Transdermal patch of acetylsalicylic acid as an alternative dosage form: A review

Hayder F. Alhamdany[1*], Mohanad A. Alfahad[1]

[1] Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq.

Corresponding author: Ph.hayderfouad89@uomosul.edu.iq

ABSTRACT

As a substitute for traditional systemic administration, many topical treatments have lately evolved. Transdermal drug delivery systems (TDDSs) are the most appealing of these methods due to their low rate of failure, simplicity of distribution, superior efficiency and preference amongst users. TDDS has the potential to be useful not just in medicines, but also in the skincare sector, particularly cosmetics. Since this approach means the development of local administration, it can minimize local drug level accumulation and inappropriate drug distribution to regions not primarily tailored by the medication. Aspirin (acetylsalicylic acid) is becoming the preferred choice against which subsequent antiplatelet medicines are measured in terms of lowering the cardiovascular risk while remaining inexpensive. Along with its substantial presystemic metabolism, orally administered acetylsalicylic acid has the potential of gastrointestinal negative impacts albeit at modest dosages and necessitates regular administration. Transdermal administration avoids the gut and would be more practical and healthier for aspirin usage, particularly during repeated doses. The present review highlights general aspects of aspirin primed as a TDDS as an appropriate topical preparation.

Keywords: Aspirin, TDDS, permeation, plasticizers.

تطورت العديد من العلاجات الموضعية مؤخرًا كبديل للإعطاء الدواء للغرض العام. تعد أنظمة توصيل الأدوية عبر الجلد أكثر هذه الطرق جاذبية نظرًا لانخفاض معدل فشلها وبساطة التوزيع وكفاءتها العالية وتفضيلها بين المستخدمين. لدى أنظمة توصيل الأدوية عبر الجلد القدرة على أن تكون مفيدة ليس فقط في الأدوية ، ولكن أيضًا في قطاع العناية بالبشرة ، وخاصة مستحضرات التجميل. نظرًا لأن هذا النوع يعني اعطاء الدواء موضعيا بطريقة متطورة ، فيمكنه تقليل تراكم مستوى الدواء موضعيا والتوزيع غير المناسب للدواء في المناطق التي لا فائدة من التواجد فيها. أصبح الأسبرين (حمض أسيتيل الساليسيليك) هو الخيار المفضل بين الأدوية التي تمنع تجمع الصفيحات الدموية والتي بدورها تقليل مخاطر القلب والأوعية الدموية مع افضلية انخفاض تكلفة الاسبرين. بالإضافة الى تعرض الدواء الى عملية الأيض ما قبل المركزي ، فإن حمض أسيتيل الساليسيليك الذي يتم تناوله عن طريق الفم لديه القدرة على إحداث تأثيرات سلبية على الجهاز الهضمي وإن كان ذلك بجرعات متواضعة وايضا يتطلب تناوله بانتظام. تتجنب أنظمة توصيل الأدوية عبر الجلد القناة الهضمية وتعتبر أفضل عمليا وصحيا لمستخدمي الأسبرين ، خاصة أثناء الجرعات المتكررة. يسلط هذا البحث الضوء على الجوانب العامة للأسبرين معدة على أنها أنظمة توصيل الأدوية عبر الجلد كمستحضر موضعي مناسب.

الكلمات المفتاحية: اسبرين ، أنظمة توصيل الأدوية عبر الجلد ، النفاذية ، المواد التي تزيد الليونة.

