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Smart Approach For Transdermal Drug Delivery System Loaded With Hyaluronic Acid

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Abstract: It was discovered that puncturing human skin with micron-sized needles increased the permeability of the skin to a model drug, calcein. Microneedles are hollow or solid cannulae used to deliver drugs. Microneedle are strong and long enough to break through the barrier, but they are also short enough to not stimulate the nerves. These are painless and irritation free delivery. It is provided direct entry of drug through the skin layers. Accurate dosing, complex release pattern, local delivery, and improved biological drug stability. TDDS patch no fear of needle and ease of administration. Dissolving microneedle made of biodegradable materials including various polymers and sugars that have medicinal properties. Weigh all polymer as per requirement, that is HPMC: CMC (4:3) and dissolved in 5ml of distilled water. Add slowly powdered polymer in ascending order, apply continuous stirring. Apply heat to make homogenous mixture at temperature 60^{o}C for 4 minutes with continuous stirring. Transdermal patches, which provide a reduced dose of the medicine at a predefined rate, have been created to increase clinical efficacy of the drug and patient compliance.

Keyword: - PVP, PVA, HPMC, CMC, Hyaluronic acid, TDDS Patches

1.INTRODUCTION

A transdermal patch, also known as a skin patch, is an adhesive patch applied to the skin that contains medication that is intended to be absorbed into the bloodstream through the skin. This frequently encourages the healing of a body part that has been hurt. The regulated release of the medication into the patient is a benefit of transdermal drug administration over other forms, such as oral, topical, etc. However, the fact that the skin is a very effective barrier poses a challenge to development. Transdermal patches can administer a wide range of medications.

1.1 Transdermal Drug Delivery Systems' Basic Components

a.Polymer: - The drug's release from the device is managed by the polymer. The following polymers could be advantageous for transdermal devices:

b. Natural Polymer: - For instance, gelatin, shellac, zein, proteins, gums and their derivatives, natural rubber, starch, and waxes are all examples of cellulose derivatives.

c.synthetic Elastomers: - Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

d. Synthetic Polymers: - PA, PC, Polyethylene, Polypropylene, Polyacrylate,

Polyamide, Polyurea, PVP, Polymethyl methacrylate, Epoxy etc.

e. **Drug: -** Drug The drug should be carefully chosen in order to construct a transdermal drug delivery system properly. The following are some characteristics of a medicine that are ideal for transdermal distribution.

f. **Permeation Enhancer: -** These chemicals increase skin permeability by altering the skin's capacity to act as a barrier to the flux of a desired penetrant.

1.2 TYPES OF TRANSDERMAL PATCHES

i. **One layer medication in adhesive: -** In this form, the medicine is included in the sticky layer. The adhesive layer is in charge of delivering the medicine onto the skin in addition to holding the other layers together. There is a backer and a temporary liner around the adhesive layer.

ii. **Multilayer drug in adhesives: -** This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

iii.Drug in adhesive reservoir: - This technique involves sandwiching a membrane that regulates flow rate between an impervious backing layer and a drug reservoir. The medicine is only released through the rate-regulating membrane, which may or may not be microporous. The medication may be in a solid polymer matrix, a solution, suspension, gel, or another form in the drug reservoir compartment. It is possible to use a polymeric membrane with a hypoallergenic and drug-compatible outside surface.

iv.Drug in adhesives matrix: - The addition of a semisolid matrix containing a medication solution or suspension thatis in direct contact with the release liner characterizes the Matrix system design. The element causing skin adherence is built into an overlay and arranges itself in a concentric pattern all around the semisolid matrix.

2.Methodology or Materials and Methods

2.1 Materials

Ethyl cellulose, Polyvinyl pyrrolidone (PVP K-30), Polyvinyl alcohol (PVP), Dibutyl phthalate (DBP) and dibutyl sebacate (DBS), Linseed oil, L-menthol, Resin, hydrates, Polylactic acid, HPMC, PEGDMA and all the other chemical of analytical reagent grade.

