

## Design and *In Vitro* Evaluation of Transdermal Drug Delivery System for Aspirin

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### ABSTRACT

Aspirin has become the gold standard to which newer antiplatelet drugs are compared for reducing risks of cardiovascular diseases, while keeping low cost. Oral aspirin has a repertoire of gastrointestinal side effects even at low doses and requires high frequent dosing because it undergoes extensive presystemic metabolism. Transdermal delivery offers an alternative route that bypasses the gut and may be more convenient and safer for aspirin delivery especially during long-term use. This study comprised formulation of aspirin in different topical bases. Release studies revealed that hydrocarbon gel allowed highest drug release. *In vitro* permeation studies revealed high drug permeation from hydrocarbon gel. Several chemical penetration enhancers were monitored for augmenting the permeation from this base. Combination of propylene glycol and alcohol showed maximum enhancing effect and, hence, was selected for biological investigation. The biological performance of the selected formulation was assessed by measuring the inhibition of platelet aggregation relevant to different dosage regimens aiming to minimize both drug dose and frequency of application. The results demonstrated the feasibility of successfully influencing platelet function and revealed that the drug therapeutic efficacy in Transdermal delivery system is dose independent. Biological performance was re-assessed after storage and the results revealed stability and persistent therapeutic efficacy.

**Keywords:** Aspirin; Transdermal; Cardiovascular diseases; Platelet aggregation inhibition.

### INTRODUCTION

Aspirin, which has been known as an antipyretic and analgesic for 100 years, has undergone a resurgence of popularity since it became appreciated in the 1980s as the most cost-effective agent for the secondary prevention of coronary artery disease. Aspirin is also the basic antiplatelet agent for all kinds of acute disease that may cause platelet-dependent thrombotic vessel occlusion. It is recommended as the first-line antiplatelet drug. Aspirin imparts its primary antithrombotic effects through the inhibition of PGH-synthase/COX by the irreversible acetylation of a specific serine moiety. The resultant decreased production of prostaglandins and TXA<sub>2</sub> likely accounts for the therapeutic effects, as well as the toxicities, of aspirin. Aspirin-induced inhibition of TXA<sub>2</sub> and PGI<sub>2</sub> has opposing effects on hemostasis. Aspirin is rapidly absorbed in the stomach and upper intestine. The oral bioavailability of regular aspirin tablets is approximately 40–50% over a wide range of doses. A considerably lower bioavailability has been reported for enteric-coated tablets and sustained-release, microencapsulated preparations. Orally administered aspirin requires high and frequent dosing because it undergoes extensive presystemic hydrolysis in the gut and liver into salicylic acid which is devoid of antiplatelet activity. Continuous exposure of new platelets to aspirin is necessary to achieve prolonged inhibition of platelet aggregation (The plasma concentration of aspirin decays with a half-life of 15–20 min. Despite the rapid clearance of aspirin from the circulation, the platelet-inhibitory effect lasts for the life span of platelet because aspirin irreversibly inactivates platelet COX-1. The mean life span of human platelets is approximately 10 days. Low-dose aspirin or controlled-release preparations may result in somewhat preferential inhibition of platelet COX over endothelial COX. In order to spare prostacyclin formation and reduce gastrointestinal side effects, very low doses of aspirin have

been introduced; however, gastrointestinal side effects may in part be due to local action of aspirin and may not be completely avoided with this strategy. Transdermal delivery offers an alternative route for administering aspirin that bypasses the gut and may be a more convenient, safer and non-invasive mean for aspirin delivery especially in case of long-term use. The low bioavailability of dermal aspirin and the avoidance of direct contact with COX-1 expressed on gastric mucosal cells may provide a safer means of inhibiting platelet function. Our goal was to design a transdermal formulation for aspirin characterized by high therapeutic efficacy, safety and stability. Two main strategies were implemented. In the first strategy, certain bases belonging to different classes of dermatologic semisolid formulations were monitored in order to optimize drug release, permeation through skin and stability. The second strategy involved incorporation and evaluation of numerous penetration enhancers. Finally, the biological performance of a selected optimized formulation was assessed via different dosage regimen aiming to minimize – as far as possible – both the dose of the drug as well as its frequency of application. Furthermore, investigating the biological performance of the selected formulation after storage, indicative of its stability, was not beyond the scope of this paper [3].