INTRODUCTION

Acetyl salicylic acid or Aspirin (Figure 1) was historically used as an antipyretic and painkiller for decades, yet its popularity becomes overwhelmed by recognition of its antiplatelet effect in the 1980s to become one of the top list drugs in the prevention and treatment plan of ischemic heart disease [1]. Aspirin was suggested as a first-line antiplatelet medication in all acute diseases that might result from platelet dependent thrombotic blockade [2,3]. The primary antithrombotic effect of aspirin is achieved by the persistent acetylation of a specific serine amino acid residue, which inhibits Prostaglandin H synthase (cyclo-oxygenase); the enzyme that trigger platelet aggregation [4,5]. Aspirin's health benefits, as well as its hazards, are most likely due to its ability to reduce synthesis of prostaglandins and thromboxane A2 (Figure 2). The inhibition of thromboxane A2 and prostaglandin I2 by aspirin has conflicting effects on hemostasis, for instance, platelet agreeability, adhesiveness, and intravascular clotting [6,7]. Absorption of aspirin given by ordinary oral dosage form occurs in the upper part of the small intestine [8]. Conventional aspirin pills have a bioavailability of 50–75% while enteric-coated tablets and sustained-release microencapsulated formulations have much lower bioavailability [9]. Since aspirin encounters a significant pre-systemic breakdown in the stomach and liver into salicylic acid, which lacks antiplatelet action, oral administration necessitates high and recurrent dosage to accomplish long-term suppression of platelet aggregation [9,10].
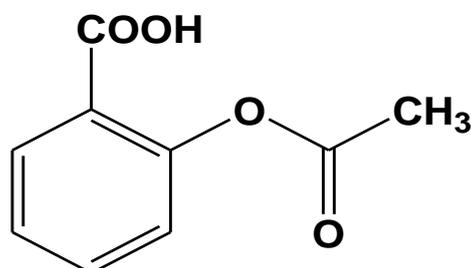

Figure 1: Chemical structure of acetylsalicylic acid (Aspirin)

Aspirin has been used as a platelet aggregation inhibitor in a dose ranging between (75-325 mg) [11,12]. In this low dose of aspirin, it has been suggested to prevent prostacyclin production and decrease gastrointestinal negative consequences. However, oral aspirin still has a potential digestive problems which may be related to aspirin's local irritation due to its acidic nature alongside with systemic inhibition of prostaglandin [13]. Transdermal drug delivery has been considered as a potential systemic delivery approach which can deliver the drug through the skin to the systemic circulation at a predetermined rate over a long period of time. It might be a more practical, gentler, and non-invasive method in particular for long-term use [14]. Transdermal patches of aspirin can avoid gastrointestinal side effect due to the lack of direct contact with

gastrointestinal mucosal membrane and also can avoid its first pass hepatic metabolism [15].

In the present review, we try to spot the light on the transdermal drug delivery system as a potential dosage form to deliver aspirin systemically and compare the current available dosage form of aspirin with TTDS as an alternative delivery system. Also,