2.2 Method of Preparation

a) Preparation of master mold

MN's mold was fabricated containing 340um x 340um x 300um (LxWxH) wider, length and height and had 640 um center-to-center spacing the mold cavities (MNs holes) were prepared by mechanical method using needle top were pork into the mould surface. Standard mould was fabricated using materials (resin and hydrate) by hand rolling method. Prepared mould was placed for 24 hours under room temperature.

b) Preparation of polymeric microneedle arrays (MN's)

The natural and biodegrable polymeric solution used to fabricate the microneedles transdermal patch. The polymer solution of polyvinyl alcohol (PVA) about 20% w/v was dissolved in purified water at 90°C at a ratio of 0.80gm PVA per 1ml of purified water, stirred using magnetic stirrer for 20 minutes. Once the smooth consistency of polymer solution was prepared, allow the solution to pour in to the microneedles standard mould. Then standard mould containing polymer solutions were attached under centrifuges apparatus and allow immediately centrifuged at 1500 rpm for 15 minutes for even and uniform distribution of the solution in to the mould. After the centrifugation mould should be removed carefully and allow it to stand for 24-48 hours for complete drying of the microneedles. To take out microneedles from the mould, it kept under the freezer for 30 minutes at 4-5°C for easy removal of microneedle (MNs).

b) Fabrication of Transdermal Patches

Transdermal patches were fabricated using established fabrication technique with some modifications. Prepared 10% polymer solution, 0.75gm PVP and PVA dissolved per 1ml of purified water. 1gm of dextran per 1ml of PVP/PVA solution was mixed. This Prepared polymer solution were poured in microneedle mould arrays [20-26]. It kept for 12 hours for completely dried and removed microneedle (MN's) arrays with supported backing layer of 10% polymer backing layer.

2.3 Characterization of Microneedle Transdermal Patch

a) Scanning electron microscopic (SEM) analysis

Prepared microneedle array was investigated for magnification, tilt degree, width, spots and other imaging characteristics on SEM images. Microneedle arrays were mounted on the disc and morphological characteristic feature scanned in scanning electron microscope (SEM) in

highvacuum mode, attached ETD detector at 10-5 Torr and 15 kV, model (FEI Quanta TM ESEM, QUanta 200 FEG; FEI, Oregon).

b) Differential scanning calorimetry (DSC) analysis

The sample of microneedles were investigater under differential scanning calorimetry (DSC) system model (Netzsch 204 F1 Phoenix®; Geratebau GmbH, Bavaria). Microneedles sample were heated at a lenear heating rate of about 10ºC/minutes from 25 ºC to 250 ºC, generated graph and report were analysed with Netzsch-compatible software, parameter such as, melting peak, delta Cp of microneedle arrays.

c) Measurement of mechanical strength and swelling index

Quantitative and qualitative assessment of microneedle was observed included the experimental variability artificial skin were designed related to anatomical variation as the human skin structure, using polymer (CMC/dextran) thin film fabricated using 40:2 ratio. In contrast microneedle arrays with different geometrics delivered. On the other hand, insertion force was approximately constant, enabling deeper and more reproducible insertion with greater proportion pores.

c) Measurement of dissolution efficient of microneedle arrays

In this measurement, the application of microneedle were investigated, including the type of bioactive cargo to be dissolution time release, dissolution pH specific, dissolution by-products and estimated mechanical strength. In additions, we demonstrated six type of microneedle from different type of polymer together. We created microneedle from, (i) Carboxymethyl cellulose (CMC); (ii) Polyvinyl pyrrolidone (PVP); (iii) CMC/PVP at 60:40 dry weight ratio; (iv) PVP/PVA 20:10 at dry weight ratio; (v) CMC/dextran at 50/50 dry weight ratio; (vi) PVP/HPMC at 60:40 dry weight ratio. Microneedles from all the seven geometric polymers were fabricated and sample successfully dissolves in particular solvent for specific time and 5.4-7.2 pH buffers to demonstrate the dissolution efficient.

