**Preparation and characterization of poorly soluble drug in different gel bases for transdermal**

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**Abstract**

Aspirin (acetylsalicylic acid) 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. So, the aim of this study was to use three penetration enhancers (oleic acid, propylene glycol and propanol) to improve the transdermal delivery of acetylsalicylic acid. The mixtures were incorporated into two gel bases; Methyl Cellulose (MC) and Carbapol 940. The prepared formulations were tested for drug content, organoleptic characters and in vitro drug release. Drug content data showed good results (85-94%). In vitro release data showed the maximum drug release was from carbopol 940 using propylene glycol as penetration enhancer (88%) after 3h. Release kinetics of prepared formulations revealed that all formulations follow diffusion model except C5 which exhibited zero order kinetic.

**Introduction**

Atherosclerotic vascular disease may manifest as coronary heart disease (e.g. angina pectoris, myocardial infarction, sudden death), cerebro-vascular disease (e.g. stroke and transient ischaemic attack) or peripheral vascular disease (e.g. claudication and critical limb ischaemia). Atherosclerosis is a progressive inflammatory disorder of the arterial wall that is characterized by focal lipid-rich deposits of atheroma that remain clinically silent until they become large enough to impair arterial perfusion or until ulceration or disruption of the lesion results in thrombotic occlusion or embolisation of the affected vessel. The possibility that anti-inflammatory compounds might be effective in the prevention of cardiovascular disorders, including myocardial infarction, stroke and thrombosis was anticipated when aspirin was found to reduce platelet aggregation induced by several physiological stimuli [1]. The efficacy of oral aspirin treatment in the secondary prevention of cardio and cerebro vascular disease has been established [2, 3]. The blood-thinning properties of aspirin are based on its inhibition of prostaglandin synthesis in the blood platelets. Platelet aggregation plays a crucial role in thrombosis, hence usefulness of aspirin as anti-aggregating agent [4]. The most frequently reported side effects of aspirin, when administered orally, are abdominal discomfort along with other gastrointestinal effects. This has limited its widespread clinical use for the prevention of cardiovascular events [5]. Thus, the use of low dose aspirin daily, which is virtually devoid of a measurable antiinflammatory effect, has been investigated [6]. Transdermal delivery offers an alternative route for the administration of low-dose aspirin for the treatment of atherosclerotic vascular disease. It will retain the inhibitory effect of aspirin on platelet COX-2 and minimize that on vascular COX-1, thus continuous low-dose aspirin therapy can be used without the reported risks on GI tract [7, 8]. Aspirin is polar at physiological pH and it is rapidly hydrolyzed to salicylic acid in the skin, which is rich in enzymes, like esterases. Hence it is not a good candidate for this form of delivery. However, little aspirin is required per day to suppress platelet COX, particularly when it is delivered continuously. In vitro studies showed that the skin acts as a reservoir for aspirin, with as much as 10% to 15% absorbed over 24 to 48 hours after a single application [9]. A 1993 study showed that aspirin in monohydroxy alcohols applied directly to the skin surface, selectively inhibited the activity of cyclooxygenase in platelets [10]. However, a large dose (750mg) of aspirin was required, which necessitated a large volume applied over a wide area.

Our goal was to design a transdermal formulation for aspirin characterized by high therapeutic efficacy, safety and stability. The main strategy was implemented in incorporation of aspirin into certain bases belonging to different classes of dermatologic semisolid formulations were monitored in order to enhance drug solubility, release and then efficacy,

# Materials and methods

#  Materials

Aspirin, oleic acid, propylene glycol, propanol and Methyl Cellulose powder (MC) were purchased from Sigma Aldrich (Germany); Carbopol 940 was obtained from Goodrich Chemical Company (England).

# Methods

# *Mixing of aspirin with different penetration enhancers*

Aspirin was individually mixed oleic acid, propylene glycol, propanol. for preparation step.

# *Preparation of different bases*

*1) Methylcellulose (MC)*

Methylcellulose is cellulose ether in which methyl groups have been substituted for hydroxyl groups on the 2-glucopyranose residues. High viscosity grades of methylcellulose are used in pharmaceutical gels. The gels are demulcent and have good surfactant properties, which permit easy spreading on body tissues. Therefore, methylcellulose gels are used as dressings for burned tissue because they minimize water loss and are easily removed. The high viscosity grades are used in ophthalmic preparations. A methylcellulose gel was investigated for topical administration of tetracycline HCl.

The weighed amount of gelling agents was sprinkled gently using magnetic stirrer in 100 ml beaker containing boiling distilled water (in case of MC). Stirring was continued until a thin hazy dispersion, without lumps, was formed. Leaving over night in the refrigerator may be necessary for complete gel dispersion [11]. The prepared base was medicated with aspirin at a concentration of 10% .

*2) Carbopol 940*

The weighed amount of carbopol 940 was sprinkled little by little, into the vortex of 100 ml distilled water, placed in beaker and stirred with magnetic stirrer at high speed. Stirring was continued until a thin dispersion, without lumps, was obtained, stirring speed was then reduced, to allow foam to break and to maintain a good liquid turn over while adding the calculated amount of triethanolamine (1.65 parts by volume to 2 parts carbomer) required to form the gel [12]. The prepared base was medicated with aspirin at a concentration of 10%.

***Organoleptic Characters***

The prepared gel bases were tested for their color, odor, texture, phase separation or bleeding as well as the feel upon application (stiffness, grittiness, greasiness) once the preparation is applied on the skin and also after two minutes of application.

