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FORMULATION AND EVALUATION OF CONTROLLED RELEASED AT ORVASTATIN INSITUGELS FOR THE TREATMENT OF PERIODONTAL DISEASES

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ABSTRACT

Thetreatmentforperiodontaldiseasesincludessystemictreatmentwithantibiotics.Localadministrationusing intra-pocketdrugdeliverywithsolgeltechniquesisrecentlyevaluated.Bonetissueregenerationisanimportantfactortobeconsideredfortreatmentassociatedwithchronicperiodontitis.Thisresearchworkrevealstheformulationandinvitroevaluationofperiodontalpocketeddrugdeliveryofatorvastatin,abonetissueregenerator,usingsol-geltechnique.Atotalof sixformulationswerepreparedwithpolylacticcoglycolicacid(PLGA)andsolventconcentrationskeepingthedrugconcentration50mgthroughoutthestudy.Thedrugexcipientcompatibilitieswereperformedusing IRspectroscopy.Formulationstudiesweredonebyconsideringspreadabilitystudies,viscosities,solgeltransitiontemperaturesandinvitrodrugrelease.Noabnormalorshiftinpeakswereidentifiedandsupportstheselectionofpolymerforfurtherformulationstudies.Itwasidentifiedthatthereleaseratewasdirectlyproportionaltodrugconcentrationindicatingthefirstorderreleasekineticsof atorvastatin.Also,basedontheHiguchiandKorsmeyerpeppasmodels,itcouldbeinterpretedthatthepreparedformulationsfollowNonFickiandiffusiontransportmechanisms.Itwasidentifiedthatalltheformulationsshowedgoodphysicalappearance byformingclearsolutionswhenprepared. The pHofalltheformulationswereinbetween5.9to6.1indicating that they were slightlyacidictoneutraland could beadministeredtotheoralcavity. Basedongellingproperties, spreadability and syringeability andviscosityprofiles, the formulationF4showed betterprofilecomparedtotherestoftheformulations.In vitrodrugreleasestudiesrevealedthattheformulationsfollowedfirstorderkineticswithnonFickiandiffusionmechanism.Sustainedandprolongedrelease was achievedforalltheformulations.FormulationsF5 and F6 had prolonged drug releaseofupto50days.However,consideringallthephysicochemicalparametersandinvitroreleaseprofilesintoaccounttheoptimizedformulations was considered to be F4.Thisformulationisfurtherproposedto be considered forin vivostudies.

Keywords: Atorvastatin, Periodontal diseases,Bonetissueregeneration,In situgels,PLGA,Controlledrelease

INTRODUCTION

Periodontaldiseaseisagroupofillnesseslocatedinthegumsanddentalsupportstructures(ligamentandalveolarbone)andare producedbycertainbacteriaencounteredinsubgingivalplaque.Themainsymptomscomprisegingivalinflammation,formation ofperiodontalpocket,alveolarboneloss,abscess,ortoothmobility[1].Theconventionaltreatmentcomprisingscalingandrootplaning(SRP)presentslimitationsincertaincasesinvolvingdeepperiodontalpockets,inaccessibleareas,orsevereperiodontitis.Therefore,severaladjunctpharmacologicaltherapieshavebeentestedtoimproveitsoutcomes.Systemicandlocaldeliveriesofdrugssuchasantibiotics,bisphosphonates,anti-inflammatorydrugs,anticytokines,probiotics,andprebioticshavebeentestedsofartoreducebacterialloadandtocontrolinflammation[2].Mitigationinbonetissuelossandfurtherbone-regenerationhelpsinmanagementofchronicperiodontitis.Likewise,theuseofstatinsinperiodontaltreatmenthasbeenexplorerecently.Statins,orinhibitorsof3-hydroxy-3-methylglutarylcoenzyme-Areductase(HMG-CoAreductase),areagroupofdrugs,usedprimarilytotreathyperlipidemiaandtopreventcardiovasculardiseases.Theydiffermainlyintheirringstructure,andthesestructuraldifferencesmodifytheirpharmacologicalpropertiesincludinghydrophilicityandlipophilicity.Thelactoneringispresentinanactiveform(alreadyhydrolyzed)inallstatinsexceptforsimvastatin,lovastatin,andmevastatin,inwhichthelactoneringisactivatedintheliver.Thelactoneformofthestatinsenablestheirtransport,metabolism,andclearance.

