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Transdermal Drug Delivery System: A Tool for Novel Drug Delivery System

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Abstract

The human skin is a readily accessibl esurface for drug delivery. Skin of an average adult body covers a surface of approximately 2m2 and receives about one- third of the blood circulating through the body. Over the past decades, developing controlled drug delivery as become increasingly important in the pharmaceutical industry. The human skin surface is known to contain, on anaverage, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessibl eorgans of the human body. There is considerable interest in the skin as a site of drug application both for local and systemic effect.

However, thes kin, in particular the stratum corneum, poses a formid able barrier drug penetration there by limiting topical and Transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and Transdermal delivery syste(NDDS).

Keywords: NDDS, Transdermal, Imporance

Introduction

Optimumtherapeuticoutcomesrequirenot onlyproperdrugselectionbutalsoeffectivedrug delivery.Thehuman skinisareadilyaccessible surfacefordrugdelivery.Overthepastthreedecade s, developingcontrolleddrugdeliveryhasbecomei ncreasinglyimportantinthepharmaceutical ind ustry.Thepharmacologicalresponse,both thedesiredtherapeuticeffectandtheundesiredad verseeffect,ofadrugisdependenton theconcentrationofthedrugatthesiteofaction,w hichinturn dependsuponthedosageformandtheextent ofabsorptionofthedrugatthesiteofaction[1].Oneh ighlysuccessfulalternative deliverymethodisthetransdermal. Skinofanaverageadultbodycoversa Surfaceof approximately 2m2andreceivesaboutone- thirdofthebloodcirculatingthroughthebody.Th e deliveradrugintothebodythroughtransdermal la yerofskin,itisnecessarytounderstandaboutthesk in. A)Thestratified,vascular,cellularepidermis,B) Underlyingdermisofconnectivetissuesand C)Hypodermis.

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Themultilayeredepidermisvariesinthickness,dependingoncellsizeandnumberofcelllayersofepidermis,rangingfrom0.8mmonpalmsandsolesdownto0.06mmontheeyelids.Table1givesthickness,waterpermeabilityanddiffusivityofwaterthroughepidermis.a)Stratumcorneum

Thisistheoutermostlayerofskinalsocalledashorneylayer.Itisapproximately10µmthickwhendrybutswellstoseveraltimesthisthicknesswhenfullyhydrated.Itcontains10to25layersofdead,keratinizedcellscalledcorneocytes.Itisflexiblebutrelativelyimpermeable.Thestratumcorneumistheprincipalbarrierforpenetrationof drug. Thearchitectureofhorneylayermaybemodeledasawall-

likestructure.Inthismodel,thekeratinizedcellsfunctionasprotein“bricks”bilayersThereissufficientamphiphilicmaterialinthelipid fraction,suchaspolarfreefattyacidsandcholesterol,tomaintaina bilayerform.

b)Viableepidermis

Thisissituatedbeneaththestratumcorneumandvariesinthicknessfrom0.06mmontheeyelidsto0.

8mmonthepalms.Goinginwards,itconsistsofvariouslayersasstratumlucidum,stratumgranulosum,stratumspinosumandthestratumbasal.Inthebasalelayer,mitosisofthecellsconstantlyrenewstheepidermisand

thisproliferationcompensatesthelossofdeadhorneycellsfromtheskinsurface.Asthecellsproducedbythebasallayermoveoutward,

theyalter morphologically. Dermis

Dermisis3to5mmthicklayerandiscomposedofamatrixofconnectivetissue,whichcontainsbloodvessels,lymphvesselsandnerves.Thecutaneous bloodsupplyhasessentialfunctioninregulationofbodytemperature.Italsoprovidesnutrientsandoxygentotheskinwhileremovingtoxinsandwasteproducts.Capillariesreachtowithin0.2mmofskinsurfaceandprovidesinkconditionsformostmoleculespenetratingtheskinbarrier.

Hypodermis

Thehypodermisorsubcutaneousfat tissuesupportsthedermisandepidermis.Itservesasafatstorage area.

Thislayerhelpstoregulatetemperature,provides nutritionalsupportandmechanicalprotection.Thetransdermaldrugdelivery,drughastopenetratethroughallthesethreelayersandreachintosystemiccirculationwhile

oftopicaldrugdeliveryonlypenetrationthincase

rough stratumcorneumisdesired.

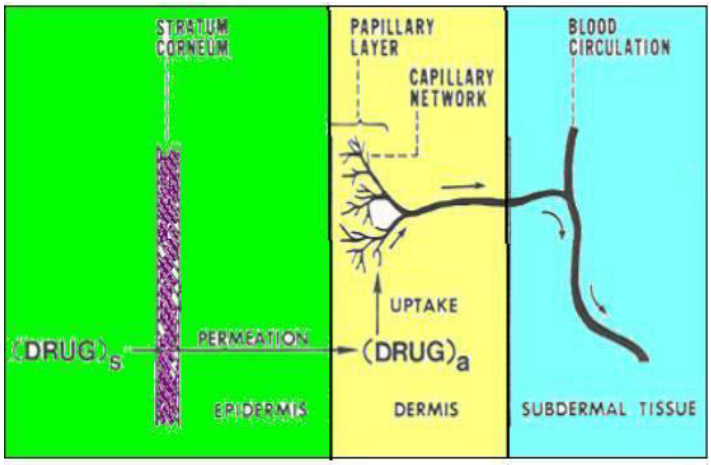
Fundamentalsofskinpermeation[6]

Untilthelastcenturytheskinwassupposedtobeimpermeablewithexceptiontogases.However,inthecurrentcenturythestudyindicatedthepermeabilitytolipidsolubledrugs.Alsoitwasrecognizedthatvariouslayersofskinarenotequallypermeablei.e.epidermisislesspermeablethandermis.Afteralargecontroversy,alldoubtsaboutstratumcorneumpermeabilitywereremovedandusingisotopictracers.