***Homogeneity Test***

 A small quantity of each base is pressed between the thumb and index finger and the consistency of the base is noticed (weather homogeneous or not) and if there is any coarse particles appeared or detached on fingers. Also, the homogeneity can be detected when a small quantity of the base is rubbed on the skin of the back of the hand.

***In vitro drug release studies***

The in vitro drug release experiments were performed during 3 h by the dialysis bag diffusion technique. The release profile aspirin from different gel bases formulations were performed. The bag was mounted between the donor and the receptor compartments. The receptor medium consisted of 500 ml of phosphate buffer pH 5.5. The stirring rate and temperature was 100 rpm and37 ◦C respectively. At appropriate intervals, 2ml aliquots of the receptor medium were withdrawn and immediately replaced within equal volume of fresh buffer. The amount of drug released was determined UV spectrophotometrically at 302 nm.

***In vitro drug release kinetics***

The data obtained from the experiments were analyzed by means of personal computer to establish the order of the drug release. The release data were analyzed using the following linear regression equations.

A) Ct = CoKt for zero order kinetics.

B) Log Ct = - Kt/2.303 + log Co for first order kinetics

C) Q = Dt (2A-Cs) 1/2Cs for Higuchi model (Higuchi, 1962).

Where

Q is the amount of drug released per unit area at time t,

D is the drug diffusion coefficient in the matrix,

A is the total amount of drug present in the matrix per unit volume, and Cs is the drug solubility in the matrix. Stating the proper mode of release is based on the correlation (r) for parameters involved, were the highest correlation coefficient represent the actual mode of the release.

# Results and discussion

**Characterization of the Organoleptic Character and Homogeneity Test**

 According to the physical investigation of the tested bases, the organoleptic characters of the studied bases show good texture, homogeneity and ease of spreading (table 1).

**Table (1):-** Result of organoleptic characters investigation and homogeneity test of different gel bases.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Formula | Code | Texture | Homogeneity | Spreading | pH |
|  MC  | Oleic acid | C1 | Good | Good | spread Easily  | 4.21 |
| Propylene glycol | C2 | Good | Good | spread Easily | 5.19 |
| Propanol | C3 | Good | Good | spread Easily  | 5.6 |
|  Cabopol 940 | Oleic acid | C4 | Good | Good | spread Easily | 4.32 |
| Propylene glycol | C5 | Good | Good | spread Easily | 4.35 |
| Propanol | C6 | Good | Good | spread Easily | 4.9 |

**In vitro drug release studies**

From table (2) and figure (1), the aspirin % release from different gels can be arranged in descending order as follows: C5 > C6 > C3 **>** C4**>** C1> C2**.** It is clear that propylene glycol in carbopol 940 exhibits the best release while propylene glycol in MC exhibits the worst release among all investigated formulations.

**Table 2:** In vitro drug release from different gel bases

|  |  |
| --- | --- |
| Time (min) | Release of Aspirin (mg %) |
| C1 | C2 | C3 | C4 | C5 | C6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 29.45 | 25.8 | 39.2 | 33.48 | 32.9 | 35.7 |
| 60 | 37.11 | 34.2 | 48.12 | 41.5 | 44.8 | 47.15 |
| 90 | 45.8 | 41.6 | 55.8 | 49.8 | 56.9 | 58.9 |
| 120 | 53.78 | 51.7 | 67.5 | 57.4 | 65.73 | 67 |
| 150 | 69.4 | 63.6 | 78.6 | 66.5 | 79.15 | 78.45 |
| 180 | 78.62 | 72.5 | 85.4 | 79.46 | 88 | 87.94 |

**Figure (1):** In vitro drug release from different gel bases

**In vitro drug release kinetics**

From the data listed in table (3), it is clear that aspirin behaves in its release from different investigated gel bases as diffusion model except C5 which exhibits zero order release kinetics.

**Table 3:** In vitro drug release kinetics from different gel bases

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Formula | Kinetic order or model | Intercept(a) | Slope(b) | Correlation(r) | Rate Constant (k) | t1/2(min) |
| C1 | ZeroFirst**Diff.** | 12.561.95-2.7 | 0.35-4.9 | 0.990-0.996**0.997** | 0.359-4.88 | 139132104.7 |
| C2 | ZeroFirst**Diff.** | 13.851.96-5.9 | 0.48-6.5 | 0.9988-0.9947**0.9991** | 0.486-6.5 | 102.783.459.3 |
| C3 | ZeroFirst**Diff.** | 11.71.98-12.6 | 0.58-7.8 | 0.979-0.984**0.988** | 0.584-7.9 | 85.566.640.3 |
| C4 | ZeroFirst**Diff.** | 17.51.94-7.2 | 0.56-7.8 | 0.968-0.984**0.989** | 0.56-7.8 | 8864.841 |
| C5 | **Zero**FirstDiff. | 14.691.95-5.5 | 0.492-6.58 | **0.9993**-0.99680.9922 | 0.319-0.076.987 | 51.5-61.485.21 |
| C6 | ZeroFirst**Diff.** | 14.691.95-5.5 | 0.492-6.58 | 0.9213-0.8928**0.9922** | 0.492-0.0086.588 | 101.5-82.157.59 |

**Conclusion**

Aspirin was successfully incorporated in different gel bases and characterized. All investigated formulations had good organoleptic characters. In vitro release profile showed that the aspirin % release from different gels can be arranged in descending order as follows: C5 > C6 > C3 **>** C4**>** C1> C2**.** It is clear that propylene glycol in carbopol 940 exhibits the best release while propylene glycol in MC exhibits the worst release among all investigated formulations. Release kinetics of prepared formulations revealed that all formulations follow diffusion model except C5 which exhibited zero order kinetic.

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