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Recent advancement of Polymeric transdermal drug delivery system for emetic drug therapy

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Abstract

Thisworkdescribetheformulation and characterization of Ondansetron HCL transdermal patchestomanage and deliverdrugcontentinappropriatemanner. The purpose of this research study focused on the development of polymer base transdermal films containing Ondansetron HCL by solvent evaporation technique and analysis of dissolution kinetics. Auxiliary substances represented an important role in pharmaceutical forms, in first stage, drug content and excipients compatibility were performed and verifiedbetween TDS1 9.80 ± 0.125 $\mu g \cdot cm^{-2} \cdot h^{-1}$TDS3 20.12 ± 0.125 $\mu g \cdot cm^{-2} \cdot h^{-1}$ and TDS8 22.11 ± 0.125 $\mu g \cdot cm^{-2} \cdot h^{-1}$. Release studies were done at36°C transdermal drug delivery system ex-vivo drug permeation study was found optimized results. In-vitro drug release kinetics were done at 32 °C ± 1 °C with a Franz diffusion cell. The results obtained were analysed and confirms the active substances with two matrix-forming polymers of FT-IR. At pH 5.5 to 7.4, flux values were between 15.22 ± 0.125 $\mu g \cdot cm^{-2} \cdot h^{-1}$, 20.12 ± 0.380 $\mu g \cdot cm^{-2} \cdot h^{-1}$; 30.12 ± 0.380 $\mu g \cdot cm^{-2} \cdot h^{-1}$; 40.2 ± 0.380 $\mu g \cdot cm^{-2} \cdot h^{-1}$; 22.11 ± 0.380 $\mu g \cdot cm^{-2} \cdot h^{-1}$; 30.14 ± 0.380 $\mu g \cdot cm^{-2} \cdot h^{-1}$; 50.11 ± 0.380 $\mu g \cdot cm^{-2} \cdot h^{-1}$. Thisstudyconfirmed therate of penetration and creatingnovelapproaches of Ondansetron HCL deliverywithpolymersolution. Thisnovelapproaches of Ondansetron HCL loaded transdermal patcheshasincreasedtheapplication of antiemeticdrug of theirconventionalroutes of drugadministrationviaskindelivery.

Keywords: Drugdeliverysystem, Anti-emetics, Polymericpatch, Skinpenetration.

1. Introduction

OndansetronHClis a highlyselective 5-HT3 receptor-antagonist. OndansetronHCliswidelyprescribedastherapyforanti-emtics and nausea/ ThisOndansetron HCL blocksinititation of thevomitingrelex. Duringchemotherapy and radiationtherapytheagentsproducestheactivation of vegalafferentsby 5-HT3 receptors and causedtherelease of 5HT (serotonin) inthesmallintestineand thesesignalsactivatethevomitingreflexorcausesnausea[1,2]. Inaddition, administration of OndansetronHClinitiatsvomitingreflexblockageinperipheralnerves. OndansetronHClalsorelatedtoassociated, thechemotherapyorradiationtherapyagentsalsocausestheactivation of 5-HT (serotonin) releaseinthearea of postrema, itissitu atedonthefloorof thefourthventricles, itisresponsiblefortheproduction of vomitingreflexcentrally CTZ mechanism[2, 3]. However, OndansetronHClisefficienttomanagetheemesiscentralmechanism. TheChemotherapy and radiationtherapyagentscausestehemesisbecuasethe 5-HT3 receptorsaresituatedbothinperipheralnerves and alsocentral CTZ, thusOndanstronHCliscandidatetomanagethesebothmechanism.Accordingtothestudied, Ondansetrondoesnotalterthenormalfunction of the CNS and notproducesthesedationoranyimpairperformance.Ondansetronaffectedfromtheacidicmedium, theefficacy of thedrugreducesduetothebioavailabilitydecreases. Severalstudiedconcludedefficacy of Ondansetronalteronconventionaldossageform. One of thewell-knowntechniquetoavoidproblemsassociatedwiththeseeffects of OndansetronHClminimizedbyinvolved transdermal drugdeliverysystem. Thissystemprovidedthecontrolleddelivery of thedugintocirculatorysystem and bypassthedrugfrom GIT degradation[4,5,6].

