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AN OVERVIEW ON TRANDERMAL PATCHES AND THEIR RECENT APPLICATION

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ABSTRACT

Transdermal patches are adhesive patches which provides controlled release action over period of time This review concentrates on the microneedles transdermal patches & their application. Microneedle patches are the 3D structure that bypass the skin barrier & produce local effect .We study the development of the microneedle patches .Types of microneedle patches & their material gives the information about the formulation microneedle patches. Recent application of the microneedle patches with different delivery system.

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INTRODUCTION

The most common oral drug delivery methods have some drawbacks, such as first-pass metabolism, drug degradation, etc., because of enzymes, pH, etc. in the gastrointestinal tract.A unique medication delivery mechanism was created by Chien in 1992, Banker in 1990, and Guy in 1996 to address these issues.It was a transdermal delivery system or transdermal patches.This technology creates medicated adhesive patches that, when applied to the skin, disperse a therapeutically useful dose of medication across the skin.They come in a variety of sizes and include multiple ingredients.They transport active compounds into systemic circulation via skin barriers after being applied to intact skin.A transdermal patch keeps the medicine it contains, which has a high dose, on the skin[1].

Drugs can enter the skin through three different passageways:

a) Sebaceous glands
b) Hair follicles.through
C)Sweat duct

Types of TDDS[2].

Types of TDDS	STRUCTURE
Medication layer in adhesive	Adhesive +drug
Reservoir system	Drug kept in backing layer
Matrix system	Drug dispersed in adhesive polymer matrix
Micro-reservoir system	Drug dispersed in aqueous solution

Advantages& Disadvantages[2]

Advantages	Disadvantages
Self administration	High cost
Improved patient compliance	Molecular size restrictions
No interaction with GI fluids	No rapid release
Flexibility of termination	Variation in barrier function
Avoids FPM	Local irritation

Component of transdermal system[2]

A] Polymer matrix

a] Natural polymer-e.g shellac, gelatin,wax,gums etc
b]Synthetic elastomer-e.g ECO rubber, silicon rubber, neoprene,etc
c] Synthetic polymer-e.g PVA,PVC etc

B] Drug

C]Permeation enhancer e.g menthol,glycol,lauric acid,sodium EDTA etc
D] Pressure sensitive adhesive–e.g polyacrylates,polyisobutylene,silicon based adhesive etc
E]Backing laminate-e.g vinyl ,polyethylene,polyeter film etc
F]Release linear-e.g paper fabric,polyethylene ,polyvinyl chloride
G]Other excipients like plastisizer & solvents e.g chloroform,acetone isopropranol etc

Marketed recent formulation.

Drug	System	Clinical use	Shelf life	Ref
Buprenorphine	Matrix system	to treat osteoarthritis	6MONTHS -1YR	3
Diclofenac	Drug in adhesive system	Painkiller,NSAID	3-4yr	4
Ketorolac	Reservoir system	Treatment of toothache	6months-1yr	5
Insulin	Microeneedle	For diabetic patient	Once get open,takes about 28 days to expire	6
Furosemide	Film type	Treatment of CHF,liver disease etc	Upto 3yr	7
Ampicillin	Membrane type	As a antibiotic	Refrigeration at least 72 hr	8
Climaderm	Matrix system	Postmenstrual syndrome	Upto 36 months	9

CHF: CONGESTIVE HEART FAILURE

Microneedle patches-

The MN's are actually too small to perceive with the naked eye; they measure below than one millimetre in height [10].This micron-sized needle establishes a conduit for the drug molecule to diffuse by puncturing the skin's top layer, stratum corneum that works as a greater obstacle to the actives' diffusion and opens a channel which permits direct drug molecule diffusion much more beneath the surface swiftly.Virgil A. Place and Martin S. Gerstel initially proposed the idea of MN in the 1970s [11].Have enabled transdermal administration of even extremely complex compounds, likes proteins, vaccines, plus peptides.Although There are several various several kinds of microneedles, such as coated, hollow, solid, and dissolving MNs, all MNs are eventually utilised to deliver drugs quickly and effectively. [12] As compared to hypodermic needles, this technique may be more expensive and have worse dosing accuracy.Drugs with modest doses (a few milligramme per kilogramme of body weight) are favoured because they can be inserted into or applied on top of the tips of microneedles in a suitable amount.Care should be used when using MN to stop dirt from "bouncing off" the surface of the skin. The dosage could get out or pierce the skin to varying amounts if the instrument is not kept vertically [13].

