Prepared Trans-dermal Patches: PhysicalAppearance: Allthepreparedtrans-dermalpatcheswerevisuallyinspectedforcolor, clarity, flexibility and smoothness [8].

Thickness of the Patch: Thickness of each trans- dermal patch was determined via utilizing a micrometer screw gauge placed at six distinct positions. The average thickness and standard deviation values of six readings were calculated for each batch of drug loaded patch [9].

Weight Uniformity: It was studied byindividually weighing10randomlyselectedtransdermalpatches and average weight was calculated on digital balance (Shimadzu, AUX220, Japan). The individual weights should not deviate significantly from the average weight [10].

Drug Content: An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator (Rajendra Electrical Industries Ltd, Hyderabad). Then the whole solution is sonicated, filtered, drug in solution is estimated by appropriate dilution and analysedby (Shimadzu, Japan) UV – Spectrophotometrically[11].

Percentage of Moisture Uptake: The weighed films were kept in a desiccators (Borosil Hyderabad, India) at room temperature for 24 hours and then exposedto84 %relativehumidityusingasaturated solution of potassium chloride. Finally the films were weighed and the percentage of moisture uptake is calculated as the difference between the finalandinitialweightwithrespecttoinitialweight [12].

Percentage moisture uptake = [Final weight -Initial weight/Initial weight] * 100

Folding endurance: The folding endurance of patches was determined by repeatedly folding a strip of film at the same place till it tends to break. Itisdeterminedasthenumberoftimesthefilmisfolded at the same place either to break the film or to develop visible cracks [13].

In-vitro* Release Studies:In-vitro*drug release of trans-dermal patches can be studied using Franz diffusion cell (most commonly used) with an effective permeation area of 1.0 cm^2 and receptor cell volume of 10 ml. The temperature is maintained at 32°C ± 0°C. The syntheticcellophane membrane was mounted between upper donor and patch placed on upper receptor compartment of the diffusion cell. The lower receptor

compartment is filled with 10 mlphosphate buffer pH 7.4 which is constantly stirred onamagneticstirrer(RemiHyderabad,India)at
100 rpm. 2 ml samples were withdrawnfromreceptorcompartmentthroughthe sampling portat predetermined time interval and are analysed for drug release at 247 nm spectrophotometrically[14](Shimadzu, AUX220, Japan).

Drug Release Kinetics Mechanism: To interpret themechanismandkineticsofdrugrelease,the result outcome of *in-vitro* drug release study were applied with different kinetic equations like zero order (% drug release *vs*. time), first order (log % unreleased drug *vs*. time) and Higuchi matrix (% drug release *vs*. square root of time). Drug release data was further analysed by Peppas equation, $M_t/M_\infty=kt^n$, where Mt is the amount of drug released at time t and M∞ is the amount released at time ∞, the Mt/M∞ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent, a measure of the primary mechanism ofdrugreleasetodefineamodel which will represent a better fit for the formulation. Regression co-efficient (r^2) values were calculated for the linear curves obtained by regressionanalysis of the above plots [15].

RESULTS: In the present work, transdermal patcheswerepreparedbyusingsolventevaporation method as it was feasible and simple. The best parameters obtained for clopidogrelbisulphate patches were evaluated based on drug release.

TABLE1:FORMULAOFCLOPIDOGRELBISULPHATETRANSDERMALPATCHES

Ingredients	CBF1	CBF2	CBF3	CBF4	CBF5	CBF6	CBF7	CBF8	CBF9
Clopidogrelbisulphate(mg)	50	50	50	50	50	50	50	50	50
PVP(mg)	250	250	250	250	250	250	-	-	-
HPMC(mg)	250	750	1250	-	-	-	250	750	1250
EC(mg)	-	-	-	250	750	1250	250	750	1250
DMSO(ml)	15	15	15	15	15	15	15	15	15
PEG-400(ml)	15	15	15	15	15	15	15	15	15
Chloroform:ethanol(ml)	10	10	10	10	10	10	10	10	10

Evaluation Data of Clopidogrel bisulphateTransdermalPatches: Thefollowingstudieswerecarriedtofindtheeffectofdifferentratiosof polymers in combination.