Humanskinisaccesible and prominientsurfaceforOndansetronHCldelivery. Skinhold of anaverageadultbodycoversapproximately 2 x2 and skinrecievedaboutone-theird of bloodcirculationthroughbody. Inadditions, skinonanaverageholds 10-75 hairfollicles and 200-300 sweatductsoneverysquarecentimeter (cm2). However, skinis a choice of routes of drugdelivery, forvariousdruginsafe and by -passroutefrom GIT degredation and flexibleadministration, easetoterminatetheapplication.Inparticularstratumcorneum, layer of theskinproducesthemainbarriersfordrugtoreachthecirculatorysystem and producessystemicresponses. Inadditions, currectstudieddesignedtoenhancedthetopicalapplication, and enhancedtheskinpermeation and improvesbioavailabilityforOndansetronHCl[7,8].Fromthepastdecades, several transdermal drugdeliverysystemweredesigned and impactlittlechangeinthedelivery of drug.

Presentstudyisthemodification of thecomposition and severalbiodegradablepolymersincorporatedwhichleadstonoveldrugdeliverysystem.

Duetoexcellentbarrier of theskin, stratumcorneum (SC), theneedforsafe and effectivemechanismtoimprovetherate of drugpermeation and transdermal absorptionrecognized. Linseedoil, herbaloilsafe and leastsideeffecthasbeenshowntoincreasetheskinabsorptionbyalteringthe transdermal formulationenhancedpermeationratetocrossover SC. Thisstudypreparedanti-emeticdruggroup 5HT-3 antagonistOndansetronHCl, forease and controlleddrugdeliverysystemusinglinseedoil, polymer PVP/PVA (10:5) and plasticizer PEG. Moreover, thedrugrelease, skinpenetration and transdermal physically, chemical and mechanicallywereevaluated [9,10,11].

2. Material and methods

2.1. Materials

OndansetronhydrochloridewaspurchasedfromYaroChemicals, Bangalore, India. Hydroxypropylmethylcellulose (HPMC),Edragit L100,Polyvinylpyrrolidone (PVP), and Polyvinylalcohol (PVA: MW125,000) were obtained fromYaroChemicals, Bangalore, India . Chloroform, Polyethyleneglycol 400, sodiumchloride, and Dibutysebacate (DBS) werepurchasedfromSigma-AldrichChemical. India.Linseedoil, castoroil (pharmaceuticalgrade), EugenolwaspurchasedfromSpectrumChemicals , New Delhi, India.Allotherchemicalswereusedof analyticalgrade.

2.2. Method

2.2.1. Formulation of drug loaded transdermal patches

Ondansetronhydrocholoricacid transdermal patchwerepreparedusingthesolventcastingevaporationmethod. Inthepreparation of trandermalpatch, HPMC k4, Polyvinylpyrrolidone, Eudragit L100 about 420mg and Polyvinylalcoholweremixedin 3ml of phosphatebuffersolution of 5.4pH and formedpolymericsolutionindifferentratiosbyusingmagneticstirre datroomtemperature. ThepuredrugOndansetronHClabout 16mgmixedinpreparedpolmericsolutionapproximately 1.2mg/squarecentimeterpatchmixedbymagneticstirrerfor 30minutes.Thenpouredthetotalmassslowlyatcenter of theglassringwithbackinglayer of alumiumfoilareadyholdit. Thesolutionweredriedunderroomtemperatureapproximately 36-40ºC and driedfor 48hoursunderinvertedconicalfunnelwithcottonplugging of

theglassplatemouldforslowroomtemperatureevaporationforcompletedrying. After 48hours obtainedtheresultantdriedpatch and keptundersealedplasticpouches and storeunderdesiccatorsforfurtherassay and application[12,13].