Apartfromtheirlipid-loweringproperties,statinspossesspleiotropiceffectsduetotheirantiinflammatory,antioxidative,antibacterial,andimmunomodulatoryproperties.Statinshavealsobeenreportedtohaveanaboliceffectsonthebonebyaugmentingbonemorphogenetic protein-2(BMP-

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

2)expression,thuscontributingtowardsthedifferentiationandactivityofosteoblasts(OBs).Inviewoftheirbeneficialproperties,statinshavebeenpresentedasnewpotentialcandidatesforimprovingperiodontaltherapyoutcomes[3-4].Forbonetissueengineeringapplications,muchoftheliteratureregardingregenerationofbonehasfocusedonthedeliveryofbonemorphogeneticproteins(BMPs)andvascularendothelialgrowthfactor(VEGF),twogrowthfactorsthathavebeenwidelyinvestigatedforuseintheregenerationofbone.TheeffectsofstatinsonVEGFproductionarebeginningtobeelucidated.Simvastatin,atorvastatin,androsuvastatin,butnotpravastatin,havebeenfoundtoaugmentVEGFmRNAexpressioninosteoblasticcellsin vitro[5].

Controlleddeliverysystemsaredesignedtoslowlyreleasethedrugforlongeravailabilityandlongerdruguse.Theseformsofdosageorthedeliverysystemsareoftencalledcontinuous,controlled,prolonged,timed,slow,prolongedandextendedrelease. Asontoday,fivedrugproductsareavailableonthemarketintheintra-pocketindustry.Thefollowingareavailable:tetracycline,metronidazolegel,minocyclineointment,chlorhexidinechipandresorbablepolymerdoxycyclinehyalite[6-7].

Literature survey revealed that there are no formulations available on PLGA based atorvastatinin situ hydrogels for periodontal applications. Inthepresentresearch,thesmartgels(sol-gel)wereemployedtoformulateaperiodontalmedication(atorvastatin)withpolylactic-co-glycolicacid(PLGA),acopolymerofpolylacticacid(PLA)andpolyglycolicacid(PGA)wasselectedforformulationofinsituperiodontalgelsthatshowphasetransitionduetophysiologicalenvironmentalchanges.PLGAwillaffordgelsofgoodmechanicalstrengthsandformthermosensitivehydrogels[8].Withthehelpofthesyringe,whichisfittedwithanintra-pocketneedle,theycanbe easilydeliveredintotheperiodontalpocket.Thepolymerchangesitsconformationintoagelatbodytemperature(37^{o}C).Thedeliverysystemiseasytomanageandhasalongtimeduetotheformationofgel.Theirpreformulationandformulationstudieswereevaluatedandwillbediscussedinfurthersectionsofthisarticle.

MATERIALSANDMETHODS

Materials and chemicals

Poly(D,L-lactide-co-glycolide)lactide:glycolide (50:50), mol. wt. 30,000-60,000 was obtained from Sigma Aldrich, India. Atorvastatin (calciumsalt) was a gift sample from Nishka Labs, India. All other chemicals obtained were of analytical grade and purchased from local market.

Drugexcipientcompatibilitystudies

FT-IRspectralstudieswereconductedbyscanningdrugand polymer alone,and combinationofdrugand polymer usingpotassiumbromidepelletizationtechnique[9].Forpreparingpellet,usingacalibratedweighingbalance,1mgofdrugwasinitiallyweighedfollowedbyaddingofpotassiumbromidetomakeupthefinalweightto100mg.Itwasmixedthoroughlywithmortarandpestle.Themixturewasthenpressedunderpelletholdertogetthepotassiumbromidepellet.ThepelletwaskeptinShimadzuFT-IRspectrophotometerandscanningwasconducted.Similarprocedurewasadaptedtoexcipientalone.Forcombinationofdrugandexcipient,1mgofdrugand1mgofexcipientwereweighedinitiallyandthefinalweightwasmadeupto200mgwithpotassiumbromide.

Preparationofin situgels

PLGAischosendueitsoptimalabilityinformationofbiodegradablegels[10].A total of six formulationswerepreparedwithdifferentcombinationsofcopolymerandsolvent(ethylacetate)keepingthedrugconcentrationas50mgthroughoutthestudy.Theformulationsareshowninin Table 1.