### MATERIALS AND METHODS

#### Materials:

Aspirin, (Mumbai, India). Polyethylene glycol was purchased from Sisco Research Laboratories (India). Polyethylene glycol 400 was purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). Polyethylene glycol and oleic acid were purchased and Propylene glycol was purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). Carboxymethyl cellulose sodium was purchased from S.D. Fine Chemicals Ltd. (Mumbai, India), Urea was purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other materials were of analytical grade.

#### Methods:

##### Preparation of different bases for transdermal film:

##### *O/w emulsion hydrophilic base (Hydrophilic Ointment USP):*

Twenty-five grams of each of stearyl alcohol and white petrolatum were melted on a water bath maintained at 70 °C. One

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gram of sodium lauryl sulphate was dissolved in 25ml of water, the solution was heated to the same temperature and 12 g of propylene glycol was added. The oleaginous phase was added slowly to the aqueous phase while stirring constantly. The mixture was then removed from heat and stirred until it congealed [2].

#### **Polyethylene glycol water soluble base (Polyethylene Glycol Ointment NF):**

Sixty grams of polyethylene glycol 400 and 40 g of polyethylene glycol 3350 were heated on a water bath to 65 °C, allowed to cool and stirred until congealed [1].

#### **Carboxymethyl cellulose sodium gel (5%):**

The weighed amount of the sodium salt of carboxymethyl cellulose was dispersed with high shear in cold water. Once the powder was well dispersed, the solution was heated with moderate shear to about 60 °C.

#### **Plasticized hydrocarbon gel (Plastibase):**

Liquid petrolatum was gelled by addition of approximately 5% of polyethylene glycol, the mixture was heated and then shock-cooled.

#### **Release studies of aspirin from different bases:**

The prepared bases were medicated with aspirin at a concentration of 20%, release experiments were carried out according to the paddle method using phosphate buffer at pH 5.5.

The medicated bases (375 mg) were spread evenly on the surface of a watch glass of 5.3066 cm<sup>2</sup> surface area and covered with a stainless steel mesh screen). The assembly was placed at the bottom of the USP dissolution tester. The height of the paddle from the surface of the assembly was adjusted to 2.5 cm. The vessel contained 900 ml of the buffer solution and the temperature was adjusted at 32 °C and the speed at 50 rpm. Aliquots of 5 ml were withdrawn through sintered glass filter from the release medium at each time interval and replaced by equal volume of fresh buffer solution. Samples were assayed spectrophotometrically for aspirin content at 302 nm using Shimadzu UV Spectrophotometer (2401/PC), Japan. The amount of drug released per unit surface area was plotted against time [4].

#### **In vitro permeation studies of aspirin through full thickness rat abdominal skin:**

The abdominal hair of male Wistar rats (200–250 g) was removed carefully using electric razors. After the animals were sacrificed, the abdominal skin was excised and the adhering fat eliminated. The skin used was of thickness 700 ± 50 µm.

This membrane was mounted on vertical Franz-type diffusion cell with the dermis facing the receptor compartment. The donor side was charged with 187.5 mg of the investigated base containing 20% aspirin. The membrane surface area available for diffusion was 8 cm<sup>2</sup>. The donor chamber was covered with parafilm. The receptor compartment was filled with 100 ml of phosphate buffer (pH 7.4).

The temperature was maintained at 37 ± 0.5 °C and the receptor compartment was constantly stirred at 300 rpm. Samples of the receptor fluid (1 ml) were withdrawn at various time intervals up to 24 h and replaced immediately with equal volume of fresh buffer solution to maintain constant volume and then the samples were assayed spectrophotometrically at 302 nm using Shimadzu UV Spectrophotometer. The percentage values of cumulative aspirin permeated were calculated. Several chemical penetration enhancers belonging to different groups were incorporated into hydrocarbon gel base to investigate their effect on permeation. The tested enhancers comprised: oleic acid, methyl myristate, PG, a combination of PG and alcohol, limonene, DMSO, urea.