Fig. 1 2x2 cm^2 drug loaded transdermal patches

2.3. Characterization of drug loaded transdermal patches

OndansetronHClpreparedtrandermalpatchwerecharacterizeddifferentparameter'stoevaluatethe quantitatively and qualitativelystability of itsphysical, chemical, and therapeuticsefficacy.

2.3.1.Physical appearance

OndansetronHClevaluated of itsphysicalstatebeforetreatedwithdifferentpolymers and plasticiser. Thephysicalevaluationincluded, physicalappearance, purity, meltingpoint, assaysolubilitydetermination[14].

2.3.2.Compatibilitystudies

Compatibility of drugOndansetroHClwithdifferentratioorpolymers and plasticiserwereevaluatedbyusing UV-Spectrophotometer (model: Elico SL. 164). ThepreparedpolymericsolutionwithOndansetronispouredout 5ml dilutedin 5.2-7 pHPhosphatebufferexaminedat 310 nmwavelength. Thelinearityrange (ug/ml) and coefficient of correlation and accuracyweredetermined.

2.3.3.Determination of patchthickness

Trandermalpatchthicknessweredeterminedbyusingmicrometer (model: Mitutoyo) and screw-gauge and measuredanyfivedifferentlocations of thepatches. Anaverage of thesesixreadingwasmeasured and recorded.

2.3.4.Determination of drugcontent

Drugcontentevaluatedbymeasuringfive transdermal patchesindividuallyat 249 nmbyusing UV/VisSpectrophotmeter (Model: Lamda 25, PerkinElmer), and recordedthereadingobtained. About 1 cm of patchcutoff and dissolvedin 2 ml of polymericcastingsolution and furtherdilutedwith 5 ml of purifiedwater and filtered.
Thedrugcontentismeasuredbycorrelatethepercentageobtained.
Thisdilutedsolutionisanalysedbyusing UV/visSpectrophometerat 249 nm, and obtainedresultiscomparedwiththefivepatchreadingwithrespecttotheaveragereadingrecorded[14 ,15,16].

2.3.5.Deterniation of moisturecontent

Transdermal patchisweighedindividuallyaboutfivesamplewithdrawn and notetheinitalweight of each. Thesepatchwereplacedunderthedesiccatorat 40-45ºC temperaturemaintained and treatedwithCalciumChloridefor 24 hours. The transdermal patchindividuallyrecordedtheweightafterconstantweightachieved[17].
Thedifferenceinbetweeninitalweight and finalweightiscalculatedwithrespecttotheaveragefourweightistakenforanalysis. Presence of excessmoisturecouldaltertherate of penetration, qualitativelyalterthephysical and chemicalstability of patch.

$$\textbf{\%Moisturecontent} = \frac{\boldsymbol{Initial\ weight - Final\ weight}}{\boldsymbol{Intial\ weight}}\ \boldsymbol{x100}$$

2.3.6.In-vitrodrugreleasestudies

Thein-vitrodrugreleaseprofileevaluatedusingmodifiedFranzdiffusioncell (model, PermeGear). The transdermal patchiscarefullyplacedinbetwenthedonor and receptorcompartment.
Thepatchwasplacedsuchthatthebackingmemberaneopentoatmosphere.
ThePhosphatebuffersolution of pHrange 5.4 to 7.4 isprepared and fillwithtemperaturemaintaing 34 ºC -36 ºC insurroundingjacket.
Thereceptormediumisstarttorotateswiththehelp of magneticstirrerat 50-65 RPM. Transdermal patchagainrecheckeditshouldtouchedtheliquidsurfaceorizontallyformoleculestopassaway.
Intimeinterval of 1 hourto 8 hours, samplefromthecompartmentiswithdrawnfor UV spectroscopyanalysis of percentagein-vitropermeationratedetermination.
Selectedanyfourpatchshouldtreatedsuchway and recordanaveragereadings [18,19].