Development of microneedle patches[14.15,16]

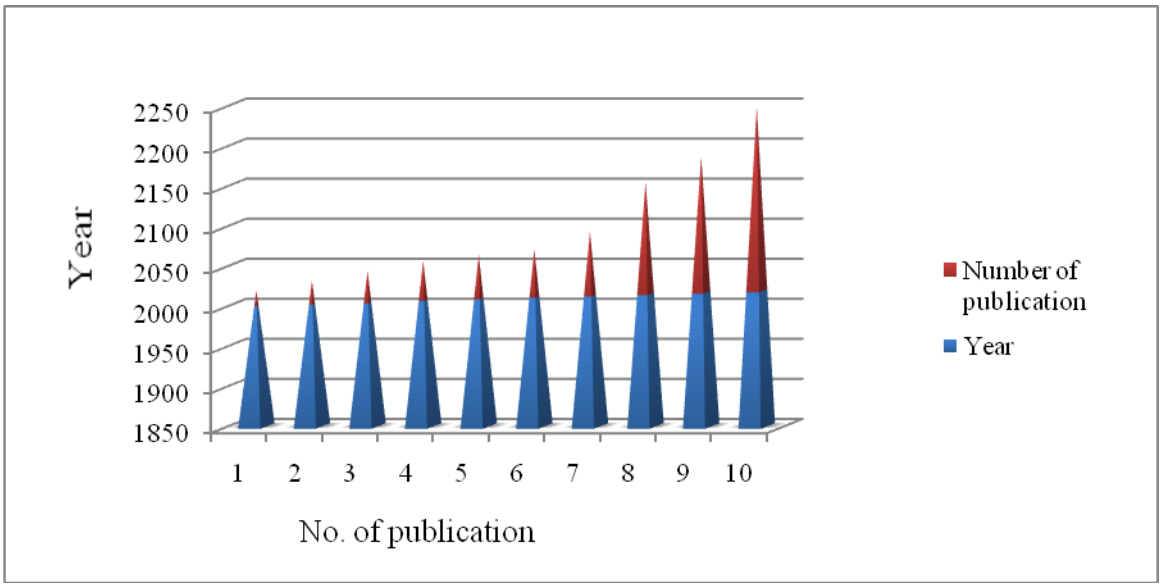


Fig 1: Development of microneedle patches[2000-2019]

Ideal characteristics of microneedle patches

Microneedle range from 50 to 900 micrometres in height or length and have a diameter of 1 millimetre.[10,17] The designed MNs to penetratemust be capable the skin deeply without breaking.MNs ought to be the right size[18]These have been created to improve self-medication and enable individualised medicine at various dose levels[19].These patches must adhere well or at least similarly to conventional transdermal patches.

Advantages & disadvantages[20].

Advantages	Disadvantages
The stratum corneum serves as a direct direct path to the body for drug transport	The small size of the microneedle limits the amount of medication that can be administered
Drug action begins quickly	Temporary inflammation and allergies may result
Controlling microneedle compositions allows for the delivery of precise medication doses	Sophisticated technologies are required to manufacture a microneedle patch with reproducibility;
Microneedles bypass the initial metabolic stage.	Microneedle patches require a storage container to hold them hygienically and without damage during distribution from the manufacturers to the patients.
Due to their short length and compact size, microneedles are painless and secure.	
The patch application requires less technical knowledge.	

Types of microneedle patches[21-29].