#### **Assessment of the biological performance of aspirin in transdermal delivery system:**

The inhibition of platelet aggregation was taken as a pharmacodynamic parameter for evaluating the bioavailability of the drug. Male Wistar rats weighing 200–250 g were kept on standard diet and maintained under controlled conditions of humidity (30–70%) and temperature (24 ± 2 °C) and fasted overnight before blood collection.

#### **Effect of dosage regimen:**

The biological performance of aspirin in hydrocarbon gel base containing 40% PG and 10% alcohol was assessed in male Wistar rats via measuring the effect of different dosage regimens (300, 150, 75 and 30 mg; dosage regimen B, C, D and E, respectively) on platelet aggregation aiming to decrease both aspirin dose as well as the frequency of application. Aspirin (300, 150, 75 or 30 mg) [dosage regimen B, C, D or E, respectively] in an equal weight of hydrocarbon gel containing 40% PG and 10% alcohol, was spread as a film of surface area 5.3066 cm<sup>2</sup> on aluminum foil and applied by an adhesive tape on the naked back region of the animals of the test groups (*n* = 6). The same formula without aspirin was applied to the control groups (*n* = 6) for each dosage regimen. Each of the tested doses was applied three times (on the same position) according to the following schedule: application on the first, fourth and seventh days. The adhesive tapes were removed 48 h after application. Blood samples were withdrawn from the orbital sinus of the animals on the 10th day [72 h after (the last) applications

However, for the dose of 30 mg, application was done once and blood samples were withdrawn on the fourth day. The absorbance of platelet-rich plasma falls as platelet aggregate. The amount and the rate of fall are dependent on platelet reactivity to the added agonist if other variables such as temperature, platelet count and mixing speed are controlled. Blood (4.5 ml) was collected in plastic tubes containing 0.5 ml sodium citrate (0.9%). Platelet-rich plasma (PRP) was generated from citrated blood by centrifugation at 200 × *g* for 15 min. Platelet-poor plasma (PPP) was prepared from the remaining volume of blood by centrifugation at 1600 × *g* for 15 min. PRP (450 µl) were added to an aggregation cuvette containing a stirring bar and 50 µl of aggregation inducing agent (adenosine diphosphate, 10<sup>-3</sup> mol/l) were added. PPP (500 µl) was placed in the other cuvette. Platelet aggregation was then measured turbidometrically until the response reached a plateau or for a period of 3 min using the whole Blood Aggregometer. The main indicator of platelet function was maximal aggregation intensity induced by ADP and inhibited by the administration of aspirin.

#### **Effect of storage:**

The biological performance of aspirin in hydrocarbon gel base containing 40% PG and 10% alcohol was reassessed as previously described according to dosage regimen E (30 mg of aspirin applied once) in male Wistar rats after storage at 40 ± 2 °C/75 ± 5% RH for 6 months. The medicated base was spread as a film of surface area 5.3066 cm<sup>2</sup> on aluminum foil and applied by an adhesive tape on the naked back region of the animals of the test groups (*n* = 6). The same formula without aspirin was applied to the control groups (*n* = 6) and then its platelet aggregation inhibiting effect was reassessed as previously described [7].

## **RESULTS AND DISCUSSION**

#### **In vitro release studies of aspirin from different bases:**

Release profiles of the drug from the investigated bases were obtained by plotting the amount of aspirin released (mg/cm<sup>2</sup>) as a function of time.

Drug release from carboxymethyl cellulose gel was high, reaching 97.50 ± 3.18% within 4 h. vaseline-PG (7:3) base; (×) vaseline-almond oil (7:3) base; (\*) vaseline-liquid paraffin (7:3) base; (○) Vaseline liquid paraffin (6:4) base; hydrocarbon gel base; ( ) PEG ointment base; hydrophilic ointment base Vaseline, being a substantially anhydrous base, assures the stability of aspirin but affords very low drug release.

