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A Comprehensive Review Of Methods For Measuring The Bioadhesivity Of Bioadhesives In Transdermal Products.

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Abstract: Transdermal drug delivery systems have gained significant attention due to their potential for controlled and sustained drug release. The bioadhesivity of transdermal patches, largely determined by the properties of bioadhesives, plays a crucial role in ensuring efficient drug delivery and patient comfort. This review provides a detailed examination of methods for measuring bioadhesivity in transdermal products. Ex vivo and in vitro techniques are discussed, including their principles, advantages, limitations, and applications. Additionally, standardization and validation of measurement protocols are addressed to ensure accurate and reliable assessment of bioadhesive performance. By synthesizing existing literature, this review aims to enhance our understanding of bioadhesivity measurement and facilitate the development of innovative transdermal drug delivery systems.

Keywords: transdermal drug delivery, bioadhesivity, bioadhesives, measurement techniques, ex vivo methods, in vitro methods, standardization, validation

Introduction:

Oral administration has emerged as the primary and favoured method for delivering therapeutic agents . This preference can be attributed to various factors, including the willingness of patients to accept this route, the simplicity of administration, the ability to ensure precise dosing, the cost-effectiveness of manufacturing, minimal sterility requirements, the adaptability of dosage forms, and the typically extended shelf-life of products.

Bioadhesion refers to the attachment of a natural or synthetic polymer to biological surfaces like mucus membranes or cell layers. When it binds to mucus, it's called mucoadhesion; when it binds to cells, it's cytoadhesion. Mucoadhesion occurs through mechanical and chemical bonds between the polymer and mucin, while cytoadhesion happens via specific interactions with cell receptors. An example of cytoadhesion is lectin binding to carbohydrate residues on epithelial cells, promoting mucoadhesion.

In terms of drug delivery systems, bioadhesive systems aim to prolong the presence of a drug at the absorption or action site. They potentially improve drug bioavailability compared to conventional forms, offer controlled drug release, reduce administration frequency, and enhance patient compliance. Various bioadhesive or mucoadhesive drug delivery systems like tablets, films, hydrogels, and suppositories have been developed for trans-mucosal routes.

Bioadhesive materials also find use in therapeutic applications like tissue engineering, wound care, and surgical glue formulation. In drug delivery systems, bioadhesion mainly refers to the adhesion between

formulation components and biological tissue surfaces. Polymers of natural or synthetic origin, with various charges and solubility properties, are used for their adhesive characteristics. Natural polymers such as chitosan, sodium alginate, and gelatin are preferred for being biodegradable, biocompatible, and environmentally friendly, although they have limitations like batch variations and microbial contamination risks.

1.1 OVERVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM

A transdermal drug delivery system is a way to apply patches to the skin to distribute medication. The medicine is released into the bloodstream by these patches at a regulated and planned rate. This controlled release aims to enhance the effectiveness of the drug while minimizing potential side effects. As transdermal drug delivery systems transfer the medication through the skin to the systemic circulation over an extended period of time, achieving regulated drug release is a crucial component of these systems.
A subset of transdermal drug administration known as transdermal therapeutic systems consists of self-contained dosage forms that are administered to undamaged skin. They introduce medications into the systemic circulation at a regulated pace. Transdermal drug delivery is appealing because it can prevent gastrointestinal problems, circumvent hepatic first-pass metabolism, increase patient compliance, and give stable plasma profiles over an extended period of time. Drugs with short half-lives benefit greatly from this strategy since it lessens systemic side effects and improves therapeutic efficacy.

Pressure-sensitive adhesive (PSA), backing laminates, release liner, polymer matrix or drug reservoir, drug penetration enhancers, and other excipients including plasticizers and solvents are the essential parts of a transdermal device. These components work together to ensure optimal drug delivery through the skin.[1]

Transdermal drug delivery devices, also referred to as "patches," are designed to distribute a dose of medication through a patient's skin at a controlled rate and for a predetermined amount of time. This ensures that the drug remains consistently concentrated in the bloodstream for a prolonged amount of time. Because the formulation may be quickly removed, these patches have benefits such improving patient adherence and offering flexibility in dosage modifications.

Approved transdermal drug delivery systems cover a range of medications, including scopolamine, nitroglycerin, clonidine, estradiol, fentanyl, nicotine, testosterone, oxybutynin, methylphenidate, buprenorphine, rivastigmine, rotigotine, and granisetron.

When creating a transdermal formulation, several important technical factors must be taken into account:

• Measuring the drug's molecular weight and figuring out the necessary daily dosage.

• Verifying that the medication is compatible with plasticizers, polymers, adhesives, and other additives utilized in the formulation.

Determining the appropriate size of the patch to optimize drug delivery and patient comfort.

• Assessing the finished product's chemical and physical stability.