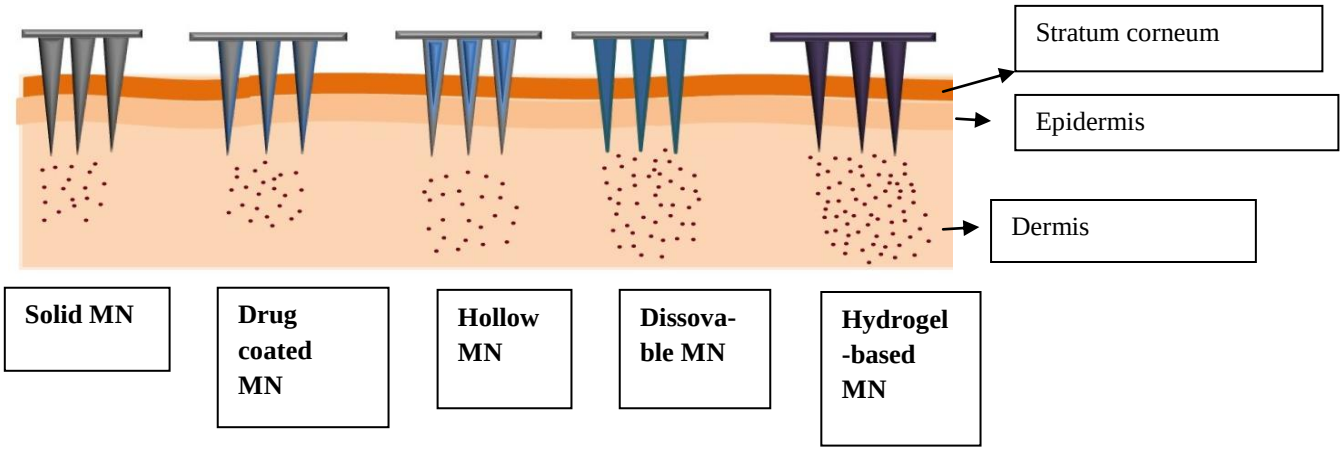
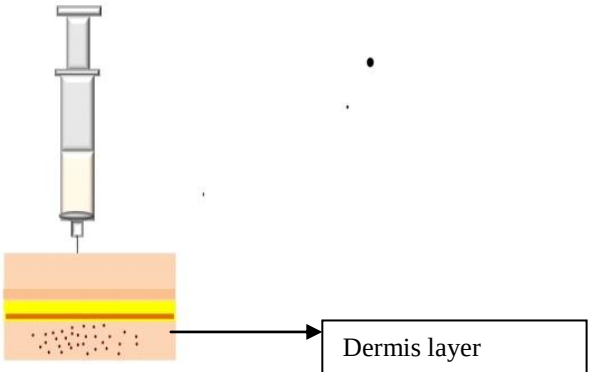


Fig 2-Types of microneedle patches

Types of microneedle patches[30-31].

Types of microneedle	Delivery efficiency	drug dosage	action begins	Delivery schedule	Patch wearing time	Packaging
Solid	There is still some drug in the patches, Low efficacy	High efficacy	Slow release of diffusion	Several hours	Several hours	Separate packaging of microneedle & formulation
Coated	High efficacy	Low efficacy	Rapid Dissolution	Several minutes	Several minutes	
Dissolving	High efficacy	Low efficacy	Dependent on formulation	Several minutes to week	Several minutes	
Hydrogel	Low efficacy	High efficacy	Slow release of diffusion	Several hours	Several hours	

Comparison of transdermal patches with hypodermic needles for the administration of drugs [19]