Table I:Formulationpreparationsandtheircombinations

Formulation	PLGA (mg)	Atorvastatin Calcium (mg)	Ethylacetate (mg)
F1	100	50	900
F2	200	50	800
F3	250	50	750
F4	300	50	700
F5	400	50	600
F6	500	50	500

Evaluationofpreparedin situgels

Formulatedgelswerevisuallyinspectedfortheirappearance. The pHfortheformulationswasdeterminedusingacalibratedpHmeter(MettlerToledo).Calibrationisdonewithreadytousecalibrationsolutionsof pH4.01,9.21and7.00[11].Theelectrodesweredippedinthecalibratedsolutionsandthereadingsweremeasur

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

ed.Atoleranceof±0.05wasconsideredasacceptablerange.Oncethecalibrationiscompleted,theelectrodeswerecleanedwithdeionisedwaterbeforeusingforpHmeasurementofindividualformulations(F1toF6).Anaverageof five readingswastakenandtheresultswerenoted.

Determinationofsol-geltransitiontemperatureandgelationtime

Thequantitiesthataremention edinTable1wereweighedin5mlglassvials,sealedwithstoppersandpolypropylenecaps, andlabelled.Thesevialswereshakenoccasionallyuntilthedrugandpolymerwerecompletelydissolved.Thevialsweretransferredtoawaterbathandwereobservedatdifferenttemperaturesetpointsandthe gelationtemperaturewasidentified.Gelformationwasindicatedbylackofmovementofthemeniscusupontiltingofthevial.Thetimetakentoformgelationataspecifictemperaturewasnotedusingastopwatchanditwasdeterminedasgelationtime[12].

Syringeabilityandspreadability

Theformulatedgelsweretransferredtoa 5mlplasticsyringeandtothat21Gneedlewasattached.Syringeabilitywasconsideredacceptediftheformulatedgelwaspassedthroughthesyringeeasily.Theformulatedgelswereintendedtospreaduniformlytotheaffectedperiodontalportion.Tosimulatethisefficiency,theformulations(ofquantity1grameach)couldspreadbetweentheglassslidesforatimeof1min.Spreadability wascalculatedusingtheformula:

S=M.L/T

WhereS=Spreadabilityoftheformulation

M=Massweighttieduptotheslide(125ginthisstudy)

L=Lengthoftheglassslide

T=Timemeasurement(1mininthisstudy)

Determinationofviscosity

ViscositymeasurementsfortheformulationsmentionedinTable1weredoneusingBrookfieldviscometer(LVDVIIIU,BrookfieldEngineeringLabs.USA).Theformulationsweretakeninabeakerandmaintainedatroomtemperature.Measurements werecarriedoutusingspindlenumber62at50rpmforatimeof10min[13].

Determinationofdrugcontent

Thepreparedformulations(F1toF6)wereanalyzedforthedrugcontentbytaking1mlofthepreparedgelintoa 50mlvolumetricflask.Toit,a3mlof6.8pHbufferwasaddedandshakenwelltodissolvethedrug.Then,thevolumewasmadeup tothemarkbypH6.8bufferandthesolutionwaskeptasideforovernight.Thedrugcontentwasdeterminedbymeasuringtheabsorbanceat247nmfor(atorvastatincalcium)usingUV-Visiblespectrophotometer(ShimadzuUV1280),usingthestandardequationobtainedfromthestandardplot.

In vitrodrug-releasestudies

The 5 ml vials with glass stopperswereusedforthisstudy.Usingdisposable1mlsyringeand18Gneedlesdrawn1mlofthe preparedformulationandtransferredto5mlvials.Tothem,added1mlofpH 6.8phosphatebuffer(simulatedgingivalfluid), shakenwelluntilauniformsolutionwasachieved andexposedthemto37.5°CbykeepingtheminaBDincubator.Sampleswerewithdrawnoncethesolutionswereconvertedtogels.A1mlof dissolution fluid was collected atatimeintervalofevery24hupto50daysbyreplacingwiththesame volumeofpH6.8phosphatebuffer.Thesamplesolutionsweretransferredintothe10mlvolumetricflaskswherethevolumewasmadeupto10mlwithpH6.8phosphatebuffer.Thesolutionwasfilteredthrough a 0.45 µ Whatman filter paper andtransferredtoa cuvettetothemeasuretheabsorbanceat247nmusingUV-visiblespectrophotometer (Shimadzu UV-1280).Cumulativedrugreleasewascalculatedbymeasuringthedrugcontentusingstandardcalibrationplot.