This may be due to its high lipophilicity and viscosity. Incorporation of certain proportion (30%) of propylene glycol, almond oil (glycerol fatty acid ester) or liquid paraffin (hydrocarbon oil) markedly increased percentage drug released from this base after 4 h from 2.97 ± 0.41 to 35.66 ± 0.16, 22.22 ± 0.57 and 28.44 ± 0.41, respectively; this increase is significant (*p* < 0.001). These results run parallel with the patent pointing out that the addition of these substances did not only stabilize aspirin but also dissolved it. However, increasing the amount of incorporated liquid paraffin to 40% did not increase the cumulative amount of aspirin released, but conversely decreased it this decrease is also significant (*p* < 0.01). Hydrocarbon gel base allowed complete drug release after 4 h. This quick release may be attributed to easy migration of drug particulates through a vehicle which is essentially a liquid. Polyethylene glycol ointment base allows easy drug release (84.83 ± 0.78% after 4 h). The cumulative amount released from

hydrophilic o/w base was less than that from the PEG base (56.67 ± 0.29% after 4 h).

#### In vitro permeation studies of aspirin:

##### Permeation of aspirin from different bases:

Percentage values of cumulative aspirin permeated were calculated and listed in **Table 1**. The data revealed that after 24 h the amount of aspirin permeated from hydrocarbon and carboxymethyl cellulose (CMC) gel bases was higher than that from the hydrophilic ( $p < 0.05$ ) and polyethylene glycol ( $p < 0.001$ ) ointment bases and that the permeation from these bases was far better than from vaseline base ( $p < 0.001$ ). Hydrophilic ointment base showed higher permeation of the drug than expected from the

in vitro release data. This may be due to the presence of sodium lauryl sulphate which actually can be considered as a penetration enhancer because it has the potential to solubilize lipids of the stratum corneum. Besides allowing complete drug release within 4 h, hydrocarbon gel showed high permeation. This may be due to its paraffin content which forms a greasy film on the skin, inhibiting moisture loss and improving hydration of the horny layer. The permeation of aspirin from CMC gel base was high during the first 5 h, and then it decreased markedly. This may be explained by the decrease of concentration gradient between the donor phase and the receptor phase after permeation of a large amount of aspirin to the receptor phase.

**Table No. 1: Permeation of aspirin from different bases**

Time (h)	Cumulative aspirin permeated (%) from				
	CMC gel	Vaseline	Hydrocarbon gel	PEG ointment	Hydrophilic ointment
0.5	3.26 ± 0.24	2.45 ± 0.17	1.25 ± 0.33	1.77 ± 0.24	1.50 ± 0.41
1	8.05 ± 0.57	2.98 ± 0.17	2.00 ± 0.50	3.97 ± 0.48	3.12 ± 0.65
2	24.24 ± 2.26	4.16 ± 0.33	5.66 ± 0.41	11.71 ± 1.36	8.20 ± 0.65
3	37.53 ± 1.98	6.11 ± 0.33	9.63 ± 0.65	17.69 ± 1.98	14.34 ± 0.69
4	50.63 ± 2.26	8.11 ± 0.57	14.16 ± 4.10	26.79 ± 0.85	19.21 ± 0.45
5	61.46 ± 2.83	9.63 ± 0.65	20.27 ± 3.54	33.14 ± 1.29	24.36 ± 0.65
24	74.02 ± 1.84	10.43 ± 0.48	77.25 ± 3.68	55.35 ± 7.36	70.64 ± 3.96

Each value represents the mean ± S.E. (n = 3).

Vaseline, being an anhydrous, lipophilic base showed a very slow in vitro release of the drug and consequently low in vitro permeation. A great effort has been devoted to improve the permeation of aspirin from this base and also to increase its stability. Some stabilizing agents such as almond oil, liquid paraffin and propylene glycol were considered for this purpose. Vaseline-liquid paraffin (7:3) base affords a marked enhancement of permeation of aspirin compared to that from Vaseline base

( $p < 0.001$ ); however, increasing the amount of incorporated liquid paraffin to 40% did not enhance permeation, but conversely decreased it **Table 2**. These results correlate with the in vitro release studies. Liquid paraffin did not only stabilize aspirin but also dissolved it; therefore, it has an enhancing effect on absorption of aspirin. Also, propylene glycol is a co solvent which not only solubilizes aspirin, but also can alter the skin structure, thereby modifying the percutaneous absorption.