Hypodermic needle

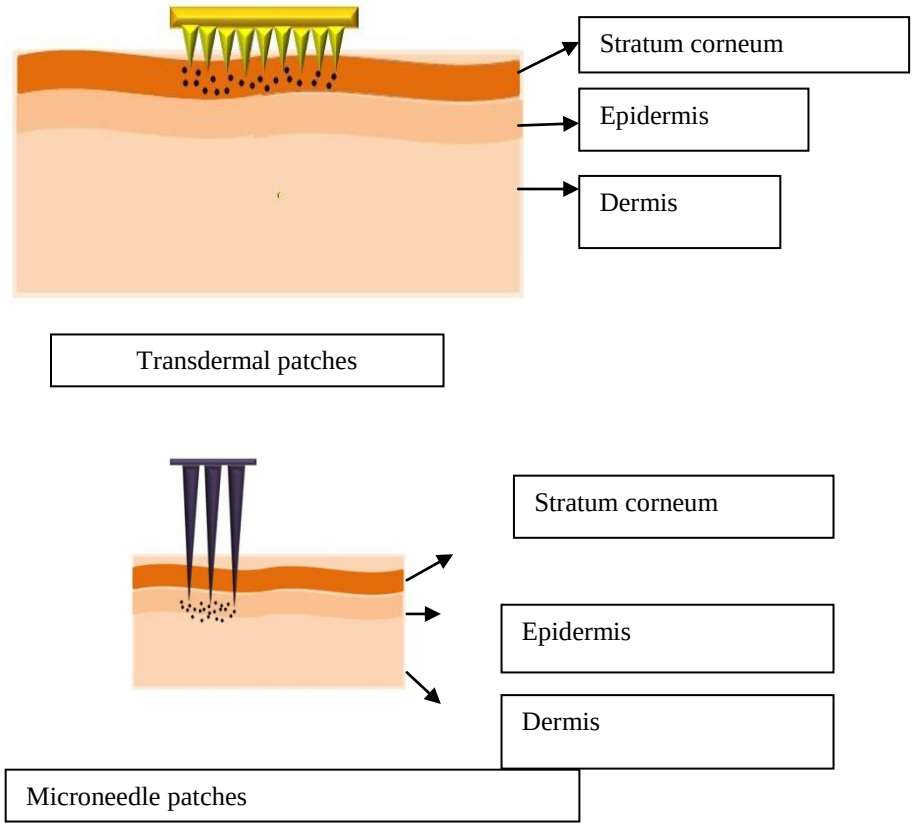


Fig 3-Comparative Analysis Of Hypodermic Needle, Transdermal Patches, Microneedle Patches

Microneedle arrays: Recent Research

Transdermal medication administration typically involves the use of hypodermic needles, whereas topical lotions only penetrate minimally beneath the skin's surface[32].However, because to their discomfort, hypodermic needles are not generally accepted.The main issue with transdermal patches is that some medication molecules cannot adequately enter the skinOnly a select few compounds, such as lipophilic and low-molecular-weight molecules, medicines, can get by way of the stratum corneum, which works likes strong obstacle.[32] In order to reach the skin's microcirculation and achieve Devices that only provide minor trauma to the stratum corneum include microneedle arrays.and allow for systemic dissemination via transdermal channels.Microfabrication, a process used to create microneedles, has been reported to produce them with an average height of 50–900 m, diverse forms, as well as substances like metals, silicon, and polymers. [33].They are tall adequate to pierce and the dermis small enough to prevent piercing the dermal vascular systemor triggering skin nerves. a microneedle is applied toward the skin'ssurface-level painless puncture skin; epidermis to create tiny the pores in water from which medications can enter and distribute throughout the skin's microcirculation [34].A microneedle tool combines the advantages of a transdermal patch and a hypodermic needle into a single small patch made up of needles that are only a few microns long [35].The stratum corneum may now be penetrated by hydrophilic and high-molecular-weight substances thanks to the development of sophisticated microneedle technology [35].These defining features of the technology include higher compliance with treatment instructions, self-administration, improved biodistribution, and efficiency[35]. It also has a speedier start to action (quicker administration), and it is more efficient.Microneedles make temporary compliance with treatment instructions, self-administration, improved biodistribution, and efficiencys inside stratum corneum in order to inject skin-impermeable medications through them.The diffusion rate of drugs into the interstitial fluid and microvasculature of the skin is affected by micropore closure following microneedle-based drug delivery, which is another crucial factor in the evaluation of microneedles [36].

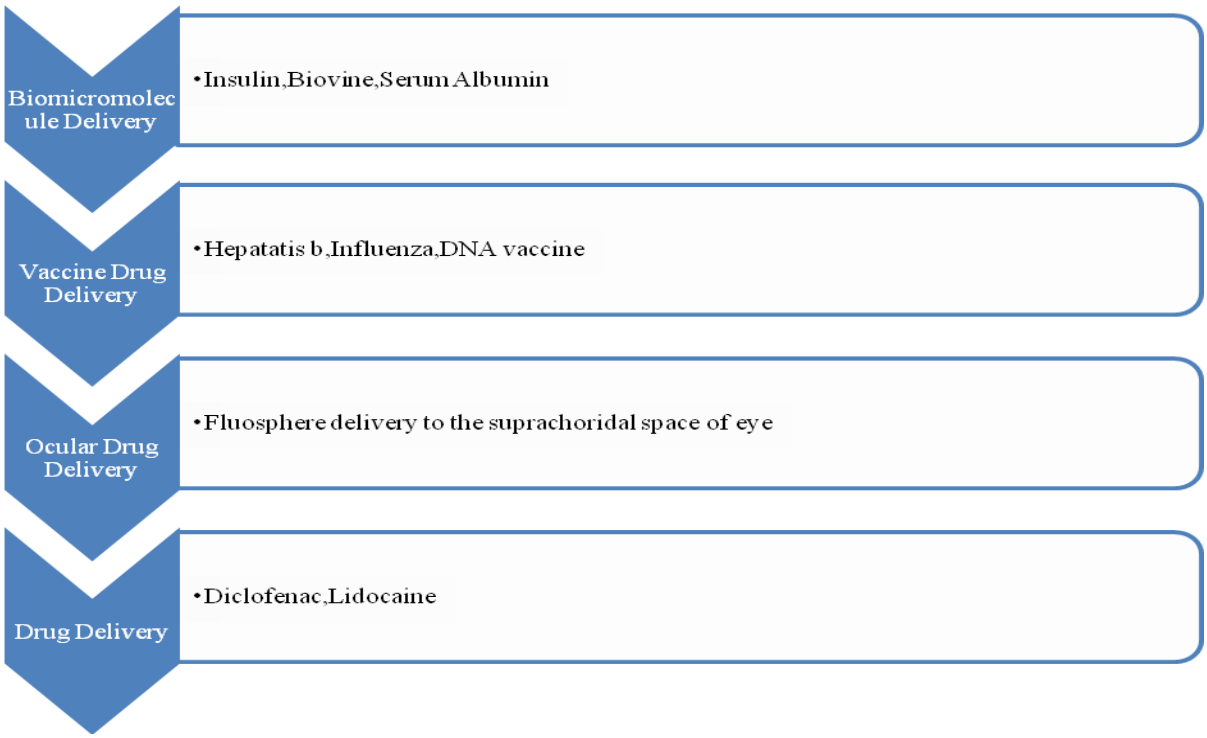
Material Used for Microneedle Patches [37-38].