3.Result & Discussion

TDDS patch is a new modern drug delivery technique through skin. These drug administration techniques cause no discomfort. Microneedle are strong and long enough to break through the barrier, but they are also short enough to not stimulate the nerves. These are painless and irritation free delivery. It is provided direct entry of drug through the skin layers. Accurate dosing, complex release pattern, local delivery, and improved biological drug stability. TDDS patch no fear of needle and ease of administration. Dissolving microneedle made of biodegradable materials including various polymers and sugars that have medicinal properties. The transdermal patch, also known as a skin patch, is an adhesive applied to the skin that contains medication that is intended to be absorbed into the bloodstream through the skin.

3.1 Requirement: -

- **Chemical: -** Hydroxypropyl methylcellulose, Carboxymethyl cellulose, Distilled water (PEG – 400) Elastomers.
- **Drug –** Hyaluronic Acid
- **Apparatus –** Beaker 250ml, Spatula, Glass rod, Glass Petridis, Electric weighing balance.

3.2 Procedure: -

- **Preparation of Polymer Solution**

i. Weigh all polymer as per requirement, that is HPMC: CMC (4:3) and dissolved in 5ml of distilled water.
ii. Add slowly powdered polymer in ascending order, apply continuous stirring.
iii. Apply heat to make homogenous mixture at temperature 60ºC for 4 minutes with continuous stirring.

- **Preparation of Microneedle Mold**

i. Mix hydrate mixture (pistil) in appropriate quantity and make soluble as per requirement.
ii. With the help of needle puncture as (4x6) area.
iii. Keep it on place (dry place) for 24 to 48 hours.

- **Preparation of Microneedle and Loaded Hyaluronic Acid**

i. Clean the mold, with the help of H_2O_2 and cotton body.
ii. Add slowly the polymer solution on surface of mold.
iii. After dropping on the surface, hammer continuously to help easily penetration in the holes of molds.
iv. Once a layer formed on mold slop dropping and cleans the surface.
v. Place this mold at safe and open environment for drying the microneedles.
vi. Remove slowly microneedle from the mold.

3.3 Evolution of Transdermal patches

Transdermal dosage form development is a challenging process that requires substantial investigation. Transdermal patches, which provide a reduced dose of the medicine at a predefined rate, have been created to increase

clinical efficacy of the drug and patient compliance. In order to guarantee their expected performance and reproducibility under the stipulated environmental circumstances, evaluation studies are now even more crucial. These researches, which can be categorized under the following groups, are prescient of transdermal dosing forms:

3.3.1 Physiochemical Evolution

- **Thickness:** - At various spots along the transdermal film, the thickness is measured using a travelling microscope, dial gauge, screw gauge, or micrometer.
- **Uniformity of Weight:** -By individually weighing 10 randomly chosen patches and figuring out the average weight, weight variation is explored. The weight of a person shouldn't differ noticeably from the average weight.

- **Drug Content Determination:** - In a shaker incubator, a precisely measured quantity offilm (about 100 mg) is dissolved in 100 mL of a suitable solvent in which the medication is soluble. The solution is then agitated continuously for 24 hours. The entire solution is then sonicated after that. Following sonication and filtering, the amount of medication in the solution is determined spectrophotometrically by the proper dilution.

- **Moisture Content:** - The produced films are weighed separately and maintained atroom temperature in desiccators with calcium chloride for 24 hours. The films are weighed once more after a certain period of time until they display a steady weight.
- **Interaction Studies:** -The compatibility of the medicine with the excipients is one of the elements that affect a formulation's stability. To create a stable product, the drug and excipients must be compatible with one another. As a result, it is essential to identify anypotential physical or chemical interactions because they may impair the bioavailability and stability of the medication. The compatibility studies are crucial for formulating newexcipients that have never been used in formulations containing the active ingredient. Bycontrasting their physicochemical properties, such as assay, melting endotherms, distinctive wave numbers, absorption maxima, etc., interaction studies are frequently conducted in thermal analysis, FT-IR, UV, and chromatographic procedures.