2.3.7.Ex-vivodrugpermeationstudies

Ex-vivopenetrationstudywasdonebydetermination of thecontentpermeationthroughthrdermalskin of albinomouse. A freshexcised SC section of albinomouseabdominalskinistreatedinisotonicsolution. Prepared transdermal patch (withoutanyinterspace) placedoverthe SC excisedskin of albinomouseintothecompartment. Dermalside of theskintouchedthereceptorsliquidsideinhorizontalposition. Thecompartmentliquidstemperature, concentration, rate of stirring and time of treatmentisdesignedasperthein-vitroanalysedreport. AftertreatmentunderthecompartmenttheEx-vivopermeationreportisgenerated and reportedtheprocedure of averagefivereadingnotedown[20,21,22].

3. Results and discussion

Table 1. Composition of (ODH TDDS) Ondansetron HCL Transdermal Patches.

S. No.	Patch number	Composition polymer 100: PVP/PVA (mg)	Percentage of plasticiser (%)	Texture
1	TDDS1	400:000	10 %	smooth, flex
2	TDDS2	400:000	20 %	smooth, flex
3	TDDS3	400:050	30 %	smooth, flex
4	TDDS4	400:100	20 %	smooth, flex, thick
5	TDDS5	400:150	10 %	Smooth
6	TDDS6	400:200	20 %	smooth, flex, thick
7	TDDS7	400:250	10 %	smooth, flex, thick
8	TDDS8	400:300	10 %	smooth, flex, thick
9	TDDS9	400:350	20 %	flex, thick
10	TDDS10	400:400	20 %	Thick

3.1.1. Physio-chemicalevaluation

Thephysicalevaluationleadssettoshowedthemeltingpointranges 176.0 to 180 ºC byusingdigitalmeltingpointtester (model:Qlab Rd-1), Solubilityshowedwithaqueousphase 0.240mg/mL (roomtemperature). Assayperformedbyusing UV/VsSpectrophotometer and HPLC at 314 nm 98.02 % purity, whitecrystallinepowder.

Table 2: Physicalcharacteristics of TDDS

S. No.	Patch number	Moisture content (wt%)	Drug content ($ugcm^{-2}$)	Water absorption (wt%)	
				75 % RH	93 % RH
1	TDDS1	1.3	426.5	1.32	1.81
2	TDDS2	1.5	429.4	1.36	1.85
3	TDDS3	1.8	430.1	1.38	1.89
4	TDDS4	1.11	435.5	1.41	1.92
5	TDDS5	1.16	438.5	1.45	1.93
6	TDDS6	1.19	441.8	1.46	1.94
7	TDDS7	1.21	448.3	1.48	1.95
8	TDDS8	1.23	450.1	1.51	1.99
9	TDDS9	1.45	452.8	1.53	2.12
10	TDDS10	1.49	455.7	1.56	2.16

3.2. Compatibilitystudies

Compatibility of drugOndansetroHClwithdifferentratioorpolymers and plasticiserwereevaluatedbyusing UV-Spectrophotometer. Drugpenetrate and fixedinthelongchain of PVP and HPMC about 98 % to 99%. Theholdingcapacity of watercontentrevealed PVP increaseduptake of watercontent and providemechanicalstrengthforstrain and stretch.

Thelinearityrange (ug/ml) 100/500 mg/ml concentration of 100(910.0)-200(2008.09)-300(3000.00), coefficient of correlationisobtainedas (0.99) and accuracypercentagewereobtained 99.79%. Ondansetronwerephysically and chemicallystablewithbothpolymer PVP/PVA and HPLC eaqullydistributed.