• Aiming for a balance that, depending on how long the patch is applied for, will allow for both strong adherence and simple removal.

1.2.1 TABLE: DRUG PRODUCTS AND CLINICAL USE OF TRANSDERMAL PATCHES IN THE CURRENT MARKET:

DRUG	PRODUCT NAME	CLINICAL USE
Lidocaine	Lidoderm	Pain relief
Nicotine	Nicoderm	Smoking cessation
Testosterone	Testoderm	Testosterone low level
Fentanyl	Duragesic	Chronic pain
Scopolamine	Transderm-scop	Motion sickness
Nitroglycerin	Transderm-Nitro	Angina pectoris
Oxybutynin	Oxytrol	Overactive bladder
Rotigotine	Neupro	Parkinson's disease
Selegiline	Emsam	Depression
Estradiol	Climara Pro	Menopause

[2]

1.2 TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM:

Depending on how the medication is absorbed into the body, transdermal patches are often divided into three groups:

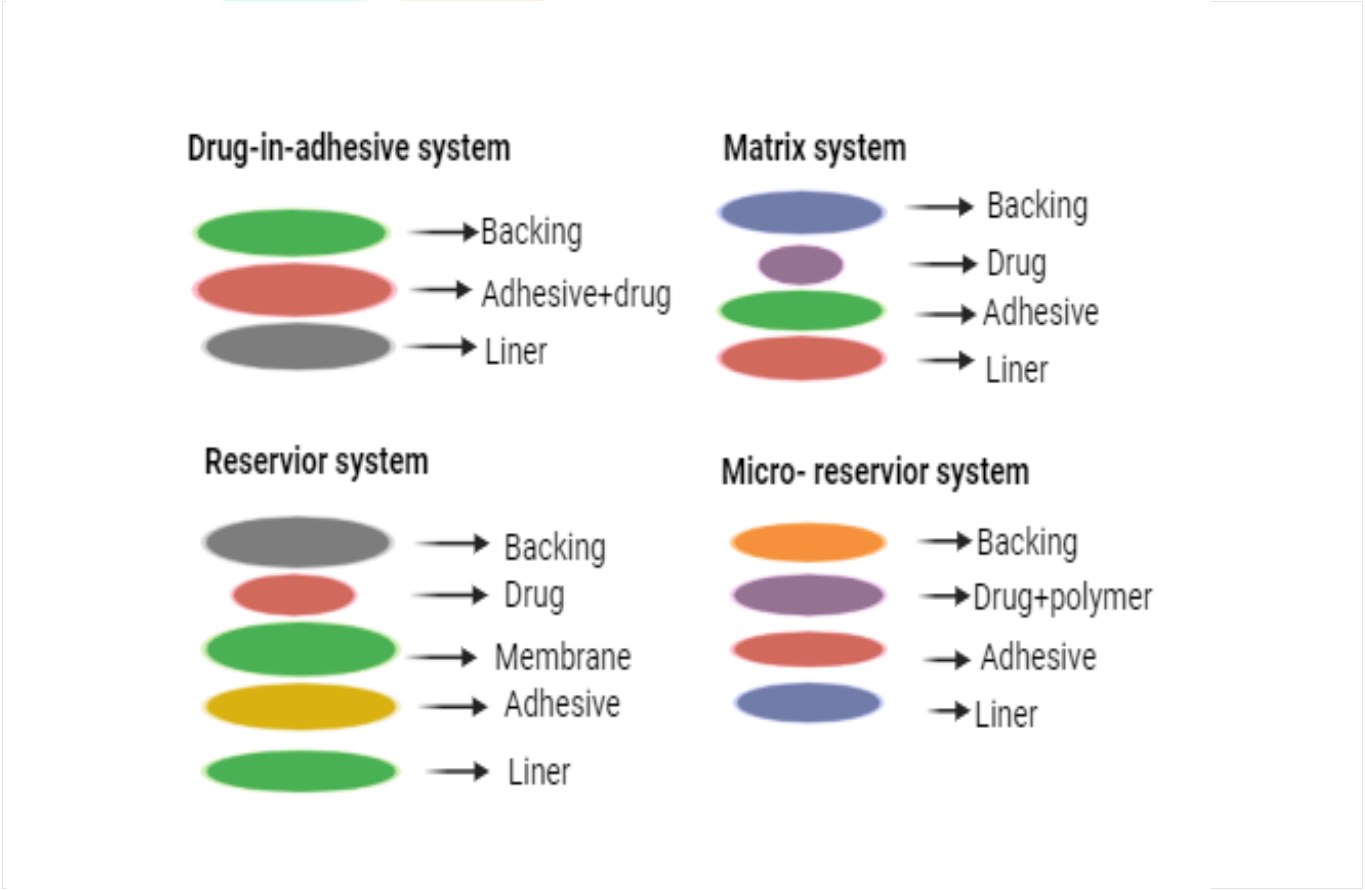


Figure 1 Types of transdermal patches

1.2.1Reservoir Systems-

The medication is kept contained in a liquid reservoir in reservoir systems. Drug molecules may be dissolved in a solvent or suspended in a viscous liquid in this reservoir. A polymer membrane that divides the reservoir from the adhesive layer controls the drug's release rate in these systems. This membrane controls the drug's diffusion and can be either porous or nonporous. The sticky layer on the membrane's outer surface ensures adhesion to the skin. Commercially available membrane diffusion-controlled systems include Estraderm (estradiol), Catapress-TTS (clonidine), Transderm-Nitro (nitroglycerin), and Transderm-Scop (scopolinamine).

1.2.2. Matrix Systems:

In matrix systems, the medicine is distributed uniformly in a polymer matrix that is either lipophilic or hydrophilic. An adhesive polymer strip is used to secure the patch to the skin after it has been covered with a backing layer. Another option is to spread the medication using an adhesive polymer that is pressure-sensitive, and then cover the entire system with an impermeable backing layer. The surface area to which the patch is applied controls release from matrix-type formulations rather than a membrane. Matrix diffusion-controlled systems with commercial availability include Minitran (Nitroglycerin), Emsam (Selegeline), Exelon (Rivastigmine), Sancuso (Granisetron), and Oxytrol (Oxybutynin).

1.2.3. Adhesive Systems:

The drug reservoir in adhesive systems is made up of the drug dispersed within the sticky polymer. The outermost layer is positioned behind an impervious backing layer. The drug release rate is controlled by an adhesive membrane located beneath the drug reservoir layer. Both the membrane and the matrix in which the drug is distributed regulate the rate of drug release in these systems. These systems can be created as multilayered systems or with just one medication layer. Examples of commercially available adhesive systems include Nitrodur (Nitroglycerin), Daytrana (Methylphenidate), and Duragesic (Fentanyl).

[3]

1.3. ROLE OF BIOADHESIVITY IN TRNASDERMAL PRODUCTS

Transdermal medication delivery methods are becoming more advanced and effective, and bioadhesivity is essential to this progress. This method involves administering therapeutic agents through the skin to be absorbed systemically into the bloodstream, bypassing initial metabolism in the liver.