we cover brief outline advantages of TDDs, physicochemical properties of aspirin which make aspirin a good candidate to be formulated as a transdermal patch, components and approaches for preparation of aspirin transdermal patches, general clinical considerations in the use of transdermal patches and their limitations.
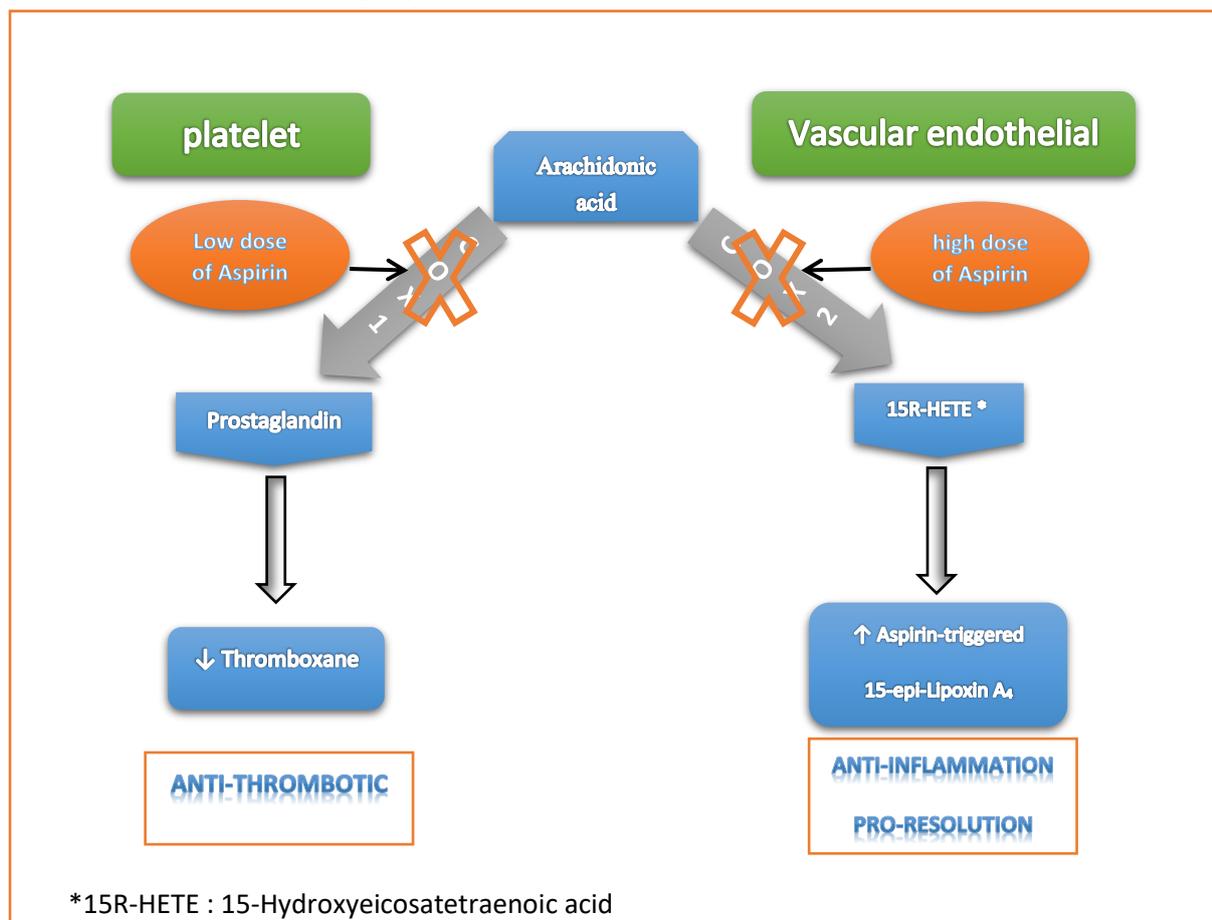

*15R-HETE : 15-Hydroxyeicosatetraenoic acid

Figure 2: Aspirin mechanism of action

Aspirin and skin as a site of administration

The skin has received a lot of interest as a possible approach for delivering systemically active medicines [16]. The potential advantages of transdermal administration are widely recognized. Transdermal therapy methods have been defined as conscious, distinct dosage forms that, when administered to undamaged skin, transport the

drug(s) to the vascular system at a regulated pace through the epidermis[17]. As a result, TDDS are expected to be developed in order to maintain good blood drug levels for curative effectiveness by employing the skin as a drug implant site [18].

Aspirin has been used to treat a variety of conditions such as fever, pain, rheumatic fever, and inflammatory conditions such as rheumatoid arthritis, pericarditis, and

Kawasaki disease. Aspirin in low dose has been considered reasonable one of the most widely used medications worldwide, with an approximate daily consumption for cardiovascular diseases which have been shown to reduce the risk of death from a heart attack or stroke in people who are at high risk or have cardiovascular disease [19,20]. There is some evidence that aspirin can help prevent colorectal cancer, though the mechanisms are unknown [21]. Aspirin blocks the enzyme cyclo-oxygenase (COX) to inhibit the production of prostanoids (prostaglandins and thromboxanes) from arachidonic acid. COX contains two isoenzymes: COX-1, which presents in most organs and generates prostaglandins and thromboxane and contributes to the maintenance of the gastrointestinal mucosal lining, kidney function, and platelet aggregation, and COX-2, which presents in specific regions (cerebral, vasculature, the juxtaglomerular apparatus of the kidney and in the placenta during late gestation, …etc) and which transcription rises during inflammation or fever [22].

Aspirin was selected as a candidate for transdermal drug delivery because it has a low oral bioavailability, a plasma half-life of 15-20 min, a molecular weight of 180.158 g/mole, partition coefficient (log P) 1.19, and an aqueous solubility of 3 mg/ml, i.e. aspirin has some desirable properties to be formulated as a transdermal drug delivery system [17,23].