RESULTS AND DISCUSSION

Drug-excipientcompatibilitystudies

DrugexcipientcompatibilitiesstudiesthroughFT-IRinferthattherearenoabnormalorshiftinpeaksidentifiedwhentheFT-IRgraphsofdrugaloneandthecombinationofdrugandpolymerwerecompared.Thescanresultsarereferredin Figure 1.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

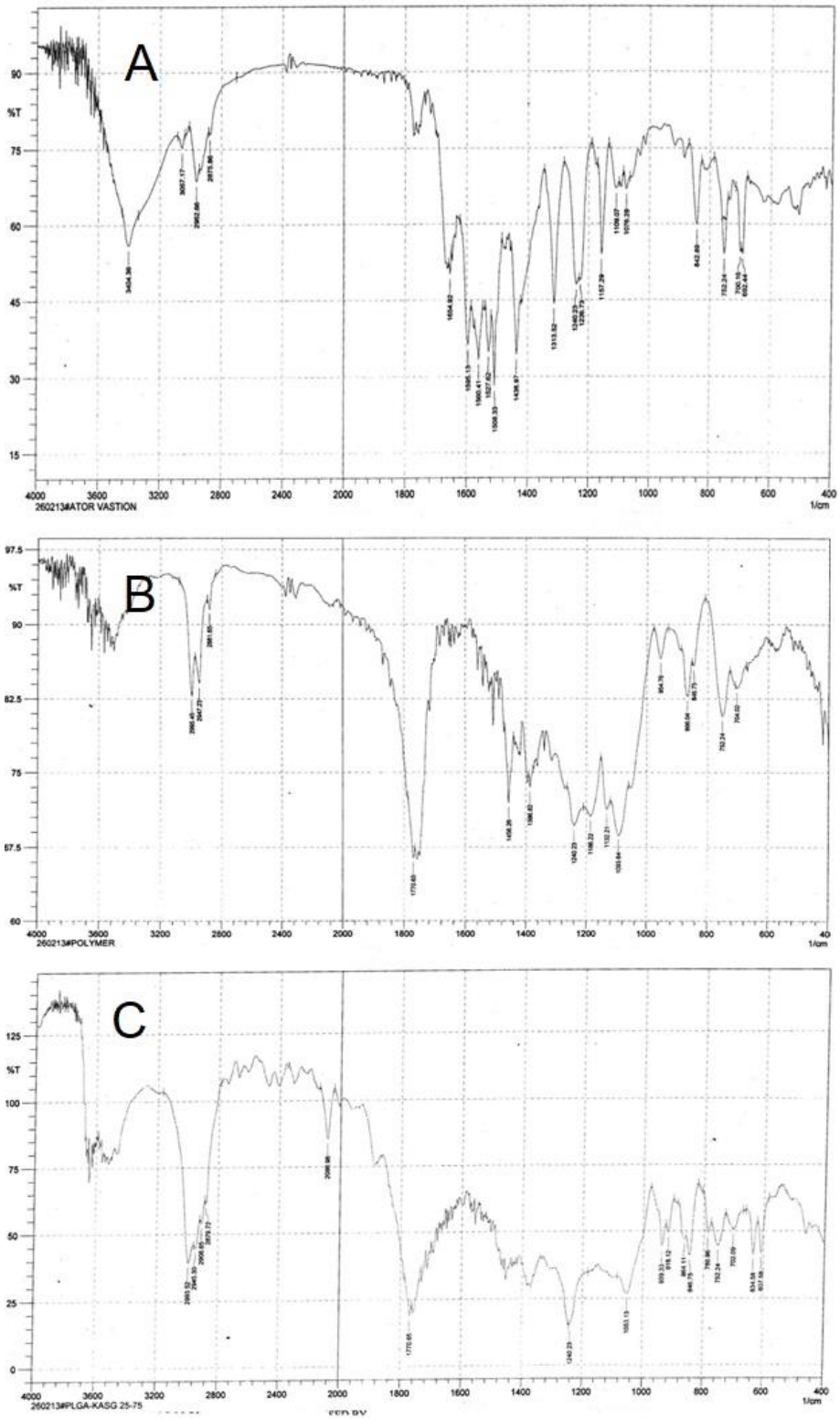

Figure 1: FT-IR spectra of (A) Atorvastatin,(B) PLGA and (C) Atorvastatin+PLGA

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Evaluationofpreparedin situgels

Allformulatedin situgelswhenobservedvisually,theyappearclearandtransparent.ThemeasuredpHwasintherangeof5.9to6.1.Itwouldbepreferableforaformulationwhichhasap Hcloseto6.8asitresemblesthepHofsaliva.ThepHvaluesaregiventheTable 2

Sol-geltransitiontemperatureandgelationtime

Itisidentifiedthatincreaseintheconcentrationofthepolymerreducesthegellingtemperatureaswellasgellingtime.Thepossiblereasonforthisphenomenonwouldbethebindingnatureofthepolymer.Anidealformulationshouldformgelattemperaturesinbetween36to37^{o}C.Formulationsthatformgelatlessthan36^{o}Cwere consideredasgelformationatroomtemperaturesforwhichadministrationthroughsyringeswouldbedifficult.Formulationsthatformgelabove37^{o}Cmightstayinliquidformevenatbodytemperaturewithoutforminggelandleakfromtheperiodontalpockets.HenceformulationF3andF4werefoundtohavedesiredgellingabilitiesastheyhaveoptimumgellingtimesandwithinthesol-geltemperaturerange.