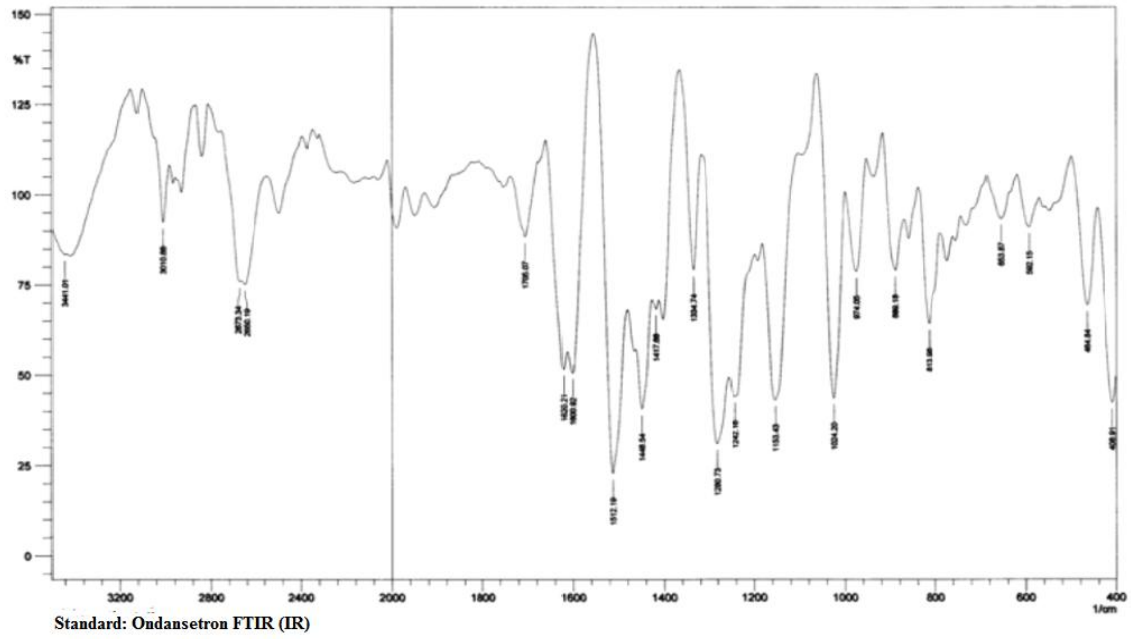

Fig. 2FTIR (IR) standarddeviation of OndansetronHCl

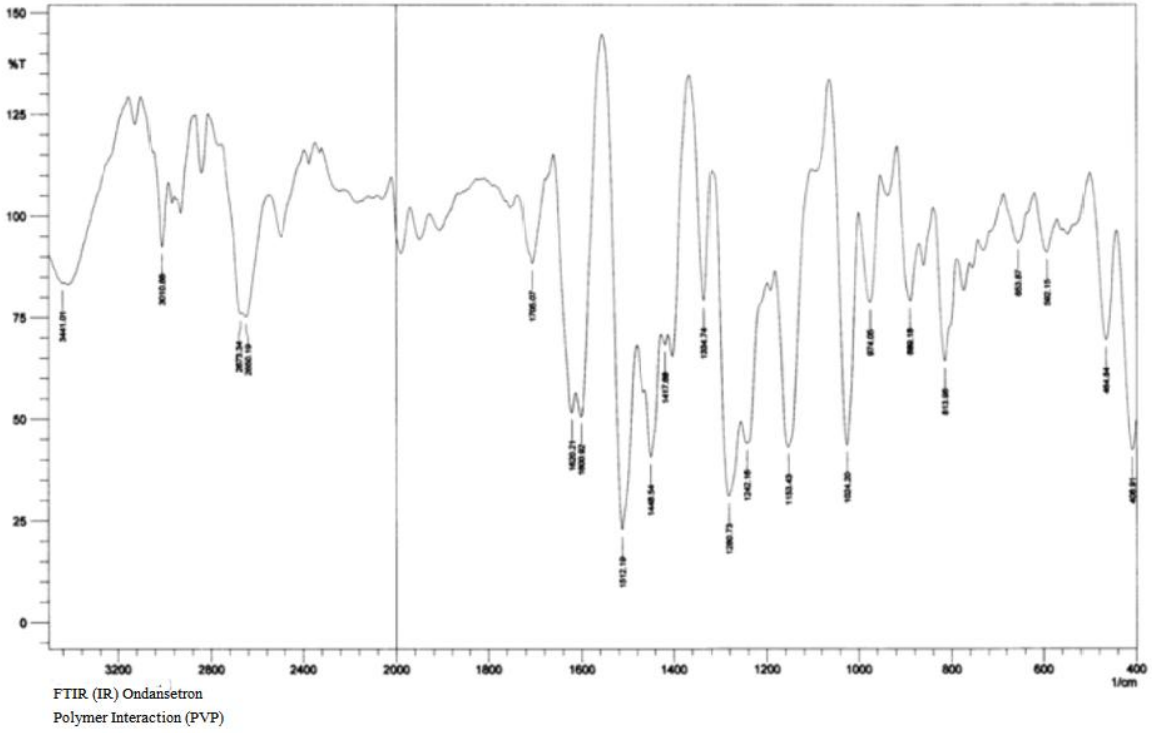

Fig. 3 FTIR (IR) Deviation of OndansetronHClwithPolymerinteraction (PVP)

3.3. Determination of patchthickness

The transdermal patchesthicknesswasvariedfrom 0.121 mm to 0.184 mm of PVP/PVA and 0.105 mm to 0.149 mm of HPLC plasticiserpatch. Thedifference of thethicknessduetothe

PVP/PVA providedmechanicallystable and flexiblepatchcompratively to HPLC patchmorethinduetothepolymerchainlinkage of closeatoms.Tensilstrengthisimprotantforthe transdermal patchitprovidethestrain and stress. Additionallystablepatchprovideease of removablefromthesite of applicationonpealoffforce. PVP/PVA haslowermolecularweightthan HPLC patch, resultinggreaterplasticisingefficacythan HPLC patches.

Table3. Patchtensilestrength and patchthickness.

S. No.	Patch	Tensile strength (mpa)	Patch thickness (mm)
1	TDDS1	6.5	0.118
2	TDDS2	7.54	0.166
3	TDDS3	5.23	0.124
4	TDDS4	4.12	0.184
5	TDDS5	5.1	0.162
6	TDDS6	4.51	0.148
7	TDDS7	5.12	0.154
8	TDDS8	4.22	0.156
9	TDDS9	4.19	0.157
10	TDDS10	5.17	0.167

3.4. Determination of drugcontent

Drugcontentevaluationrevealeddrugwereequallydistributedthroughoutthe transdermal patchitvariesfrom 425.15 ug/cm2 to 430.85 ug/cm2 average of theseisabove 99% of intendedquantity. Determination of drugcontentalsorevealedthedata of uniformilydistributed of drugthroughoutthepatch and providedthewateabsorptionratewerehigherin PVP patchthan HPLC patchabout 75% and 63% respectively. Thisphenomenonisduetothe PVP itallowedhydrophilicdiffusioneasily.

3.5. Deterniation of moisturecontent