Components and preparation methods of aspirin transdermal patches:

Generally, transdermal patches are composed of a mixture of seven crux components; namely liner, active ingredient, adhesive material, membrane, backing, permeation enhancer, and matrix filler [14]. Transdermal patch development necessitates the discovery of the appropriate mix of all required components into an efficient drug delivery system. These various methods of incorporating them give rise in various transdermal patch designs. Matrix, reservoir, multilaminate, and drug-in-adhesive are some of the most common designs [17](Figure 3). Each of these components has its rule to provide effective and easy usage properties to the patches. Liner helps to keep the patches safe throughout storing and before usage. The drug solution is available in close touch with the release liner [17]. Adhesive materials are used to glue the patch's elements collectively as well as to stick the patch to the epidermis. The membrane regulates medication delivery from reservoirs and multi-layer patches. Backing safeguards the patches out from elements [18]. Penetration enhancers interact with stratum corneum components to increase epidermal permeability, allowing for higher therapeutic levels of the drug. Finally, matrix filler will help to add mass to the matrix and, in some cases, acts as a matrix stiffener [23].
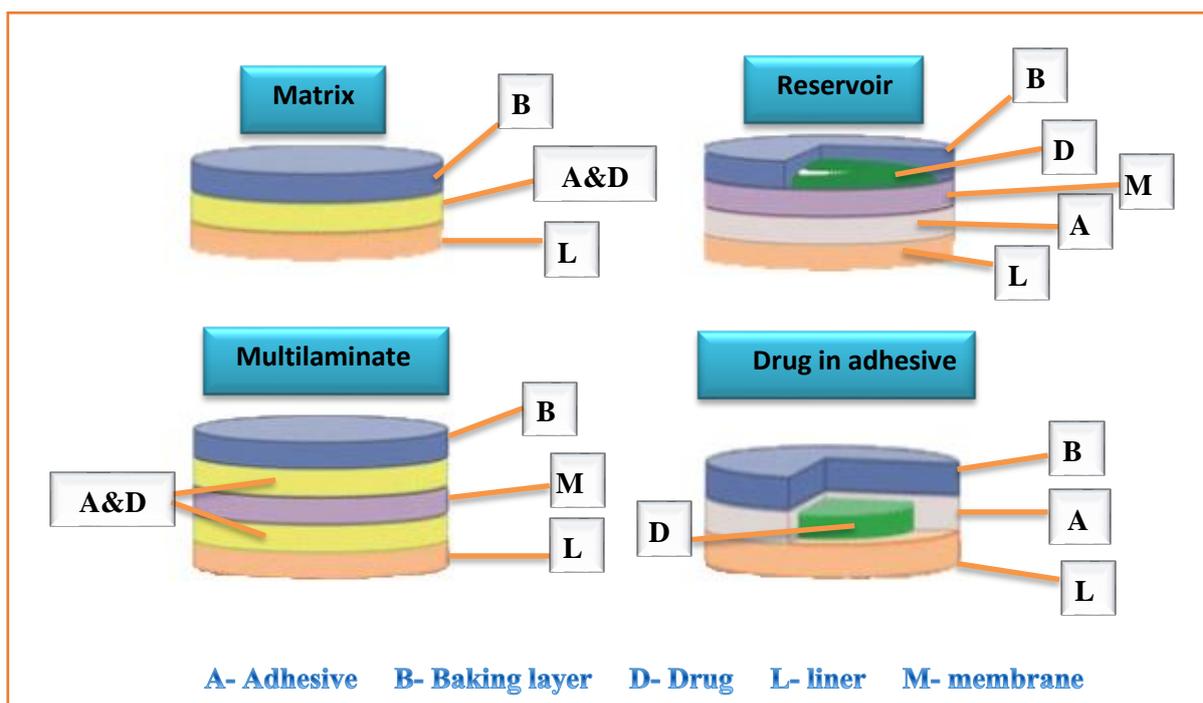
Figure 3: The four main types of transdermal patch with components

Various research studies [24–28] of aspirin transdermal patches were conducted using different types of polymers, plasticizers, and permeation enhancers to solve the issues associated with TDDS.