TABLE2:EVALUATIONDATAOFCLOPIDOGRELBISULPHATETRANSDERMALPATCHES

Batch Code	Thickness (mm)	Weightvariation (mg)	Folding endurance	Drugcontent (%)	%Moisture uptake
F1	206±6.18	135±3.51	22±2.20	96.99± 0.65	0.78± 1.02
F2	220±7.12	166±4.52	21±2.8	97.2± 0.65	0.93± 1.05
F3	232±7.18	155±4.10	28±2.40	94.99± 0.65	0.80± 1.10
F4	204±5.18	160±4.20	26±2.96	96.56± 0.65	0.40± 1.08
F5	204±5.18	170±4.62	27±2.38	95.45± 0.65	0.70± 1.07
F6	265±5.13	140±3.70	25±2.32	96.72± 0.65	0.35± 0.78
F7	280±1.60	136±3.55	31±3.1	95.55± 0.65	0.25± 0.45
F8	245±6.10	176±1.72	29±2.45	98.22± 0.65	0.40± 0.60
F9	278±4.60	165±4.20	30±2.63	97.99± 0.65	0.93± 0.75

S.D*isbeingcalculatedbytaking3 patches

TABLE 3: CUMULATIVE % DRUG RELEASE DATA OF TRANSDERMAL PATCHES IN PHOSPHATE BUFFER pH 7.4 (CBF1- CBF5)

Time(Hr)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	12	18	16	13	14
2	21	23	25	19	22
3	27	31	36	25	29
4	35	38	39	33	35
5	43	44	42	39	39
6	57	48	51	45	42
7	65	53	59	58	49
8	71	58	63	62	52
10	78	62	72	71	59
12	83	68	78	75	65
14	85	75	83	81	78
16	91	88	89	92	82

TABLE 4: CUMULATIVE % DRUG RELEASE DATA OF TRANSDERMAL PATCHES IN PHOSPHATE BUFFER pH 7.4 (CBF6- CBF9)

Time(Hr)	F6	F7	F8	F9
0	0	0	0	0
1	21	24	17	16
2	29	29	24	26
3	35	34	31	34
4	39	42	39	39
5	42	49	42	42
6	49	51	49	48
7	54	59	53	53
8	62	63	59	59
10	69	71	66	63
12	74	76	72	69
14	79	82	79	73
16	83	90	81	79