Bioadhesivity's significance in transdermal products can be outlined as follows:

1.Enhanced contact and duration: Bioadhesive components in transdermal formulations facilitate sustained contact between the drug delivery system and the skin. This prolonged contact period enhances drug penetration and absorption through the skin, leading to improved bioavailability and therapeutic effectiveness.

2. Controlled drug release: Bioadhesive polymers are utilized in formulating matrix-type patches or reservoir systems for transdermal delivery. These polymers' bioadhesive properties aid in regulating the drug release rate from the delivery system, enabling sustained and controlled delivery over an extended period.

3. Protection against displacement: Transdermal patches or films may face shear forces or physical stress during daily activities, which can result in dislodgment. Bioadhesive materials help ensure the firm adherence of the transdermal system to the skin, preventing premature detachment and maintaining the desired drug delivery profile.

4. Enhanced patient compliance: Bioadhesive transdermal systems offer greater convenience and user-friendliness compared to other dosage forms. Their ability to adhere to the skin for an extended period without requiring frequent reapplication can enhance patient compliance and adherence to the prescribed therapeutic regimen.

Commonly used bioadhesive polymers in transdermal drug delivery systems include hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), sodium carboxymethyl cellulose (NaCMC), and various acrylate-based polymers. These polymers exhibit mucoadhesive properties and can interact with the skin surface through mechanisms such as hydrogen bonding, electrostatic interactions, and physical entanglements.

1.4. Scope and Objectives of the Review:

This comprehensive review aims to meticulously explore the methodologies utilized for assessing the bioadhesivity of bioadhesives in transdermal products. Through an exhaustive examination of both ex vivo and in vitro techniques, the review seeks to elucidate the underlying principles, advantages, limitations, and applications of each method. Furthermore, it aims to address the critical aspects of standardization and validation protocols to ensure the precision and reliability of bioadhesive performance evaluation.

In order to optimize drug release kinetics and improve patient comfort, bioadhesivity plays a critical role in the review's first section, which provides an overview of transdermal drug delivery systems. It then delves into the definition, characteristics, and significance of bioadhesives in transdermal formulations, along with an exploration of the factors influencing their adhesive properties.

Ex vivo methods, including but not limited to tensile strength tests, peel tests, and texture analysis, will be thoroughly discussed to provide insights into their methodologies, applications, and relevance in transdermal product development. Additionally, various microscopic techniques and biological assays will be examined as alternative ex vivo approaches.