- **Shear Adhesion Test:** -This test determines the cohesive strength of an adhesive polymer. The level of cross-linking, the molecular weight, the make-up of the polymer, and the quantity of tackifiers used can all have an impact on the strength value. A stainless-steel plate is used to stack an adhesive-coated patch, with a specific weight suspended from the patch parallel to the plate. The cohesive strength is determined by how long it takes to remove the patch from the plate. The shear strength increases as the amount of time increases.

- **Peel adhesion test:** -Adhesion is the measurement of the patch strength between an adhesive and a substrate. The amount of force necessary to remove the adhesive coating from the steel test substrate. The composition of polymers as well as the kind andquantity of polymer molecular weight determine the adhesive capabilities. The one patchadheres to the test substrate (steel), and it is being dragged away from the substrate at an angle of 1800 degrees. Absence of residue on the test substrate suggests that the adhesive failed.
- **Tack properties:** - Tack, which is a polymer's ability to stick to a surface with little force, is crucial in transdermal systems that require little force to apply. The molecular weight, content, and testifying resins used in the polymer all affect the tack.

- **Probe tack test:** -In this, an adhesive is brought into touch with a probe tip with a specified level of surface roughness. Once a bond is formed between the adhesive and probe, the probe is removed at a set rate away from the glue, breaking the bond. Tack, which is measured in grammes, is the amount of force needed to separate the bond.
- **Thumb tack test:** -By pressing the thumb into the adhesive, the results of this subjectivetest are evaluated. Using the test requires prior testing experience.
- **Rolling ball tack test:** - To conduct this test, a stainless steel is moved along the adhesive's upper face, and the distance it travels is measured. Ball is launched oninclined track at an angle of 22.50 and has a 7/16" diameter. Less sticky polymer is seen at longer distances. The tackiness of the polymer is determined by measuring the ball's travel distance in inches. The sticky polymer's softness is determined by it.

3.3.2 In Vitro Test

You can evaluate the drug release from the produced patches using the paddle over disc method (USP equipment V). A glass plate must be covered with dry films of defined thickness that have been cut into a specific form, weighed, and fastened with an adhesive. The device was then

brought to an equilibrium temperature of 32 0.5 °C before the glass plate was submerged in 500 mL of the dissolving liquid or phosphate buffer (pH 7.4). The paddle was then turned on at a speed of 50 rpm while being placed 2.5 cm away from the glass plate. At suitable intervals up to 24 hours, samples (5-mL aliquots) can be taken out and examined using a UV spectrophotometer or HPLC. The test must be carried out in duplicate and to describe the drug dissolution profile from a controlled release dosage form and therefore there in vivo performance, it is vital to understand the drug release mechanisms and kinetics of the dosage form. There are different techniques available for determining the drug release rate of TDDS, and numerous mathematical models have been created to characterize the drug dissolution kinetics from controlled release drug delivery systems.

4. Conclusion

One of the most innovative drug delivery methods with good safety and efficacy is transdermal route. Were demonstrated to speed up passive diffusion and allow significant volumes of both chemical and biological medications to penetrate the skin at higher depths. It has more patient acceptance due to low price, excellent pharmacological action in low doses with significant reduction in GI adverse events. Transdermal patches have the potential to become the preferred method of drug delivery in the near future with some improvements to their production and drug delivery systems. They can be used safely and comfortably in elderly, intellectually challenged, and pediatric age groups without running the risk of overdosing or negative side effects. When compared to the skin damage brought on by hypodermic needle skin puncture, it has been observed that microorganisms' ability to pass through microneedle-induced skin pores within the skin is minimal and has a lower incidence for occurrence. It is intended that improvements in microneedle-based technology would improve illness prevention, diagnosis, and control, as well as the quality of life for patients around the world.

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