Moisturecontentstudiedshowedwaterabsorption and moisturecontentrateinpatch. Lowmoisturecontentpreventthe transdermal patchtocompletelydried and brittle. Accordingtotheresultslowwaterabsorptionrateprovidethestabilitty of patch. Thehigherinwaterabsorptionratemorethickerthepatches. Lowmoisturecontentpreventthemicrobialgrowth, providemechanicalsupport.

3.6. In-vitrodrugreleasestudies

Thein-vitroreleasestudyshowedthedrugpermeationratewiththepolymerinteractionaccordingto transdermal chemical, physical and mechanicalstrength.
Theevaluationrevelaedafteranalysisunder UV Spectroscopycumulativepercentagerelease and releaserate (ug/cm2/h) after 4 to 8 hoursanalysis of transdermlpatch. Itshowedpatchnumber OT2, OT4 and OT9 of linseedoilpenetrationenhancerformulationabuot (46.21%) and Oliveoil (30.09%) exhibits PVP/PVA combinationlinseedoilshownhighestcumulativepercentage of drugreleasethan, oliveoil and Eudragit and elastomerformulations.
Itwasobservedthepercentage of drugreleaseisincreasedwithincreaseintheconcentration of the PVP/PVA combination. Thisresultisbecause of theleaching of hydrophiliccapability of PVP/PVA polymers and formation of moreporeson transdermal patch. Themorepores, themoreopenpathwaytopenetratethedrugfromthepolymerintothemedium, thisphenomenoniscontrolledbythelevel of plasticizers.Accodingtothemobilitybehaviour of polymer and plasticiser, thehigherintheconcentration of plasticiser, theintermolecularattractiveforcesdecreases and resultanthigherinthediffusionrate.
Thereadingwithdrawn and notedintablebelow, aboutthepercentagecumulativerelease of patchnumer OT6 and OT9 werefollowedthedesiredrange of permeabilities of drugcorrelationcoefficientrangesfrom 0.9804 to 0.9987 forlinseedoil and PVP/PVA transdermal patch. Thisanalysisrevealedhigherintheconcentration of the PVP/PVA mayalsoleadtorapiddissolution of drugfromdiffusionfrompatch.