Subsequently, the review will shift focus to in vitro methods such as lap-shear tests, rheological analysis, and atomic force microscopy, offering detailed examinations of their principles, utility, and applicability in transdermal product evaluation. Other emerging in vitro techniques like surface plasmon resonance and tensiometry will also be explored.

Ex vivo and in vitro procedures will be compared in order to identify their advantages and disadvantages as well as factors to be taken into account when choosing a method. Moreover, the review will address the importance of standardizing bioadhesivity measurement protocols, tackling challenges in protocol development and offering validation strategies and best practices.

In the final sections, current applications of bioadhesivity measurement techniques will be outlined, accompanied by insights into emerging trends and innovations in transdermal drug delivery. Future research directions will be proposed, and the review will conclude with a summary of key findings, implications for transdermal product development, and recommendations for future research endeavors.

TESTING OF BIOADHESIVITY ON THE TRANSDERMAL PRODUCTS

BIOADHESIVES-

Bioadhesives are polymers that are both extremely biocompatible and biodegradable. They are intended to bond two surfaces that contain living tissue on at least one of them. Bioadhesives have multiple applications, such as taking the place of surgical suture and conventional drug administration system. The functional prerequisites for practical usage in minimally invasive surgery are met by bioadhesives. Bioadhesion bonding state of the biopolymers-achieved by cross-linking characteristics, chain length, and presence of different functional group- determines the bioadhesion bonding state of the bioadhesives, which can be derived from synthetic or biological source. It can cling to the biological surface or come into close touch with the biological substrate because of its biocompatibility.