A.Stratumcorneumasskinpermeationbarrier

Theaveragehuman skin contains40-70 hairfolliclesand200-250sweatductspersquare centimeter.Especiallywater-

solublesubstancespassfasterthroughtheseducts,stilltheseductsdon’t contributemuchforskinpermeation.



Thereforemostneutralmolecules Regionalvariationinwaterpermeabilityofstratumcorneumshowedin Table1andpermeationofdrugmoleculethroughskinshowedin Figure

2.Seriesofstepsinsequence:

3.Sorptionofapenetrantmoleculeonsurfacelayerofstratumcorneum.

4.Diffusionthroughitandviableepidermisandfinallyreachestodermisandthen

5.Themolecule istakenup intothemicrocirculationforsystemicdistribution.

Figure2:Amultilayerskinmodelshowingsequence ofTransdermalpermeationofdrugforsystemicdeliveryB-Intracellularversestranscellulardiffusion

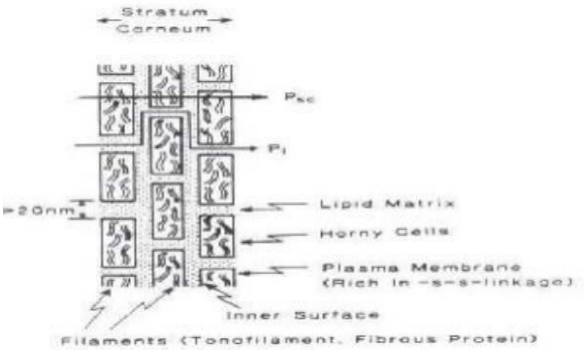


Figure3:Themicrostructureofstratumcorneum

Table1:Regionalvariationinwaterpermeabilityofstratumcorneum

Sr. No.	SkinregionThickness(μm)	Permeationrate (mg/cm2/hr)		Diffusivity (cm2/sec×1010)
1	Abdomen	15.0	0.34	6.0
2	Volarforearm	16.0	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13.0	0.85	12.9
5	Scrotum	5.0	1.70	7.4
6	Backofhand	49.0	0.56	32.3
7	Palm	400.0	1.14	535.0
8	Plantar	600.0	3.90	930.0

Intracellularregionsinstratumcorneumarefilledwithlipidrichamorphousmaterial.Indrystratumcorneumintracellularvolumemaybe5%to1%infullyhydratedstratumcorneum.

C.Permeationpathways7-9

Percutaneous absorptioninvolvespassivediffusionofthesubstancesthroughtheskin.Amoleculemayusetwodiffusionalroutestopenetratenormalintactskin,theappendagealrouteandtheepidermalroute.

1.Appendagealroute:Appendagealroutecomprisestransportviasweatglandsandhairfollicleswiththeirassociatedsebaceousglands.Theseroutescircumventpenetrationthroughthestratumcorneumandarethereforeknownas“shunt”routes.

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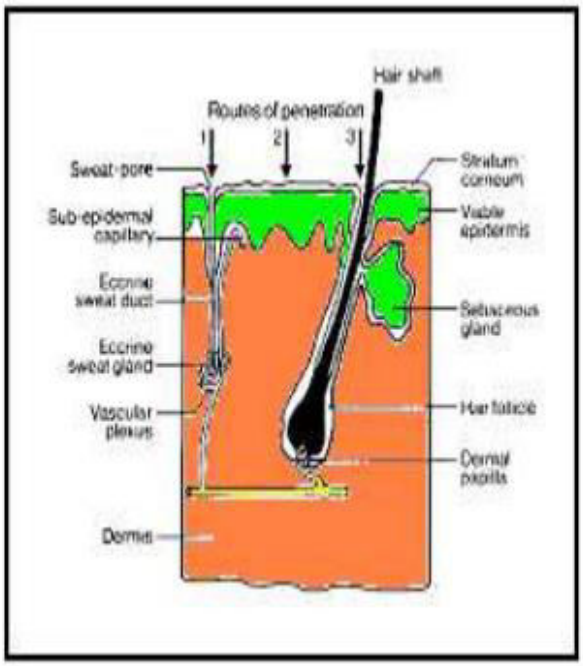

Figure4:Routesfordrugpermeation Fordrugs,which mainlycross-intacthorneylayer,twopotentialmicroroutesofentryexists,thetranscellular(intracellular)andintercellularpathways