**Table No. 2: Effect of propylene glycol, almond oil and liquid paraffin on permeation of aspirin from vaseline base**

Time (h)	Cumulative aspirin permeated (%) from				
	Vaseline	Vaseline-PG (7:3)	Vaseline-almond oil (7:3)	Vaseline-liquid paraffin (7:3)	Vaseline-liquid paraffin (6:4)
0.5	2.45 ± 0.17	1.87 ± 0.28	0.96 ± 0.14	1.71 ± 0.14	0.29 ± 0.85
1	2.98 ± 0.17	3.69 ± 0.71	1.17 ± 0.24	2.40 ± 0.57	0.48 ± 0.07
2	5.16 ± 0.33	4.63 ± 0.68	1.73 ± 0.24	2.90 ± 0.42	0.61 ± 0.14
3	6.11 ± 0.33	5.95 ± 0.14	2.11 ± 0.42	3.20 ± 0.24	1.12 ± 0.14
4	7.11 ± 0.57	6.48 ± 0.42	2.61 ± 0.65	4.40 ± 0.24	1.52 ± 0.28
5	9.63 ± 0.65	7.52 ± 0.24	3.01 ± 0.50	5.57 ± 0.71	1.55 ± 0.42
24	11.43 ± 0.48	16.64 ± 0.24	11.04 ± 0.85	27.35 ± 1.70	11.64 ± 0.42

Each value represents the mean ± S.E. (n = 3).

##### Effect of penetration enhancers:

Since transdermal delivery offers the greatest facility for controlled release of drugs, overcoming the roadblock of low skin permeability will be the crucial advance that lets transdermal delivery realize its great promise. The use of penetration enhancers offers a cheap, simple and convenient method of improving transdermal bioavailability. Several chemical penetration enhancers belonging to different groups were monitored aiming to enhance the

permeation of aspirin from hydrocarbon gel base which is an anhydrous base assuring stability of this unstable drug.

##### Effect of fatty acids and esters:

The use of 10% oleic acid as penetration enhancer showed no enhancing effect ( $p > 0.05$ ) in **Table 3**. Incorporation of 5% methyl myristate showed a decrease in permeation of the drug.

**Table No. 3: Effect of penetration enhancers on the permeation of aspirin from hydrocarbon gel base**

Time (h)	Cumulative aspirin permeated (%) from							
	Hydrocarbon gel	Hydrocarbon gel + 10% oleic acid	Hydrocarbon gel + 5% methyl myristate	Hydrocarbon gel + 40% PG	Hydrocarbon gel + 40% PG + 10% alcohol	Hydrocarbon gel + 5% limonene	Hydrocarbon gel + 10% DMSO	Hydrocarbon gel + 20% urea
0.5	2.2 ± 0.41	1.6 ± 0.24	0.5 ± 0.17	1.8 ± 0.16	2.1 ± 0.4	2.2 ± 0.48	2.6 ± 0.65	0.8 ± 0.17
1	3.0 ± 0.33	2.3 ± 0.65	0.9 ± 0.33	2.1 ± 0.44	2.9 ± 0.41	4.1 ± 0.33	4.7 ± 0.74	1.1 ± 0.24
2	5.6 ± 3.96	5.7 ± 0.57	2.8 ± 0.50	9.9 ± 1.09	22.3 ± 2.2	7.6 ± 0.33	8.2 ± 0.57	2.6 ± 0.33
3	9.6 ± 0.65	8.0 ± 0.17	6.5 ± 0.65	21.2 ± 1.6	39.3 ± 2.3	12.6 ± 0.7	11.0 ± 2.0	12.9 ± 0.3
4	14.1 ± 2.0	11.3 ± 0.8	13.3 ± 0.3	26.9 ± 2.2	45.6 ± 4.5	18.8 ± 1.0	13.9 ± 0.5	22.2 ± 0.6
5	20.7 ± 0.5	15.0 ± 0.5	18.3 ± 2.7	35.3 ± 2.8	62.6 ± 3.4	27.3 ± 1.8	16.0 ± 0.4	29.5 ± 1.7
24	76.5 ± 4.0	78.7 ± 4.3	70.3 ± 1.6	79.5 ± 4.4	82.0 ± 2.3	66.8 ± 0.8	30.0 ± 1.5	82.5 ± 2.8

Each value represents the mean ± S.E. (n = 3).