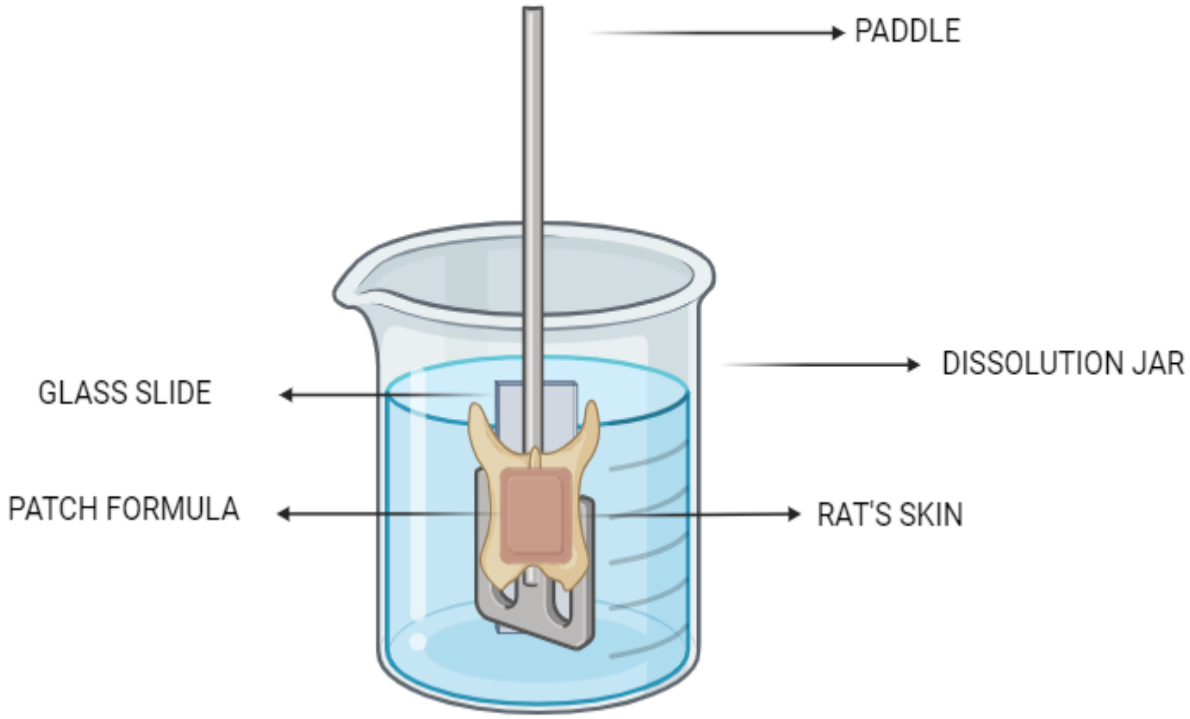


Figure 2 TEST USED TO ASSESS THE PATCHES ADHESIVE PROPERTIES

Determination of bond breaking strength

The best way to measure bond strength is to calculate the value called bond strength according to More and Williams [4][5][6] . This energy based method is used in geometry models (such as backups) and measurements and gives good results. However, two tests are required to calculate the breaking strength of the adhesive. To measure the peel strength, a peel test must first be performed Secondly, a pull test should be performed on each arm. To compute the correction resulting from plastic bending deformations, tensile strength is necessary. When determining the adhesion strength, the peel arm specification additionally accounts for the anisotropic effects brought on by the molecule orientation in the peel arm. GC adhesion strength can be calculated according to formula (1): Employing the external feature Next, keep the strain energy of retraction constant. Three, the arm's irreversible tensile (Udt) and bending (Udb) deformation, the sample breadth (b), and the peeling front (da) all contribute to the soy ma energy dissipation.[4][6][7] . The fracture strength of the adhesive was calculated using the IC Peel (2006) protocol [8]. Despite the fact that this approach was created for flexible laminates, the significant plastic deformation of the peel arms made it challenging to calculate the necessary estimate of high modulus E2. Quantification estimations and power law have shown to be superfluous. The bilinear met hod is used only for the longitudinal 25 µm peel arm and finds $\alpha = 0.0037$. A is calculated as the ratio of the high strain modulus E2 and the elastic modulus E [4][6] . In all cases, the value of α is assumed to be 0.0001. The estimated thickness for the adhesive layer is 8 µm and the modulus value is 5 MPa. Table 2 explains the importance of the adhesive breaking strength GC, bending plasticity work GD, process GD / G tot (electrical process ideas (release energy and tensile distribution of the shell) arm).) and calculates the maximum damage stress İmax (o).).

1. **The Adhesive Properties Of Transdermal Drug Delivery System (TDDs):**

A transdermal drug delivery system's (TDS) adherence to the skin is the result of several complex processes. Therefore, to evaluate the adhesive characteristics of a TDS, it is essential to determine the following:

(i) The property that allows an adhesive to form a connection with another material's surface after a brief, light pressure application (known as tack).
(ii) The matrix's ability to withstand deformation over time (creep resistance or shear adhesion).
(iii) The force required to break a section from a surface (peel adhesion).

5.1 Tack:

Tack is the adhesive property associated with the immediacy of bonding under minimal contact pressure between a transdermal drug delivery system (TDS) and the surface of another material (adherend). It can also be termed as quick stick, initial adhesion, or stickiness. Tack involves molecular interactions at the interface between the adhesive and adherend. The adhesive/adherend molecular interaction, in conjunction with surface energy, contributes to the potential adhesion force. The rheological properties of the matrix, especially its viscoelastic properties, typically determine the speed and strength of the initial bond formation. To achieve effective tack, the matrix must deform rapidly within a very short period, often within fractions of a second. Tack is improved when an adhesive can uniformly distribute stress across its volume.[9]

In the context of TDSs, tack is particularly relevant in situations requiring rapid adhesion to a specific adherend. However, in TDS application on the skin, where precision is paramount, lower tack values may suffice, as tack's role in determining efficacy or safety is generally minimal.

5.2 Creep Resistance/Shear Adhesion:

Creep resistance or shear adhesion reflects the cohesion within the matrix, indicating its ability to resist deformation under stress. This property is closely tied to the rheological behavior of the adhesive matrix. The matrix should demonstrate elastic cohesiveness and resistance to flow when subjected to stress. [10] High creep compliance suggests poor matrix cohesion, potentially leading to oozing or the presence of adhesive residues along the TDS edges after application to the skin. Apart from being aesthetically unpleasing, these residues can attract dirt and adhere to clothing or other body parts. Moreover, a TDS positioned on a joint may shift, thereby affecting the kinetics of drug release

5.3 Peel Adhesion:

Peel adhesion, which is often referred to as peel force or peel resistance, is a characteristic that transdermal drug delivery systems (TDSs) are frequently evaluated for. It goes much beyond just being a test; rather, it is an essential feature of TDSs. It is commonly known that higher levels of pain are correlated with a TDS's increased peel adherence. In a study, Chivers found a correlation between blood perfusion as determined by laser-Doppler perfusion imaging and peel force off the skin.[11]

Peel resistance is not a reliable indicator of the strength of the adhesive bond and does not always represent intrinsic adhesive performance. The TDS must be removed with a force that is noticeably greater than that which keeps it in place. This is because the backing layer and matrix must be extended before they separate and bend during removal. Medical pressure-sensitive adhesives (PSAs) need to stick to the skin securely, but after a certain amount of time, the TDS needs to be removed quickly, painlessly, and without inflicting any harm to the skin. Extending the adhesive, causing the backing to deform during stripping, and disconnecting the adhesive/surface interface—the latter being the weakest part—all require work during removal.[12]

There are several possible failure modes when a TDS, or adhesive tape in general, is peeled off a stiff surface. Failures can be classified into four categories based on how well the matrix adheres to the backing layer. The patch should ideally remove cleanly from the adherend and leave no trace. Adhesive failure results from failing to do so (case I). In instance II, the matrix can transfer to the adherend or only partially adhere to the supporting layer. In the matrix, Case III shows strong cohesive strength but weak sticky strength. In Case IV, cohesive and adhesive failure occur at the same time. Failed TDS formulation is usually indicated by failures other than case I.