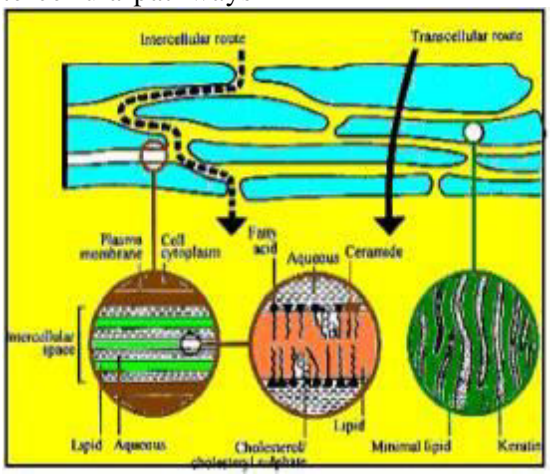

Figure5:Epidermalroutesfordrugpermeation

i)Transcellular:Transcellularpathwaymeanstransportofmoleculesacrossepithelial

1.Epidermalroute: cellularmembrane.Theseincludepassivetransportofsmallmolecules,activetransportofionicandpolarcompoundsandendocytosisandtranscytosisofmacromolecules.

ii)Paracellular:Paracellularpathwaymeanstransportofmoleculesaroundorbetweenthecells.Tightjunctionsorsimilarsituationsexistbetweenthecells.

Theprincipalpathwaytakenbyapermeantisdecidedmainlybythepartitioncoefficient(logk).Hydrophilicdrugspartitionpreferentiallyintotheintracellulardomains,whereaslipophilicpermeantstraversethestratumcorneumviatheintercellularroute.

Propertiesthatinfluencetransdermaldrug delivery10-11

Theeffectivetransdermaldrugdeliverycanbeformulatedbyconsideringthreefactorsasdrug, Skinandthevehicles.Sothefactorsaffectingcanbedividedintwoclassesasbiologicalfactorsandphysicochemicalfactors.

A.Biologicalfactors

i)Skincondition:Acidsandalkalis, manysolventslikechloroform,methanoldamagethe skincellsandpromotepenetration.Diseasedstateofpatientalterstheskinconditions.Theintactskinisbetterbarrierbuttheabovementionedconditionsaffectpenetration.

ii)Skinage:Theyoung skinismore permeablethanolder.Childrensaremoresensitive forskinabsorptionoftoxins.Thus,skinageisoneofthefactoraffectingpenetrationofdruginTDDS.

iii)Bloodsupply:Changesinperipheralcirculationcanaffecttransdermalabsorption.

iv)Regionalskinsite:Thicknessofskin,natureofstratumcorneumanddensityofappendages varysitetosite.

Thesefactorsaffect significantlypenetration.

v)Skinmetabolism:Skinmetabolizessteroids, hormones,chemicalcarcinogensandsomedrugs.Soskinmetabolismdeterminesefficacyofdrugpermeatedthroughtheskin.

vi)Speciesdifferences:Theskinthickness,densityofappendagesandkeratinizationofskinvariesspeciestospecies,soaffectsthepenetration.

B.Physicochemicalfactors

i)Skinhydration:Incontactwithwatertheperpermeabilityofskinincreasessignificantly.Hydrationismostimportantfactorincreasingtheperpermeationofskin.Souseofhumectantisdoneintransdermaldelivery.

ii)TemperatureandpH:Thepermeationofdrugincreasetenfoldswithtemperaturevariation.

Thediffusioncoefficientdecreasesastemperatur efalls.
Weakacidsandweakbasesdissociatedependingo nthepHandpKaorpKbvalues.Theproportionofu concentration nionizeddrugdeterminesthedrug in skin.
iii)Diffusioncoefficient:Penetrationofdru gdependsondiffusioncoefficientofdrug.Ataco nstanttemperaturethediffusioncoefficient ofdrugdependsonpropertiesofdrug,diffusion mediumandinteractionbetweenthem.
iv)Drugconcentration:Thefluxisproportion altotheconcentrationgradientacrossthebarrier andconcentrationgradientwillbehigheriftheco ncentrationofdrugwillbemoreacrossthebarrier.
v)Partitioncoefficient:Theoptimalpartition coefficient(K)isrequiredforgoodaction.Drugs with highKarenotreadytoleavethelipidportionofski n.Also,drugswith lowK will notbepermeated.

vi)Molecularsizeandshape:Drugabsorptioni sinverselyrelatedtomolecularweight,smallmole culespenetratefasterthanlargeones.
Idealmolecularpropertiesfortransderma ldrugdelivery[12]
Fromtheaboveconsiderationswecanconcludewi thsomeobservationsthatcantermedasidealmole cularpropertiesfordrugpenetration.Theyareasf ollows.

- Anadequatesolubilityinlipidandwaterisnecessaryf orbetterpenetrationofdrug(1mg/ml).
- Optimumpartitioncoefficientisrequiredforgoodt herapeuticaction.
- Lowmeltingpointofdrugisdesired (<200°C).
- ThepHofthesaturatedsolutionshouldbeinbetween 5to9.