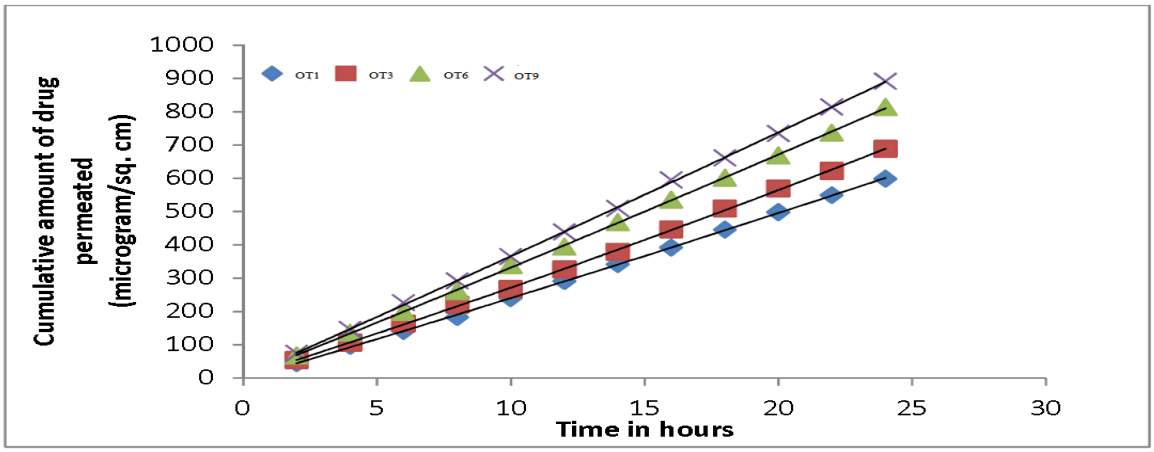

Fig. 4Percentagedrugreleaseprofile of In-vitroevaluation of PVP/PVA ratio.

3.7. Ex-vivodrugpermeationstudies

Ex-vivopermeationstudiesrevealedthemechanical, physical and chemicalefficacy of thedrugpolymercompatibility and transdermal potency. Thecumulativepercentage, releaserate and percentagereleaserate of twopermeationenhancershowedqualitativelyresults. Theobtaineddataisgivenintablebelow. However, linseedoilcomposition of OT6, OT7 and OT9 selected, givensignificantpercentagementioned. Itisconcludedlinseedoil, itislongfattyacidchainwithconsist of linolenicacidabout 68% and stearicacidabout 9-10%. Itismoresuitablefor transdermal patchaspertheEx-vivocompartmentanalysis, itisalsostablewithOndansetron andallotherpolymers.

Table 4. Cumulative (%) percentagerelease, permeationrate, and releaserate 6-8 hours. Differentpenetrationenhancerencorporated, L: linseedoil, C: Castoroil.