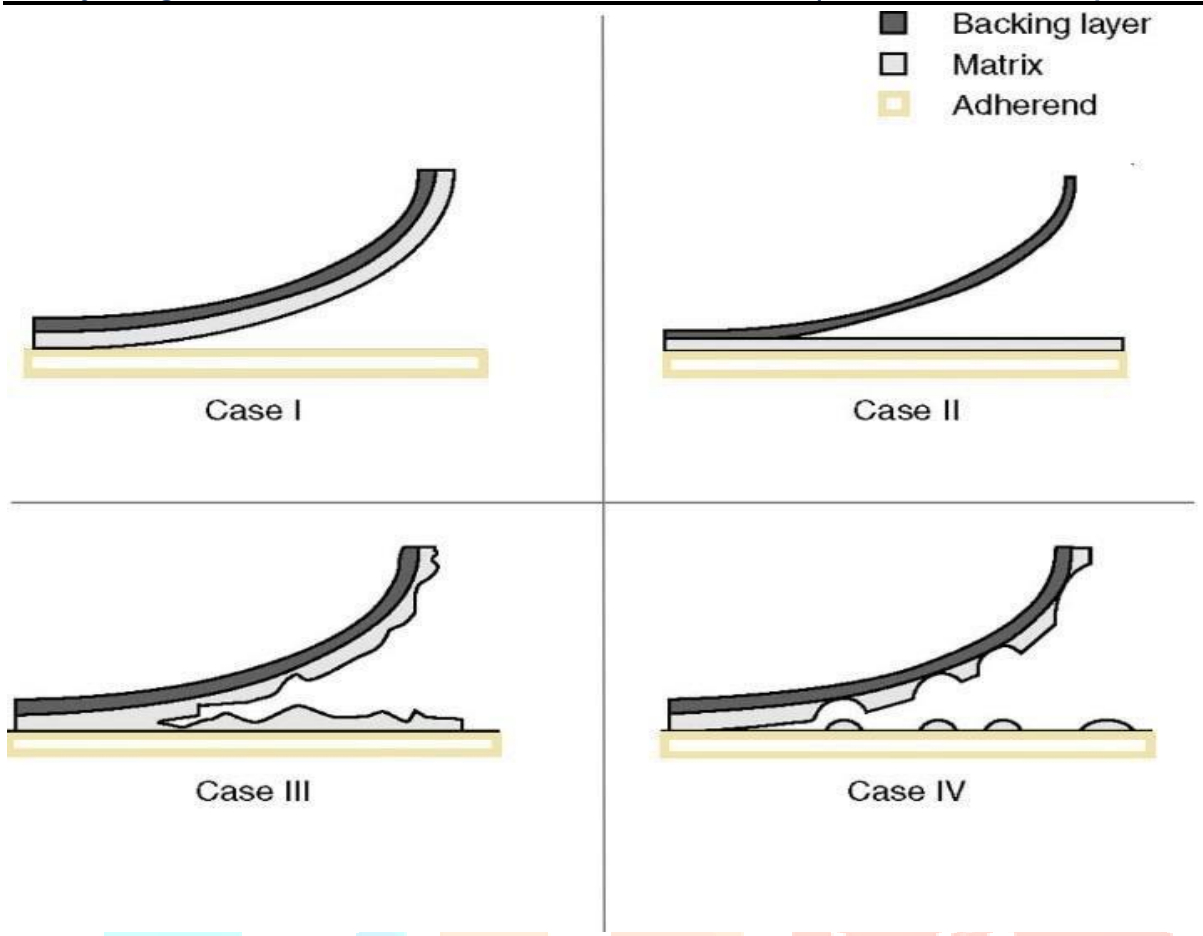


Figure 3 Transdermal delivery system modes of failure Class I and II adhesive failure and case III: cohasive failure and case IV adhesive/cohasive failure[12]

6.Test for Measuring TDS Adhesion Properties[12]

Examinations utilized in the pharmaceutical industry to evaluate the adhesive capabilities of Transdermal Drug Delivery Systems (TDDS) derive from established protocols formulated by prominent entities within the adhesive tape and label industries, as well as standard-setting bodies[12].

6.1 Tack test

Measuring the speed at which an adhesive reaches its optimal adhesion can be challenging. Therefore, various tack tests have been developed to assess the bonding strength after a brief contact period under low pressure.

These tests can be divided into three primary categories:

Peel test-like tack tests.

Rolling-ball tack tests.

Probing tack tests.