Materials	Silicon	Glass	Ceramic material	carbohydates	Polymer	Metals
Advantages	Biocamptabile, hard., Maturation fabrication technique	Chemical inert, Cheap	Natural porous	Biodegradable, biocomp-tible	Biodegradable,easy fabrication	Biocomaptability,high conductivity
Disadvantage	Sharp Waste brittle	Fabricatio-n,briitle	Long fabricatio n time	High processing temperature,hygroscopicity	Low mechanical strength	High cost for nobel metals
Application	Solid Coated Hollow microneedles	Hollow micronee-dle	Hollow, dissolving needle	Dissolving microneedle	All types of microneedle	All types of microneedle

Formulation Used In Microneedle Patches[59] Polymer.

Drug	Polymer	Material used	Types	Ref no
Dihydroergotamibe mesylate	PVP	Carbohydrates	Dissolving	49
Exendin-4	carboxymethylcellulose	Carbohydrates	Dissolving	50
Vitamin k	Gantrez s-97	Carbohydrates	Dissolving	51
Glucose	Methacrylated HA	-	Swellable	52
FITC dextran	Silk fibroin	-	Swellable	53
Lidocaine	Carboxymethyl cellulose	Silicon, glass,carbohydraytes	Hollow	54-58
Lysozyme	PVP	Silicon, glass	Dissolving	59

Application of microneedle transdermal patches.



Biomicromolecules Drug Delivery.

The advancement of these technologies facilitating the delivery of biotherapeutics and biomacromolecules such as peptides, insulin, growth hormones, and immunobiological proteins.Some extremely specific examples include gelatin, bovine serum albumin, and insulin-loaded dissolvable starch microneedles.[60]

Vaccine drug delivery

Vaccine delivery by in order to avoid painful injection sites, MN's technology is intended to change hypodermic needles.Kommareddy et al. In guinea pigs, influenza subunit vaccine-coated microneedle patches were used to see if they might elicit immunological reactions that were similar to those induced by intramuscular injections. [61]for the purpose of COVID-19, Kim et al. [62] discuss by means of microneedle technology to deliver the recombinant coronavirus immunisation through the skin.Their research aided in the clinical creation of recombinant protein subunit vaccines based in Minnesota against COVID-19, SARS, MERS, and other newly newly infectious illnesses [62]. Using this technology, SARS-CoV-2 S1 subunit vaccines were delivered, resulting in strong, 2 weeks after vaccination, antigen-specific antibody responses.

[62]Ocular drug deliveryThis technology enabled the delivery of Covid-19 virus S1 subunit vaccines that produced strong, 2 week-long antigen-specific antibody responses.

For opthalmic drug transport, MN-based approaches have been observed to be better effectivecange than topical application. Patel et al. successfully tested suprachoroidal medication administration to the retina using a hollow microneedle [63]Researchers found that when monoclonal antibody against angiogenic growth is delivered such a patch on the eyes, the neovascular region is reduced by about 90%. This is according to a model for corneal neovascularization sickness.Contrarily, a synergistic therapeutic benefit is provided by the combination of a sustained release of DC101 with an anti-inflammatory drug (diclofenac) [66].Due to its minimum invasiveness, Putting on an eye patch is called uncomplicated andguarantees adequate patient adherence.A effective home-based care model for many eye conditions is made possible by such an intraocular drug delivery technique [66].In the SCS, microneedle iontophoresis holds the potential to deliver eye medications specifically into the back pole to the eye [65].