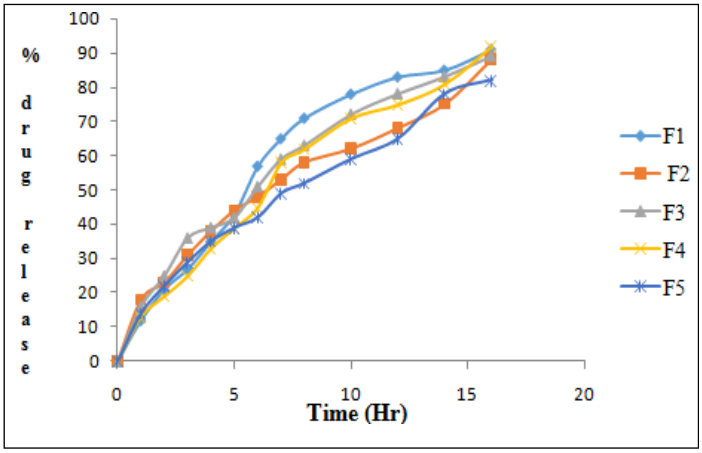

FIG.1:%DRUGRELEASEOFCLOPIDOGRELBISULPHATEFROMTRANSDERMALPATCHESF1-F5

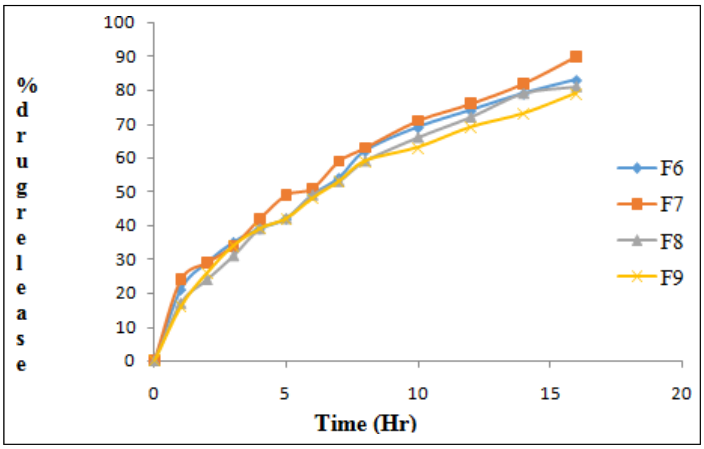

FIG.2:%DRUGRELEASEOFCLOPIDOGRELBISULPHATEFROMTRANSDERMALPATCHESF6- F9

DISCUSSION: Transdermal systems were made from polymers with excellent film-forming capabilities, such as ethyl cellulose, hydroxypropyl methyl cellulose, and poly vinyl pyrrolidone. The prepared systems fulfilled all expectations; they were thin, flexible, smooth, and transparent. The technology used to create them was also deemed good. There was a narrow standard variation for the transdermal patch thickness across all nine formulations, which ranged from 206 to 278 mm.

The researchers used a UV spectrophotometer (UV 2060 Plus Analytical Technology, India) to find out what percentage of the material was uniform in the patches. The results of the content uniformity test showed that all of the formulations were within the 99.99–99.99 percent range.The low standard deviation results show that the drug content is consistent across all formulations, and it was noted that all formulations were within the boundaries of the I. P. specifications. The patches had an average weight of 135–165 mg.There was little variation in the weights of the transdermal patches. Results showed that the typical folding endurance values were 22-30. This material absorbed between 0.25 and 0.93 percent of its weight in moisture. Studies of in vitro drug release utilizing Franz diffusion cells with cellophane membranes were used to optimize the prepared patches. Table 3, 4, and Figures 1 and 2 provide the data and plots of the percentage medication release for the transdermal patches in phosphate buffer pH 7.4. The data were evaluated at 247 nm using a UV - Spectrophotometer.

Up to 92% drug release was achieved in most formulations using a low concentration range of polymers. We hypothesize that it may achieve increased drug release with an increase in polymer concentration. However, research on drug release using the Franz diffusion apparatus found that lower concentrations of polymers resulted in greater drug release than higher concentrations. In conclusion, however, I think a low proportion of polymers is ideal for making transdermal patches. Because of its 92% drug release, the F4 formulation patch (PVP and EC) was the best batch. Zero, initially, Higuchi and Peppas's kinetic model was used to fit the cumulative quantity of medication that penetrated per square centimeter of patches across membranes displayed against time.According to the release profile, it is all formulas followed zero-order kinetics. But the improved formulation F4's release profile (r2 = 0.982 for zero order) showed that a diffusion mechanism guided the drug's release from the patches.

CONCLUSION: Pharmaceutical scientists have shown a great deal of interest in the topic of skin-based medication delivery into systemic circulation in recent years. Polymers such as HPMC, EC, and PVP were used in various ratios (1:1,1:3,1:5) to maintain a steady serum level of clopidogrelbisulphate for an extended duration. Using the solvent evaporation method, transdermal patches were created. The patches showed excellent physical characteristics. The Franz diffusion cell was used for the in-vitro experiments. Physical and chemical parameters, such as thickness, weight change, and in vitro drug release, were assessed in the transdermal patches.

After looking at a bunch of different metrics, it was determined that the polymers worked well. The medication release rate was 91% when using a PVP and HPMC combination transdermal patch, and 92% when using a PVP and EC patch. Combinations such as HPMC and EC demonstrated a 90% reduction in drug release. Reducing the polymeric content accelerated the release rate. Therefore, transdermal patches were most effectively made using low-concentration mixtures of polymers such as PVP and EC. Based on the Higuchi release mechanism, the formulation's release kinetics were zero-order.

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