The rolling-ball test, the oldest among them, involves rolling a stainless steel ball down an inclined track to make contact with an adhesive-coated surface. The distance traveled by the ball along the adhesive serves as a measure of tackiness[13]. However, this test is not ideal for low-tack TDSs due to their typically low tack values.[14]

The qualitative thumb tack test, in which the sample is softly touched with the thumb to evaluate bonding, gave rise to probe tack testing.[15][16] While simple, this method lacks quantifiability and objectivity. Probe tack tests offer a more quantitative approach by measuring the maximum detachment force. Texture analyzers can further improve this by describing the complete debonding process, which gives information about the adhesive matrix's cohesiveness and viscoelastic behavior.[17][18]

Quick stick and loop tack tests are frequently used since they work on the same principles as peel adhesion tests.19] The loop tack test measures the peel force by clamping TDS ends into a loop, gently pressing it against a surface, and then withdrawing it. The rapid stick test is similar to a 90° peel adhesion test in that it adheres the adhesive strip to a plate without the need for external pressure.[20]

6.2 Creep Resistance or Shear Adhesion Tests

Shear adhesion can be measured by measuring the force required to pull a standard TDS area from a standard flat surface (like stainless steel) in a direction that is parallel to the attached surface. Both dynamic and static testing can be used to these techniques.

The specimen is pulled from the surface steadily throughout dynamic tests, with the maximum detachment force being assumed to represent shear adhesion.[21][22]

Conversely, static tests quantify the force needed to remove the TDS over an extended period of time under a typical load or as the highest load that can be applied without resulting in significant sliding.. The adherend plate is typically angled at 2° from vertical to minimize peeling. Cohesive failure of the adhesive is optimal in shear adhesion tests, leaving adhesive layers on the backing layer and adherend plate. Failure of this kind reveals the real inner strength of the adhesive.[23][24]

6.3 Peel Adhesion Tests

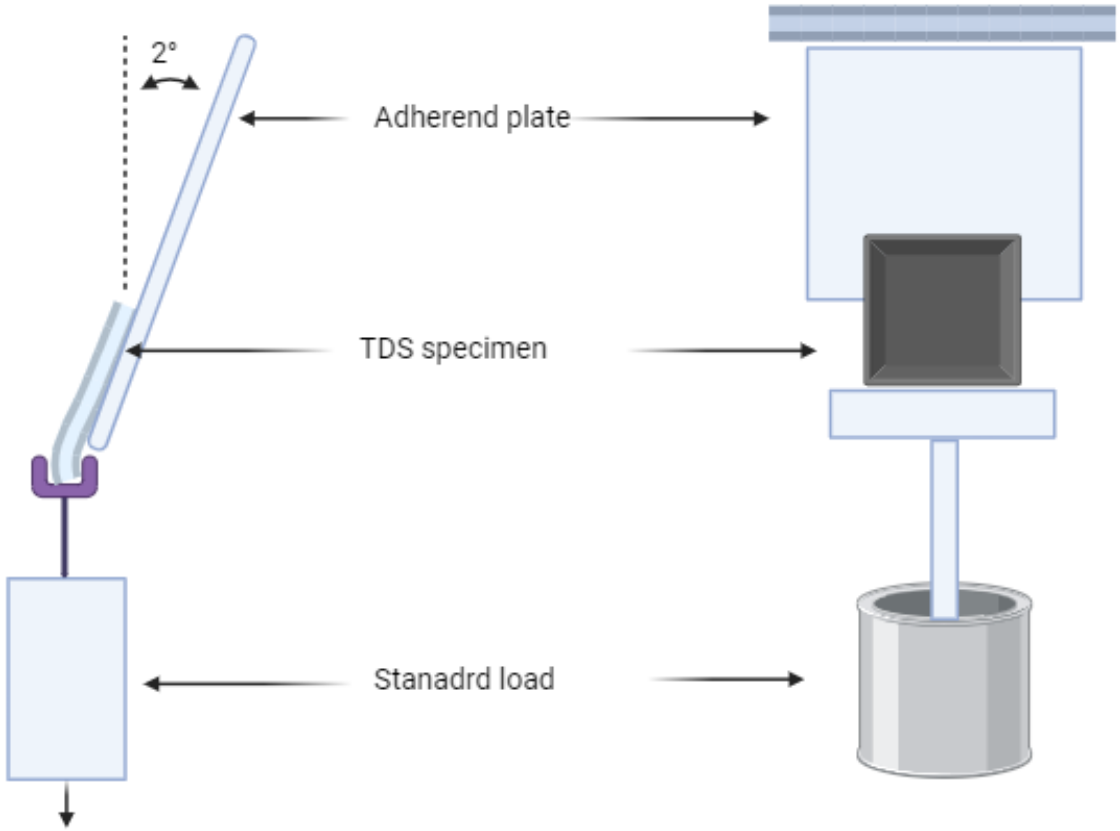
Peel adhesion can be assessed using both static and dynamic testing. In dynamic peel tests, force is applied at a predetermined rate, and the force per unit area is the outcome.[25] On the other hand, static peel tests record the amount of time before failure using a set weight.[26]

The kind of stress in the application determines the approach to choose. Dynamic peel tests are useful for TDS applications where the patch peels off the skin. Applying a TDS strip to a stainless steel test plate at a specific pressure is a standard test procedure. The strip is removed at a preset speed (300 mm/min) and angle (180° or 90°) after a predetermined amount of time.[27]

Only tensile stresses are measured in the 90° peel test, whereas shear and tensile stresses are measured in the 180° peel test. As such, there is no direct comparability of the outcomes. However, the 90° peel test is suitable for backings unable to bend through the 180° angle.