Designoftransdermaldeliverysystem[10]
Thebasiccomponentsofanytransdermal deliverysysteminclude thedrugdissolvedor dispersedinaninertpolymermatrixthat providessupportandplatformfordrugrelease.T herearetwobasic designsofthepatchsystemthatdictatedrugreleas echaracteristicsandpatchbehavior:
i)MatrixorMonolithic:Theinertpolymermat rixbindswiththedrugandcontrolsit'sreleasefro mthedevice.
ii)ReservoirorMembrane:Thepolymermatri xdoesnotcontroldrugrelease.Instead,arate-controllingmembranepresentbetweenthedrug matrixandthe adhesive layerprovidestherate-limitingbarrierfordrugreleasefromthedevice.
Technologiesfordevelopingtransdermald rugdeliverysystems[4,6,11]
Thetechnologiescanbeclassifiedinfourbasicapp roaches:
A)Polymermembranepartition-controlledTDDsystems Inthistypeofsystems ,thedrugreservoirissandwichedbetweenadrug-impermeablebackinglaminateandaratecontrolli ngpolymericmembrane.

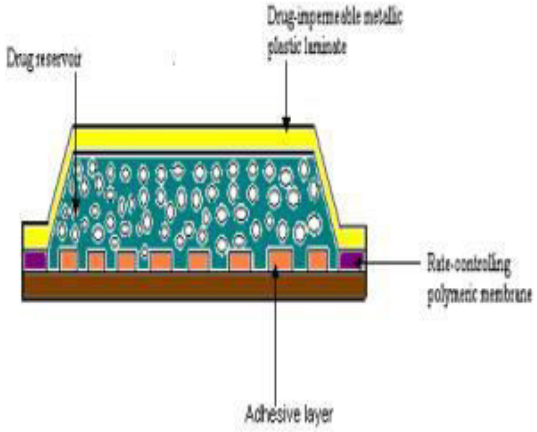

Figure6:Cross-sectionalviewofpolymermembraneperme ation-controlledTDDsystems
Thedrugisallowedtopermeateonlythroughthera tecontrollingmembrane.Thedrugsolidsarehom ogeneouslydispersedinasolidpolymermatrix,su spendedinanunleachable,viscousliquidmedium .
formacleardrugsolution.Theratecontrollingme mbranecanbeeither a microporousoranonporouspolymericmembrane e.g.ethylene-vinylacetatecopolymer,withspecificdrugperm eability.Ontheexternalsurfaceofthepolymeric membraneathinlayerofdrug-compatible,hypoallergenicpressuresensitivead hesivepolymere.g.siliconeadhesivemaybeappli edtoprovideintimatecontactofTDDSwiththesk insurface.

Varyingthecompositionof drugreservoirformulation,thepermeabilitycoe

fficientandthicknessofratecontrollingmembranecanalterthedrugreleaserate.
e.g.SomeFDAapprovedsystems– Transderm-Nitroforanginapectoris,Transderm-Scopformotionsickness,Catapres-TTSsystemforhypertension.
TheintrinsicrateofdrugreleasefromthistypeofTDDsystemisdefined by

$$\frac{dQ}{dt} = \left(\frac{K_{m/r} K_{a/m} D_a D_m}{K_{m/r} D_m h_a + K_{a/m} D_a h_m} \right) C_R$$

where,
Km/rthepartitioncoefficientforthe interfacialpartitioningofdrugfromthe reservoirtothemembrane.
Ka/mthepartition coefficientforthe interfacialpartitioningofdrugfrommembranetoadhesive.
Dadiffusioncoefficientinratecontrolling membrane.
Dmdiffusioncoefficientinadhesivelayer.
hathicknessofratecontrollingmembrane.
hmthicknessofadhesivelayer.
B)Polymermatrixdiffusion-controlledTDDsystemsInthissystem,thedrugreservoirisformedbyhomogeneouslydispersingthedrugsolidsinahydrophilicorlipophilicpolymermatrixandthenthemedicatedpolymerformedismoldedintomedicateddiskswithdefinedsurfaceareaandthickness.Thisdrugreservoircontaining polymerdiskisthenmountedonocclusivebaseplateinacompartmentfabricatedfromadrug-impermeableplasticbacking.

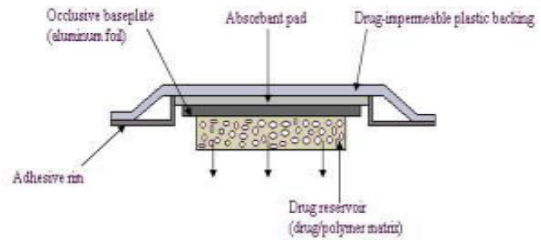

Figure7:Cross-sectionalviewofpolymermatrixdiffusion-controlledTDDsystems.
Therateofreleasefrompolymermatrixdrugdispersion-typeis

$$\frac{dQ}{dt} = \left(\frac{L_d C_P D_P}{2t} \right)^{1/2}$$

where,
Ldisdrugloadingdoseinitiallydispersedinpolymermatrix.
CPissolubilityofdruginpolymermatrix.
fusivityofdruginpolymermatrix.
igdissolvedinpolymermatrixcandiffuse
cticallyequaltoCR.
Alternately,thepolymermatrixdrugdispersion-typeTDDScanbefabricatedbydirectlydispersingdruginapressure-sensitiveadhesivepolymere.g.polyacrylateandthencoatingthedrug-dispersedadhesivepolymerbysolventcastingorhotmeltontoaflatsheetofdrug-impermeablebackinglaminatetoformasinglelayerofdrugreservoir,thisyieldsathinner patch.eg.Minitransystem,Nitro-DurIIsystemforanginapectoris.