Drug delivery

Local anaesthetic has also been administered via microneedling.Baeketal [64] suggested using microneedles in a study to provide quick and painless local anaesthetic.They created a microneedle with lidocaine coating that demonstrated skin penetration in vitro and improved drug delivery for just two minutes [64].Additionally, polymeric microneedles loaded with meloxicam created utilising poly(D,M,S)-siloxane moulds for the treatment of pain.About 100% 60 minutes later, the medication was released., according to in vitro release experiments.Chemotherapeutic drug delivery has also been successfully researched.Tamoxifen and gemcitabine delivery with the aid of MN for the the breast cancer treatment was examined by Bhatnagar and co.. [67].These medications targeted distribution helped minimise negative effects.[67]A NSAID called diclofenac sodium is frequently used to treat symptoms of pain andinflammation in conditions such as arthritis, musculoskeletal problems, toothaches, and other similar conditions.It is said that diclofenac sodium is used topically.Only around 50% of the amount supplied due to reach the pulmonary circulation the drug's extensive presystem effect in the liver.The NSAID patches are more practical and secure than the oral version.Different NSAID tablets were given to rheumatoid arthritis patients.Transdermal NSAID patches guard against adverse effects such ulcers, increased acidity, and stomach bleeding.A bruise, sprain, or strain can be treated with an NSAID analgesic patch.When these patches are administered topically the shape of a transdermal patch, the drug permeates the body and subcutaneous adipose tissue without increasing plasma drug concentrations.[68-71]Pain is frequently a symptom of oral illnesses, including recurrent pharyngitis, pulpitis, apical periodontitis, trigeminal nerve pain, etc.[72]In numerous skin procedures, topical anaesthetic creams made with lidocaine have been utilised extensively [73,74].This is because among the most often used and efficient local anaesthetics in the oral surgery is lidocaine, which has the advantages of a minimal risk of allergy, a rapid onset and modest action's duration [75].Although topical anaesthetics have the advantage of being easier to use, causing no pain or harm, lowering patient dread of pain, and preventing injection pain [76], they are not without drawbacks.An topical oral mucosal anaesthesia patch with a microneedle adhesive (Li-HAMNs) characteristics of penetration, more quickly and effectively painlessness, minimal intrusion, simplicity of use, and wet adhesion has been created using a fabrication technique that is inspired by Lego brick stacking.These Li-HAMNs, which might withstand the flexing and extending of the muscles used for chewing as well as saliva's flushing effects,were made up two parts: the PVA/CMC-Na wet-adhesive backing layer and the LDC-loaded tips, which dissolve quickly.A new transdermal drug delivery device uses microneedles (MNs), which can minimally pierce the cuticle's physical barrier [77].Four subcategories of MNs have been identified: Drug-loaded, hollow, solid, and evaporating MNs [78].They include removing tiny needles , which are strong enough to breach the cuticle and dissolve in bodily to release bioactive compounds [79-81]. DMNs are made by combining biodegradable polymers with biocompatible bioactive ingredients [82-84].Dermal anaesthetic DMNs have been the subject of numerous studies to date [85-89] and lidocaine DMNs have been employed to improve local anaesthetic distribution to the skin [81].

Future prospect

3D Printing

Microneedle production has been carried out utilising entry-level 3D printers as 3D printing technology develops.3D printers are easily used for a variety of purposes due to their low cost of purchase and upkeep.The creation of unique forms for microneedles is made possible using CAD software.The quick production and alteration of prototypes made possible by 3D printing can drastically reduce the time required for product development.Materials available for use are constrained, and entry-level 3D printers with poor resolution continue to be an issue.Although there are 3D printers with excellent resolution, the cost of the equipment is significant.However, 3D printing research has persisted in overcoming the restrictions.We anticipate that 3D printing technology will make it possible to create individualised microneedle patches depending on individual symptoms

CONCLUSION

Transdermal patches are the adhesive gives prolong release over period of time . Different type of microneedle are gives different prolong action by using different material.Microneedle patches gives prolong effect than the trandermal patches .MN` patches are used for different delivery system such as biomacromolecular drug delivey,vaccine delivery,ocular delivery,local action by using diifernet formulation method.

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