Stretching the patch and giving it a little extra length takes energy during peel. Test angle can be influenced by backing properties and matrix thickness; in certain cases, flexing requires more energy than peeling adherent. Rigid tape can be put to the TDS back for strengthening in order to reduce backing influence. This allows for quality control and matrix impact assessment on the peel process.

PSA matrix forms intermolecular bonds over time, altering adhesion in the initial weeks post-preparation. Therefore, considering matrix stabilization's impact by repeating adhesion tests over different time intervals may be beneficial.



Future Perspective:

The transdermal market is estimated at $2 billion, accounting for 10% of the $28 billion U.S. pharmaceut ical market. Although the number of drugs approved for transdermal delivery has been limited since the FDA issued the first license in 1979, market growth has been large, with only nine drugs approved. This highlights the challenges of dermal drug delivery due to physicochemical limitations. %). This growth is expected to continue as new technologies become available and the transdermal drug class continues to e xpand, making the skin a promising route for drug deliver2y in many cases.[28] Transdermal drug delivery systems are experiencing significant growth within the pharmaceutical industry. They offer an alternative route for drug administration that cannot be replicated by other delivery methods.[29]

Conclusion:

In summary, bioadhesion testing is important to optimize transdermal drug delivery and improve patient health. By evaluating the adhesive properties of bioadhesive formulations, researchers can gain insight into their effectiveness and safety. This testing will help determine the best of the process, such as the type of polymer used, its concentration, and speed of attachment, which affects the design, support, and release of the drug. The importance of bioadhesion testing lies in its ability to predict and optimize the effectiveness of transdermal drug delivery in real life. Formulations with good bioadhesive properties can remain on the skin longer, promoting better absorption and stable release of the drug in the body. This leads to effective medicine, efficiency and patient compliance. Additionally, bioadhesion tests allow researchers to address issues such as differences between individual skins and the quality of the design. Bioadhesion testing using standardized methods, advanced laboratory models, simulated experiments, and physiological conditions can more accurately predict how these systems will perform in the body and help create new replacement drugs. Overall, the importance of bioadhesion testing in optimizing transdermal drug delivery and improving patient outcomes cannot be underestimated. Through continued research and creativity, bioadhesive models have the potential to revolutionize drug delivery by providing safer, more effective, and user-friendly treatment options for a variety of Conditions

Active ingredient	Product Proprietary name	Application holder	Pressure-sensitive	TDS Design	Drug content(mg)	TDS release area(cm^2)	Amount of drug absorbed (mg/24h)	Period applicatio
Scopolamine	Transdermal Scop	Novartis	PIB	Reservoir	1.5	2.5	0.0567	3d
Testosterone	Androderm	Watson Laboratories	Acrylic co-polymer	Reservoir	12.2/24.4	37/44	2.5/5	24h
Oxybutynin	Oxitrol	Watson Laboratories	Acrylic co-polymer	Monolayer	36	39	3.9	3-4d
Tulbuterol	Hokunalin Tape	Hokurikuseiyaku	PIB	Monolayer	0.5/1/2	2.5/5/10	0.672	24h
Fentanyl	Duragesic	ALZA	Silicone	Reservoir	25/50/75/100	10/20/30/40	0,6/1.2/1,8/2.4	3d
Fluocinolone acetonide	Fluvean	Kowa	Acrylic co-polymer	Monolayer	0.4	50	Systemic absorption not relevant (local/regional effects}	12h
Clonidine	Catapres TTS	Boehringer ingelheim	PIB	Reservoir	2.5/5/7.5	3.5/7/10.5	0.1/0.2/0,3	7d
Estradiol	Alora	Watson Laboratories	Acrylic co-polymer	Monolayer	0.77/1.5/2.3/3.1	9/18/27/36	0.025/0.05/0.077/0.1	3-4d
Buprenorphine	Transtec	Grunenthal	Acrylic co-polymer	Monolayer	20/30/40	25/37.5/50	0.035/0.052/0.07	3d
Nitroglycerin	Deponit	Schwarz	Acrylic co-polymer	Monolayer	18.7/37.37/56.1	9/18/27	5/10/15	24h

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