Ammar *et al*. (2006) used different commercially available products for preparation of easily released and highly permeable aspirin patches. For instance, different release promoter bases were tested including carboxymethyl cellulose gel base; vaseline base; vaseline–propylene glycol base; vaseline–almond oil base; vaseline–liquid paraffin base; vaseline–liquid paraffin base; hydrocarbon gel base; polyethylene glycol ointment base and hydrophilic ointment base. This study has also tested different penetration enhancers to characterize the best one for the final preparation. These included fatty acids and esters, glycols and alcohols, terpenes, sulphoxides, urea, and

cyclodextrins. The study showed that the suggested transdermal formulation containing a low dose of aspirin has the potential to successfully influence platelet function. The dose-dependent digestive adverse effects of aspirin, as well as the absence of a dose–response relationship in this study assessing aspirin's antiplatelet effect in a transdermal delivery system, have encouraged the use of the lowest appropriate dose with the minimum frequency of usage to maximize efficacy and reduce toxicity. The proposed transdermal formulation, on the other hand, has illustrated satisfactory stability as evidenced by sustained therapeutic efficacy with storage [24].

On the other hand, Areeg A. Shamsher *et al* (2010) prepared transdermal patches of aspirin using a mixture of Eudragit RL: Eudragit RS (5:1) and polyvinyl acetate polymers by solvent casting method. In this

work, organic solvent ethanol: acetone (3:2) with diethyl phthalate was included as a plasticizer. Turpentine oil and lemon oil showed a significantly higher flux of ASA due to their penetration enhancer effect. In term of appearance, this study illustrated that the eudragit transdermal patch that has been created was crinkle-free, homogeneous, flexible, and clear with good skin attachment property. The formulated aspirin films have excellent stability when it comes to adjusting blood coagulation variables including (bleeding time, prothrombin time and activated partial prothrombin time) [25].

Banerjee *et al* (2012) prepared transdermal patches of acetylsalicylic acid by solvent casting method using Hydroxy Propyl Methyl Cellulose (HPMC) as a polymer and Carboxy Methyl Cellulose as a copolymer and glycerin as a plasticizer to ascertain the diffusion and permeation of aspirin and to correlate the drug delivery through skin. The authors concluded that the formulated aspirin films as an antiplatelet agent have good bioavailability with few side effects, especially when used for a long period of time [26].

Similarly, the solvent casting method was used by Voycheva *et al* (2016) to create matrix systems. The authors prepared a transdermal patch of aspirin by using eudragit E100 as a polymer with different weak organic acids as a crosslinking and plasticizers to investigate their effects on the release of aspirin from the prepared matrix. The study suggested that systems organized with water as the dissolution medium, malic acid as a bonding agent, and polyethylene glycol 400 as a plasticizer have significantly prolonged release [27].

Finally, Jirapornchai Suksaeree *et al* (2021) tried to prepare a matrix transdermal patch containing ionic liquid lidocaine/aspirin by using pectin and eudragit NE 30D as polymers, and glycerin as a plasticizer. According to the results of *in vitro* release profile and characterization studies of formulated films which conducted by texture analysis, diferential scanning calorimetry, thermogravimetric analysis and X-ray difraction, the authors concluded that Solvent-cast polymeric films made of two polymers, pectin and eudragit NE 30D, are appropriate for transdermal patches containing ionic liquid lidocaine/aspirin [28].

Physicochemical properties of aspirin enable incorporation to a transdermal patch

At physiological pH, aspirin is polar. Although the skin contains an abundant amount of enzymes like esterase that catalyze the hydrolysis of compounds containing ester bonds like aspirin [29], it is considered a good route of administration because a small quantity of the drug is required per day to inhibit platelet COX-2, particularly when given consistently with advantage to ensure minimal effect on vascular COX-1, and it can be used without gastrointestinal side effects [25,27].