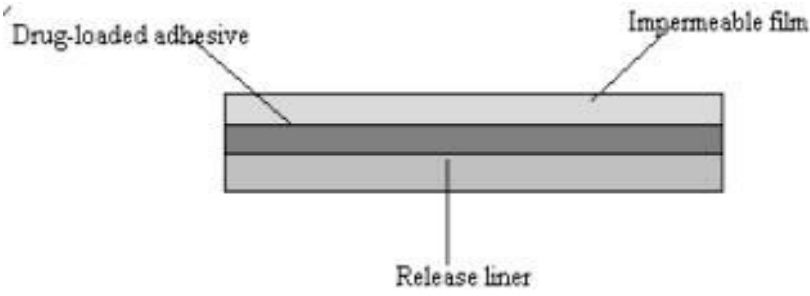

Figure8:Crosssectionalviewofanadhesivepolymerdrugdispersion-typeTDDsystemshowingvariousmajorstructurecomponents.
C)Drugreservoirgradient-controlledTDDsystemsPolymermatrixdrugdispersion-typeTDDScanbemodifiedtohavethedrugloadinglevelvariedinanincrementalmanner,formingagradientofdrugreservoiralongthediffusionalpathacrossthemultilaminateadhesivelayers.Thedrugrelease fromthistypeofdrugreservoircontro gradient-lledTDDScanbeexpressedby:

$$\frac{dQ}{dt} \quad \text{Da} \quad \text{KFa/r} \quad \text{ha(t)}$$

Ld(ha)

Inthissystem,thethicknessofdiffusionalpaththroughwhichdrug moleculesdiffuseincreaseswithtimei.e.ha(t).Thedrugloadinglevelinthemultilaminateadhesive layer isdesignedtoincreaseproportionallyi.e.Ld(ha)soastocompensatetimedependentincrease indiffusionalpathas

aresultofdrugdepletionduetorelease.

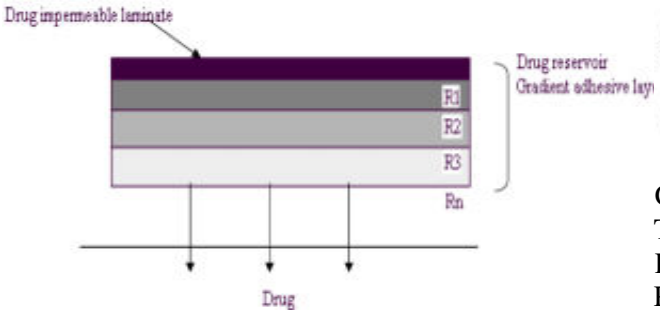

Figure9:Cross-sectionalviewofadrugreservoirgradient-controlledTDDsystem.

D.Microreservoirdissolution-controlledTDDsystems

Ahybridofreservoirandmatrixdispersion-typedrugdeliverysystems,whichcontainsdugreservoirformedbyfirstsuspendingthedrugsolidsinanaqueoussolutionofwater-miscibledrugsolubilizere.g.propyleneglycol,thenhomogeneouslydispersingthedrugsuspensionwithcontrolledaqueous solubilityinalipophilicpolymerbyhighshearmechanicalforcetoformthousandsofunleachablemicroscopicdrugreservoirs.

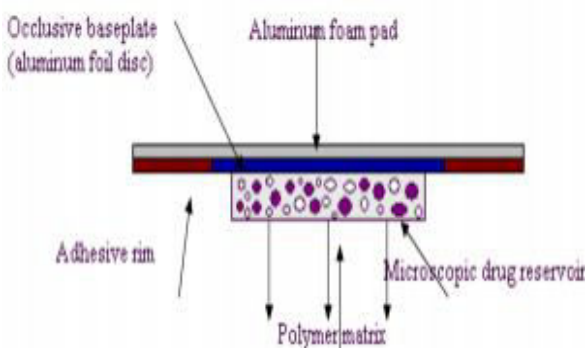

Figure10:Cross-sectionalviewofMicroreservoirdissolution-controlledTDDsystemsThisthermodynamicallyunstablesystemis quicklystabilizedbyimmediatelycross-linkingthepolymerchainsinsitu,whichproducesamedicatedpolymerdiskwithaconstantsurfaceareaandafixedthickness.Medicateddiskismountedatthecenterof anadhesivepad.

eg.Nitrodisksystemforanginapectoris.