##### Effect of glycols and alcohols:

The effect of propylene glycol on the permeation of aspirin from hydrocarbon gel base was investigated in **Table 3**. The

data revealed that incorporation of 40% PG led to a slight increase in permeation. This may be due to the role of PG as a cosolvent

which not only solubilizes aspirin but also can alter the skin structure, thereby modifying the percutaneous absorption.

The use of propylene glycol in combination with a potential penetration enhancer may offer synergistic enhancement. One possible explanation is the facilitated incorporation of the enhancer into the stratum corneum lipid alkyl domain by the interaction of PG at the polar head group region. A combination of 40% PG and 10% ethyl alcohol afforded an increase in permeation of aspirin from hydrocarbon gel base **Table 3**. Ethanol can exert its permeation enhancing activity through various mechanisms. As a solvent, it can increase the solubility of the drug in the vehicle. Further, permeation of ethanol into the stratum corneum can improve drug partitioning into the membrane. Additionally, it is also feasible that the rapid permeation of ethanol, or evaporative loss of this volatile solvent from the donor phase modifies the thermodynamic activity of the drug within the formulation. A further potential mechanism of action arising as a consequence of rapid ethanol permeation across the skin has been reported; solvent 'drag' may carry permeant into the tissue as ethanol traverses. In addition, ethanol as a volatile solvent may extract some of the lipid fraction within the stratum corneum and improve drug flux through the skin. PG permeates well through stratum corneum and its mechanisms of action are probably similar to those suggested for ethanol. On the other hand, a combination of the two vehicles, PG and alcohol, would also inhibit *in vitro* deacetylation.

#### Effect of Terpenes:

Incorporation of 5% limonene as a penetration enhancer in hydrocarbon gel base showed no enhancing effect **Table 3**.

#### Effect of Sulphoxides:

Incorporation of 10% DMSO in hydrocarbon gel base decreased the permeation **Table 3**.

#### Effect of urea:

Incorporation of 20% urea led to an enhancement effect on aspirin permeation **Table 3**. The penetration enhancing activity of urea probably results from a combination of increasing stratum corneum water content and through its keratolytic activity.

#### Assessment of the biological performance of aspirin in transdermal delivery system:

In an effort to limit GI toxicity and inhibition of endothelial PGI<sub>2</sub> formation, aspirin has been administered in very low doses. However, serious GI bleeding has been reported at oral doses as low as 30 mg/day, orally administered aspirin requires high frequent dosing because it undergoes extensive presystemic hydrolysis in the gut and liver into salicylic acid which is devoid of antiplatelet activity. Continuous exposure of new platelet to aspirin is necessary to achieve prolonged inhibition of platelet aggregation.

#### Effect of storage:

Aspirin is a highly unstable drug which is rapidly subjected to hydrolysis. To monitor the stability of aspirin formulation in hydrocarbon gel containing 40% PG and 10% alcohol, it was resubjected to biological evaluation, according to dosage regimen E, after storage at 40 ± 2 °C/75 ± 5% RH for 6 months. The percentage inhibition of platelet aggregation was found

to be 33.32, which is more or less similar to that achieved by the same dosage regimen before storage (32.55%), this is complying to the International Conference on Harmonization (ICH) conditions of less than 5% change of potency after storage.

## CONCLUSION

In conclusion, these results demonstrate the feasibility of successfully influencing platelet function by the proposed transdermal formulation containing low dose of aspirin. The dose dependent gastrointestinal side effects of aspirin and the lack of dose-response relationship in the study evaluating the antiplatelet effect of aspirin in transdermal delivery system, support the use of the lowest effective dose together with the least frequency of application to optimize efficacy and minimize toxicity. On the other hand, the proposed transdermal formulation exhibits satisfactory stability indicated by persistent therapeutic efficacy with storage.

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