According to *in vitro* experiments (Areeg A. Shamsher *et al* 2009 and Bronaugh RL *et al* 1990), the skin can act as a reservoir for aspirin, with up to 10% - 15% absorbed within 24 to 48 hours of a single application [25,30]. Therefore, a large dose of aspirin (like 750 mg) was needed, which necitsted the use of a large volume applied over a large area of the epidermis. Another study (Brendan McADAM *et al* 1995) found that aspirin in a transdermal patch (surface area of 50 cm^2) at a lower dose (84 mg and 120 mg) with or without 12% limonene as a penetration enhancer significantly

inhibited platelet cyclooxygenase-2 [31]. Another aspirin property is that it is rapidly hydrolyzed in aqueous conditions to acetic acid and salicylic acid [32]. Deacetylation can be prevented by including aspirin in propylene glycol and alcohol like vehicle [27]. Furthermore, few experiments have been made in the development of stable aspirin analogues (prodrugs) like esters and anhydrides with the hope that such compounds could well effectively penetrate the epidermis and generate ASA subcutaneously. The hydrolysis of these prodrugs within the skin was predicted to release the more polar ASA. Aspirin anhydride has been found to yield a considerable quantity of ASA with a lower hydrolysis rate over a six-hour period [33,34].

Limitations of aspirin transdermal patches

The major disadvantages include skin irritation due to aspirin hydrolysis to salicylic acid and acetic acid which are skin irritant components. Such irritation is accompanied by skin bleaching and decreased skin melanin at the application site, resulting in a white spotty appearance of the skin. The skin irritation promotes systemic absorption due to barrier rupture. Skin

photosensitization and localized erythema increased following topical application at the site of administration. Tolerance might develop following repeated administration, hence the site of administration need to be intermittently changed accordingly [35].

CONCLUSION

One of the major advantages of transdermal aspirin patches is that it offers a great chance for systemic effective concentration for the treatment of atherosclerotic vascular disease which provides an alternative route of administration, this is beside alleviating GIT upset through bypassing it. Aspirin transdermal patches will keep suppressive activities on platelet COX-2 whereas reducing its inhibitory action on vascular COX-1, allowing for long-term use of low-dose aspirin therapy without unwanted adverse effects. The TDDS provides the skin, and thereby systemic circulation, with the highest aspirin concentration compared to other topical applications. TDDS are quickly and easily described in emergency cases due to their physical presence and recognizing markers (specially for unconscious patients). These benefits promote the development of aspirin in the form of a transdermal patch.

REFERENCES

1. Collaboration AT. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Bmj. 2002;324(7329):71–86.

2. Schrör K. Antiplatelet drugs. Drugs. 1995;50(1):7–28.

3. Alhamdany H, Alfahad M. Stability evaluation of Acetylsalicylic acid in commercial Aspirin tablets available in the Iraqi market. J Adv Pharm Educ Res Jul-Sep. 2021;11(3):21.

4. Loll PJ, Picot D, Garavito RM. The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H 2 synthase. Nat Struct Biol. 1995;2(8):637–43.

5. Vane JR, Botting RM. The mechanism of action of aspirin.

Thromb Res. 2003;110(5–6):255–8.

6. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2018;46(D1):D1074–82.

7. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3):234S-264S.

8. Hobl E, Schmid RW, Stimpfl T, Ebner J, Jilma B. Absorption kinetics of low-dose chewable aspirin–implications for acute coronary syndromes. Eur J Clin Invest. 2015;45(1):13–7.

9. Bhatt DL, Grosser T, Dong J, Logan D, Jeske W, Angiolillo DJ, et al. Enteric coating and aspirin nonresponsiveness in patients with type 2 diabetes mellitus. J Am Coll Cardiol. 2017;69(6):603–12.

10. Nagelschmitz J, Blunck M, Kraetzschmar J, Ludwig M, Wensing G, Hohlfeld T. Pharmacokinetics and pharmacodynamics of acetylsalicylic acid after intravenous and oral administration to healthy volunteers. Clin Pharmacol Adv Appl. 2014;6:51.

11. Roe M. Aspirin dosing: a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE). Patient-Centered Outcomes Research Institute Washington (DC); 2015.

12. Johnston A, Jones WS, Hernandez AF. The ADAPTABLE trial and aspirin dosing in secondary prevention for patients with coronary artery disease. Curr Cardiol Rep. 2016;18(8):1–9.