Therateofdrugreleasefromthissystemisdefined by:

$$\frac{dQ}{dt} = \frac{D_p D_s A K_p}{D_p h_d + D_s h_p A K_p} \left(\frac{{}_E F_{Alr} D_1 S_1 \left(1 - B\right)}{B S_p \quad h_1} \left[\frac{1}{K_1} - \frac{1}{K_m} \right] \right)$$

ComponentsofTDDS[13]

Themaincomponentsofatransdermalpatchare:i. ReleaseLiner

Protectsthepatchduringstorage.Thelinerisremovedpriortouse.

ii.Drugreservoir

ThemostimportantpartofTDDSisdrugreservoir.Itconsistsofdrugparticlesdissolvedordispersedinthematrix.Tomakethedrugsoluble,solventsandcosolventsareused.Theeffectofsolventandcosolventshouldbeconsideredwhiledoingselection.

iii.Adhesive

Servestoadherethecomponentsofthepatchtogetheralongwithadheringthepatchtotheskin.Theadhesivemustpossessufficientadhesionpropertysothatthe TDDSshouldremaininplaceforalongtime.Pressuresensitiveadhesivesarecommonlyused fortransdermalpatchtoholdtheskin.Commonly usedadhesivesaresiliconeadhesives,polyisobutylenesadhesivesandpolyacrylatebasedadhesives.

iv.Membrane

Membranecontrolsthereleaseofthedrugfromthereservoirandmulti-layerpatches.Itmayormaynotcontainrate-controllingmembrane.Itshouldbeflexibleenoughnottosplitorcrackonbendingorstretching.Someofrate-

controllingmembranesarepolyethylene sheets,ethylenevinylacetateco-polymerandcelluloseacetate.

v.Backing

Protectsthepatchfromtheouterenvironment. Thebackinglayershouldbeimpermeabletodruga ndpenetrationenhance_.Itserves

afunctionofholdingtheentirestemandprotectsdr ugreservoirfromatmosphere.Thecommonlyuse dbackingmaterialsarepolyesters,aluminizedpol yethyleneterepthalateandsiliconizedpolyethyle neterepthalate.

Generalclinicalconsiderationsintheuseof TDDS[7,13]

Thepatientshouldbeadvisedofthefollowinggen eralguidelines.Thepatientshouldbeadvisedofthe importanceofusingtherecommendedsiteandrot atinglocationswithinthesite.Rotating locationisimportanttoallowtheskintoregainits normalpermeabilityand topreventskinirritation.

1.TDDSshouldbeapplied toclean,dryskinrelativelyfreeofhairandnotoily,i nflamed,irritated,broken.Wetormoistskincana cceleratedrugpermeationtime.Oilyskincanimpa irtheadhesionofpatch.Ifhairispresentatthesite,i tshouldbecarefullycut,notwetshavednorshoulda depilatoryagentbeused.

2.Useofskinlotionshouldbeavoidedattheapplica tionsite,becauselotionsaffectthehydrationofsk inandcanalterpartitioncoefficientofdrug.

3.Patientshouldnotphysicallyalter TDDS,sincet hisdestroysintegrity ofthesystem.

4.Theprotectingbackingshouldberemovedwith carenottotouchfingertips.TheTDDSshouldbepr essedfirmlyagainstskinsitewiththeheel ofhandforabout10seconds.

5.ATDDSshouldbeplacedatasitethatwillnotsubjecti ttobeingrubbedoffbyclothingor movement.TDDSshouldbeleft onwhenshowering,bathingorswimming.

6.ATDDSshouldbewornforfullperiodasstatedinthe product'sinstructionsfollowedbyremovalandr eplacementwithfreshsystem.

7.Thepatientorcaregivershouldcleanthehandsaftera pplyingaTDDS.Patientshouldnotrubeyeortouch themouthduringhandlingof thesystem.

8.Ifthepatientexhibitssensitivityor intolerancetoaTDDSorifundueskinirritationres ults,thepatientshouldseekreevaluation.

9.Uponremoval,ausedTDDSshouldbefoldedinitshal fwiththeadhesivelayertogethersothatitcannotb ereused.Theusedpatchdiscardedinamannersafet ochildrenandpets.

Figure11:Useoftransdermalpatch Itisimp ortanttouseadifferentapplicationsiteeverydayt oavoidskinirritation.

Suggestedrotationis:

Day1–Upperrightarm

Day2–upperrightchest

Day3–Upperleftchest

Day4–Upperleftarm,

thenrepeat fromDay1.

Table2:Examplesofmarketedtransderm aldrugdeliverysystem[4]

Sr.No.	TherapeuticagentTDDSDesign		
1	Clonidin e	Catapres-TTS(Boehringer Ingelheim)	Four-layerpatc h
2	Estradiol	Estraderm(Novarti s)	Four-layerpatc h
3	Estrad iol	Vivelle(Novartis)	Three-layersystem
4	Estrad iol	Climara(Novartis)	Three-layersystem
5	Fentan yl	Duragesic(Janssen)	Four-layerpatch
6	Nicoti ne	Prosstep(Lederie)	Multilayerr oundpatch
7	Testos terone	Testoderm(Alza)	Three-layerpatch
8	Nicoti ne	Habitrol (NovartisConsume r)	Multilayerr oundpatch

9	Nicotine	NicodermCQ(SmithklineBeecham Consumer)	Multilayer rectangular patch
10	Nicotine	Nicotrol (McNellConsumer)	Multilayer rectangular patch

Transdermalpatches[9] Bothtopicalandtransdermalproductsare intendedforexternal application.However,topicaldermatologicalproductsareintendedforlocalactionwhereastransdermaldrugdeliverysystemisusedforsystemicdrugdelivery.
Transdermalsystemdeliversmedicationsthroughtheskindirectintothebloodstream.The transdermalrouteofdrugdeliveryisbecomingpopularbecauselarge numberofdrugscanbedeliveredbythisroutetotreatvariousdiseases.Currently,transdermalpatchesareusedinseveraltherapeuticareaslikepainmanagement,smokingcessation,treatmentofheartdisease,hormonereplacementandmanagementofmotionsickness.