S. No.	**Patch number**	**(%) percentage release**	**Percentage rate (ug/cm^2/h)**	**(%) percentage release**		**Release rate (ug/cm^2/h)**	
				L	**C**	**L**	**C**
1	TDDS2	15.22	9.80	20.1	15.11	8.02	8.20
2	TDDS3	20.12	7.33	26.23	25.20	5.08	5.12
3	TDDS4	30.12	8.54	24.88	24.22	35.05	40.21
4	TDDS6	40.2	2.10	51.18	43.45	50.22	18.21
5	TDDS8	22.11	21.2	9.12	6.4	20.12	13.22
6	TDDS9	30.14	10.11	16.12	15.23	22.65	16.45
7	TDDS10	50.11	15.55	26.21	16.54	15.25	8.05

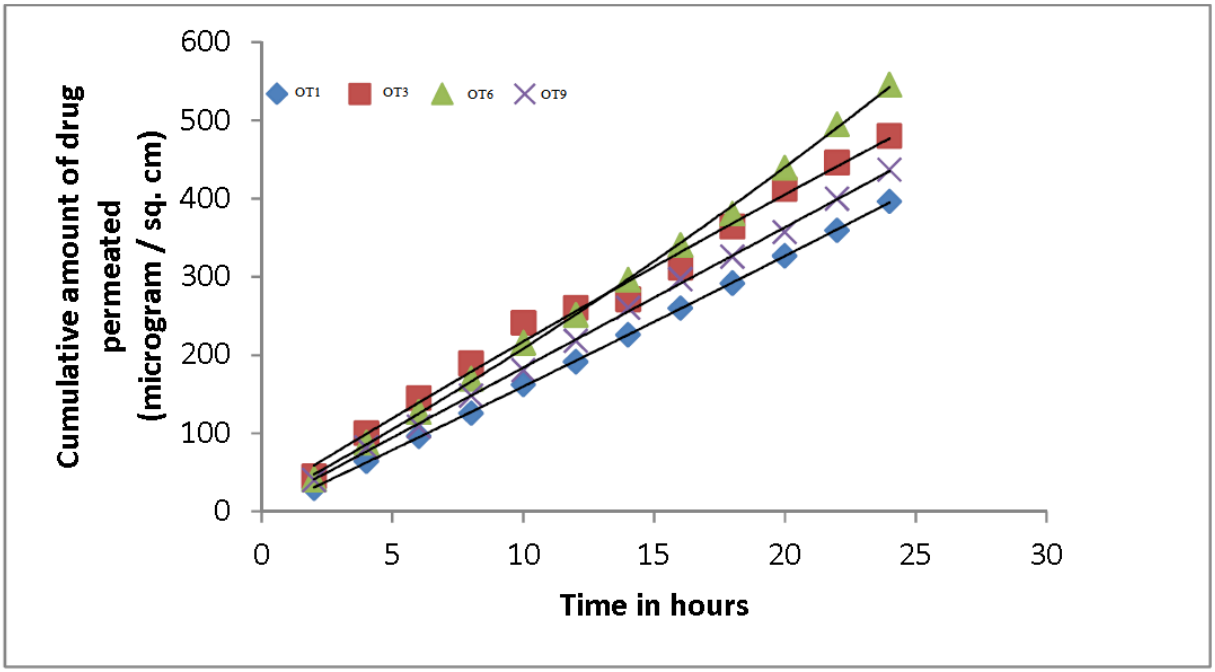

Fig. 5Ex-vivocumulativepermeationevaluationprofile of OD transdermal patch of differentratio and patches.

Conclusion

Thecontrolleddrugrelease of thedrugOndansetron HCL hasbeeninvestigated, prepared and characterizedshowedefficientresults.Accordingtothecharacterizationdrugreleaseprofileconcluded thattheformulationTDDS1, TDDS3 and TDDS8using PVP/PVA, showedsustained and prolongedreleaseprofileascomparedtotheotherpatchformulations. Itisreasonabletoconcluded PVP/PVA polymersarebettersuitedwithpermeationenhancerlinseedoilforthedevelopment of OndansetronHCl transdermal drugdeliverysystem.
Compatibilitystudiedrevealedbetterstability of OndansetronHClwiththepolymerused, physically and chemicallystable. In-vitro and Ex-vivoevaluationstudiedshowedthecumulativepercentagerelease of drug.For further studies, includingpharmacokinetic and pharmacodynamic investigations, are howeversuitable to confirm findings from this studinsuitableanimalmodels.

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