13. Nimnim AT. Effects of Non-Steroid Anti-Inflammatory Drugs on the Lower Gastrointestinal Tract. Al-Qadisiyah Med J. 2018;14(26):60–70.

14. Fathima SA, Begum S, Fatima SS. Transdermal drug delivery system. Int J Pharm Clin Res. 2017;9(01):35–43.

15. Rai AK, Prajapati SK. Development and evaluation of matrix type transdermal patches of aspirin. Orient J Chem. 2008;24(2):485.

16. Jamak VG, Ghosh B, Desai BG, Khanam J. Recent trends in transdermal cardiovascular therapy. Indian J Pharm Sci. 2006;68(5).

17. Kakkar S, Singh R. A review on transdermal drug delivery system. Innoriginal Int J Sci. 2016;1–5.

18. Mishra B, Bonde GV. Transdermal drug delivery. In: Controlled Drug Delivery Systems. CRC Press; 2020. p. 239–75.

19. Rafalsky V V, Krikova A V, Baglikov AN. Clinical pharmacology of acetylsalicylic acid as an anti-thrombotic agent. Cardiovasc Ther Prev. 2020;8(7):102–7.

20. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509–18.

21. Bibbins-Domingo K. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164(12):836–45.

22. Rane MA, Foster JG, Wood SK, Hebert PR, Hennekens CH. Benefits and risks of nonsteroidal anti-inflammatory drugs: methodologic limitations lead to clinical uncertainties. Ther Innov Regul Sci.

2019;53(4):502–5.

23. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal drug delivery system-design and evaluation. Int J Adv Pharm Sci. 2010;1(3).

24. Ammar HO, Ghorab M, El-Nahhas SA, Kamel R. Design of a transdermal delivery system for aspirin as an antithrombotic drug. Int J Pharm. 2006;327(1–2):81–8.

25. Shamsher AA, Charoo NA, Kohli K, Pillai K, Rahman Z. Effect of transdermally delivered aspirin on blood coagulation parameters. Am J Biomed Sci. 2010;2:129–41.

26. Banerjee A, Chakraverty MH al RR, Dey S, Basak D, Biswas C. Preparation and evaluation of aspirin transdermal patch using HPMC. Int J Pharma Sci Rev Res. 2012;15(1):45–6.

27. Voycheva C and Tsonou MM. Transdermal Delivery Offer for Low-Dose Acetylsalicylic Acid. J Pharm Res. 2016;1(1).

28. Suksaeree J, Maneewattanapinyo P, Panrat K, Pichayakorn W, Monton C. Solvent-Cast Polymeric Films from Pectin and Eudragit® NE 30D for Transdermal Drug Delivery Systems. J Polym Environ. 2021;1–11.

29. Lau WM, Ng KW, Sakenyte K, Heard CM. Distribution of esterase activity in porcine ear skin, and the effects of freezing and heat separation. Int J Pharm. 2012;433(1–2):10–5.

30. Bronaugh RL, Collier SW. In vitro methods for measuring skin permeation. Cosmet Toilet. 1990;105(11):86–93.

31. McADAM B, Keimowitz RM, Maher M, Fitzgerald DJ. Transdermal modification of platelet function: an aspirin patch system results in marked suppression of platelet cyclooxygenase. J Pharmacol Exp Ther. 1996;277(2):559–64.

32. Pedersen AK, FitzGerald GA. Dose-related kinetics of aspirin: presystemic acetylation of platelet cyclooxygenase. N Engl J Med. 1984;311(19):1206–11.

33. McMahon GP, O'Connor SJ, Fitzgerald DJ, le Roy S, Kelly MT. Determination of aspirin and salicylic acid in transdermal perfusates. J Chromatogr B Biomed Sci Appl. 1998;707(1–2):322–7.

34. Gerber M. Synthesis and transdermal properties of acetylsalicylic acid derivates. North-West University; 2003.

35. Paolo R, Caterina F, Gianfranco C, Stefania C, Andrea B, Gianna D, et al. Contact dermatitis due to transdermal therapeutic systems: a clinical update. Acta Bio Medica Atenei Parm. 2019;90(1):5.