TYPESOFTRANSDERMALPATCHES:[18-22]

a)Singlelayerdruginadhesive: Inthistypetheadhesivelayercontainsthedrug.Theadhesivelayernotonlyservestoadherethevariouslayerstogetherandalsoresponsibleforthereleasingthedrugtotheskin.Theadhesivelayerissurroundedbyatemporarylinerandabacking.

b)Multi-layerdruginadhesive:
Thistypeisalsosimilartothesinglelayerbutitcontainsaimmediatedrugreleaselayerandotherlayer willbeacontrolledreleasealongwith theadhesivelayer.Theadhesivelayeris responsiblefortemporaryliner-layeranda permanentbacking.

c)Vapourpatch:
Inthistypeofpatchtheroleofadhesivelayernotonlyservestoadherethevariouslayerstogetherbutalsoservesmarket,commonlyusedforreleasingofessentialoilsindecongestion.Variousothertypesofvaporpatchesarealsoavailableinthemarket whichareusedtoimprove thequalityofsleepandreduces thecigarettesmokingconditions.

d)Reservoirsystem:
Inthissystemthedrugreservoirisembeddedbetweenanimperviousbackinglayerandaratecontrollingmembrane.
Thedrugreleasesonlythroughtheratecontrollingmembrane,whichcanbemicroporous ornon porous.Inthe drugreservoircompartment,thedrugcanbeintheformofa solution,suspension,gelordispersedinasolidcanbeappliedasoutersurfacepolymericmembrane whichiscompatiblewithdrug.

e)Matrixsystem:
i.Drug-in-adhesivesystem:
Inthistypethedrugreservoirisformedbydispersingthedruginanadhesivepolymerandthenspreadingthemedicatedadhesivepolymerbysolventcastingormelting(inthecaseofhot-meltadhesives)onanimperviousbackinglayer.Ontopofthereservoir,unmediatedadhesivepolymerlayersareappliedforprotectionpurpose.
ii.Matrix-dispersionsystem:
Inthistypethedrugisdispersedhomogenouslyinahydrophilicorlipophilicpolymermatrix.Thidrugcontainingpolymerdiskisfixedontoan occlusivebaseplateinacompartmentfabricatedfromadrugimpermeablebackinglayer.Insteadofapplyingthe

adhesiveonthefaceofthedrug.

f)Microreservoirsystem:
Inthistypethedrugdeliverysystemisacombinationofreservoirandmatrix-dispersionsystem.Thedrugreservoirisformedbyfirstsuspendingthedruginanaqueoussolutionofwatersolublepolymerandthendispersingthesolutionhomogeneouslyinalipophilicpolymertoformthousandsofunreachable,microscopicspheresofdrugreservoirs.

Advancesintransdermalpatchtechnology
i)Adhesives:Fortransdermalpatchestoprovideconsistentandcontinuousdrugdeliverythroughtheskin,theymustadherewell.Thereareseveraladhesivesinregularuseintransdermal systemsincludingsiliconesandpolyisobutylenes.Neweradhesives,includingacrylates,haverecentlybecomeavailable.Acrylatesareknownaspressure-sensitiveadhesivesandtheyarepreferredbecausetheyhaveselectiveadhesivepropertiesonceincontactwiththeskin.Pressure-sensitiveadhesivescanalsoberemovedwitheaseandtheyarecompatible

withskinand variousdrugmolecules.Thepolymericnatureofa crylatespreventsthepatchesfromundergoingph ysical breakdown.

i)PenetrationEnhancers:

substanceswillnotdiffuseintotheskMinatysuffcri tratestoobtaintherapeuticconcentrations. Substancesthatreducetheskin'sabilitytoperfor mitsbarrierfunctionarecollectively knownaspenetrationenhancers.Thesesubstances maketheskinmorepermeableandtheyallowdrug moleculestocrosstheskinatafasterrate.Withreg ardtobothsafetyand efficacy,wateristheoptimumpermeationenhan cer.Byincreasingthehydrationofthestratumcor neum,thebarrierfunctionoftheskincanbereduc ed.Alcoholiscommonlyconsideredasolventintr ansdermalpatches;itactuallyservesaseffectivep enetrationenhancer.Somepenetrationenhancers removelipidsfromtheskin.[23-25]

EVALUATIONPARAMETERS:[26]

1.Interactionstudies
2.Thicknessofthepatch
3.Weightuniformity
4.Foldingendurance
5.PercentageMoisturecontent
6.PercentageMoistureuptake
7.Watervapourpermeability(WVP)evaluatio n
8.Drugcontent
9.Uniformityofdosageunittest
10.Polariscopeexamination
11.ShearAdhesiontest
12.PeelAdhesiontest
13.Thumbtacktest
14.Flatnesstest
15.PercentageElongationbreaktest
16.Rollingballtacktest
17.QuickStick(peel-tack)test
18.Probe Tacktest
19.In vitrodrugreleasestudies
20.Invitroskinpermeationstudies
21.SkinIrritationstudy
22.Stabilitystudies

AnimalModelstoStudyTransdermal Absorption[15-17]

Exvivopenetrationandpermeationareroutinelyp erformedtostudypercutaneous absorption andtransdermalpermeationcharacteristicsofdr ugsandotherchemicals.Theseexvivostudies allowthedeterminationofdrugconcentrationin theskin(penetration)andrateoftransfer acrosstheskin(permeation).Exvivoexperiments areeasytoperformandthesimplicityofmethodol ogyallowsflexibilityinadaptingthemodelinad dressingdifferent aspectsinvolvedinpreliminaryorfeasibilitystud iesinthedevelopmentofskin/transdermaldrugd eliverysystems.

Humanskinisdifficulttoobtainanduniformityi sdifficulttomaintain,sincemostofhumanskinc omes fromcadaverswhosesex,ageandgenetichistoryare uncontrolled.Whereas, animalskiniseasiertoobtainandismoreuniform. Humansandanimalshavewidedifferencesinthen umberofappendagealopeningsperunitareathick nessofskin,structureandporosityofskin,andthe sefactorsclearlyaffectthepercutaneousabsorpti onofdrugs.Onlytheprogressininvitromethodol ogywithanappropriate animalmodelcanresolvetheselimitations.Itwou ldbeasimplemathematicalexercisetopredictth eskinpermeabilityinhumansfromanimalexperi ments.Ifthereisconstantratiobetweenskinperm eabilityinhuman toanimal,independentofthedrugunderstudy.Ifc orrelationcanbeestablishedfordrugswithdiffer entphysicochemicalproperties,experimentsusi ngappropriateanimalskinwillbemorereliablein thedevelopmentalstageofskin/transdermaldru gdeliverysystems.Itappearsthathairlessguineapi gandBrattlebororatarebegoodanimalmodelsf orskin/transdermaldrugdeliverysystems,wher easssnakeappearsnottobeagoodmodeltoevaluate permeationofdrugsacrossskin(unpublisheddata).Inreviewingthestudiescomparingtransderma labsorptionof drugsbetweenanimalsandhumans,caremustbeta kento ascertaintheinfluences ofmethodologyandmodelmighthaveonthedata, andutmostcaremustbetakentoavoidanymisinte rpretationorwrongconclusions.Accordingtoth eliteratureavailablenoconsensusisavailable regardinganimalmodelswhichtrulyreflecthum anskin.

Transdermaldrugdeliverysystemshavefollowingadvantagesoverconventionaldrugdelivery.

Advantages[27-29]

1.TheycanavoidgastrointestinaldrugabsorptiondifficultiescausedbygastrointestinalpH,enzymaticactivityanddruginteractionswith food,drinkandotherorallyadministereddrugs.
2.Theycansubstitutefororaladministrationofmedicationwhenthatrouteisunsuitable,asincaseofvomitinganddiarrhea.
3.Theyavoidthefirst-passmetabolismandavoiddrugdeactivationbyliverenzymes.
4.Theyarenon-invasivesoavoidingtheinconvenienceofparenteraltherapy.
5.Theyprovideextendedtherapywithasingleapplication,improvingcomplianceoverotherdosageforms,requiringmorefrequentdoseadministration.
6.Drugtherapymaybeterminatedrapidlybyremovalof Transdermaldrugdeliverysystemsfromthesurfaceoftheskin.
7.Theyareeasilyandrapidlyidentifiedinemergencies(e.g.unresponsive,unconsciousorcomatosepatient)becauseoftheirphysicalpresence,featuresandidentifyingmarkings.
8.Theycanbeusedfor drugswithnarrowtherapeuticwindow.

Transdermaldrugdeliverysystemshavefollowingdisadvantages

Disadvantages

1.Thelimitationsoftransdermaldrugdeliveryaremainlyassociatedwithbarrierfunctionofskin, soitislimitedtopotentdrugmolecules.
2.Skinirritationorcontactdermatitisduetodrug, excipientsandenhancersisanotherlimitation.

FutureofTransdermalTherapy

Tenyearsago,thenicotinepatchhadrevolutionizedsmokingcessation;patientswerebeingtreated withnitroglycerinforangina,clonidineforhypertension,scopolamineformotionsicknessandestradiolforestrogendeficiency,allthroughpatches.Atthattime,biotechmedicinalwasstillbeingdeveloped.Duringthepastdecade,the numberofdrugsformulatedinthepatcheshashardlyincreased,andtherehasbeenlittlechangeinthecomposition ofthepatchsystems.Modificationshavebeenmostlylimitedtorefinementsofthematerialsused.

Conclusion

Successfultransdermaldrugapplicationrequiresnumerousconsiderations.Bearinginmindthatthebasicfunctionsoftheskinareprotectionandcontainment,itwouldseemexceptionallydifficult totargettheskinfordrugdelivery.However,with ourgreater understandingofthestructureandfunctionoftheskin,andhowtoalterthesepropertie s,moreand more newdrugproducts arebeingdevelopedfortransdermaldelivery.Thepropertiesofthedrug,thecharacteristicsofthetransdermaldevice,selectionofin-vivomodelandthestatusofpatient'sskin are allimportantforsafeandeffectivedrugdelivery.Thetransdermaldrugdeliverysystemcouldbeonedayoneofthebest noveldrugdeliverysystem.

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