Syringeabilityandspreadability

Syringeabilitystudiesrevealedthatin situformulationswereeasilyadministeredthrough18Gneedleatroomtemperatureof25^{o}C.Itshouldbenotedthatthisstudywasintendedtocheckwhethertheformulationscouldbeeasilyadministeredontheperiodontalpocketbutnotforparenteraladministration[14].Spreadabilitystudiesshowedthattheextentofuniformspreadingoftheformulationsdecreasedwith anincreaseinpolymerconcentration.However,anoptimumspreadabilityisdesiredtoavoidspillageaswellasoverstickinessoftheformulationwhenitadministeredtotheaffectedarea.

Viscosity determination

Viscositystudiesrevealedthat anincreaseinconcentrationofpolymerwillincreaseintheviscosityoftheformulation.Optimumviscositiesaredesiredtohavebetterflowproperties.Itwasobservedthattheviscosityofthepreparedformulationcontributedtotheproductadhesiveness,enumeratingthesignificanceofproductrheologyonthisparameter.Additionally,thegelformedin situshouldmaintainitsintegritywithoutdissolvingorerodingforaprolongedperiod.However,theviscositiesforallthepreparedformulationswerefoundtobemorethan1000dyne.sec/cm^{2}whichindicatesthattheflowoftheformulationswasadequateonlyifsyringeneedlesofinternaldiameterisbroader.Hence18G(internaldiameter0.838mm)andbelowneedlesarerecommendedforthe administrationofthepreparedformulations.

Drugcontentdetermination

Drugcontentdeterminationstudiesinterpretedthatinalltheformulations,irrespectiveofthechangeinconcentrationofpolymerPLGA,theentrapmentandhencethestabilityofthedrugwasgood,whichwasinbetween98%to101%.Thereasoncould beduetohigherviscositiesandcompatibilityofdrugwithPLGApolymer.FormulationF4wasconsideredtobebettercomparedtootherformulationsasalongwithdrugcontentotherparameterssuchassol-geltransitiontemperatures,viscositiesareinacceptableranges.The results of pH, sol-gel transition temperatures, gelling time, spreadability, viscosities and drug content of the prepared formulations during the study are given in Table 2.

Table II: Determination of pH, sol-gel transition temperature, gelling time,spreadability,viscosity and drug content of prepared formulations (n=3)

Formulation	pH	Sol-gel transition temp. (°C)	Gelling time (min)	Spreadability (gm.cm/sec)	Viscosities (dynes/cm^{2})	Drug content (%)
F1	6.0±0.03	39.0±0.6	11±0.5	13.22±0.24	1463±25	102±6.9
F2	5.9±0.08	38.8±0.5	10.5±0.4	12.11±0.64	1498±31	98±5.2
F3	6.1±0.13	36.9±0.3	9.2±0.6	11.93±0.16	1628±36	99±5.8
F4	6.0±0.17	36.4±0.9	8.1±0.7	10.45±0.28	1685±29	99±4.7
F5	6.1±0.21	35.7±0.6	6.4±0.5	09.92±0.11	1890±42	101±6.3
F6	6.0±0.19	34.9±0.8	5.5±0.3	08.12±0.09	1789±47	99±5.5

In vitrodrugreleasestudies

In vitro drug releasestudieswereperformedbyplottingcumulativeamountofdrugreleasewithrespecttotime (Figure 2).In vitrodrugreleaseinterpretationsweredonebyconsideringzeroorder,firstorder,HiguchiandKorsmeyer-Peppasplots[15].Thezeroorder,firstorder,HiguchiandKorsmeyer-Peppasplotsweremadetointerpretthemechanismofreleaseforthepreparedformulationsandareshownin Figures 2-5. Also,theresultsofdissolutionkinetics(regressioncoefficientvalues-R^{2}andlinearequations),whichweredeterminedforalltheformulationsaregiveninTable 3.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

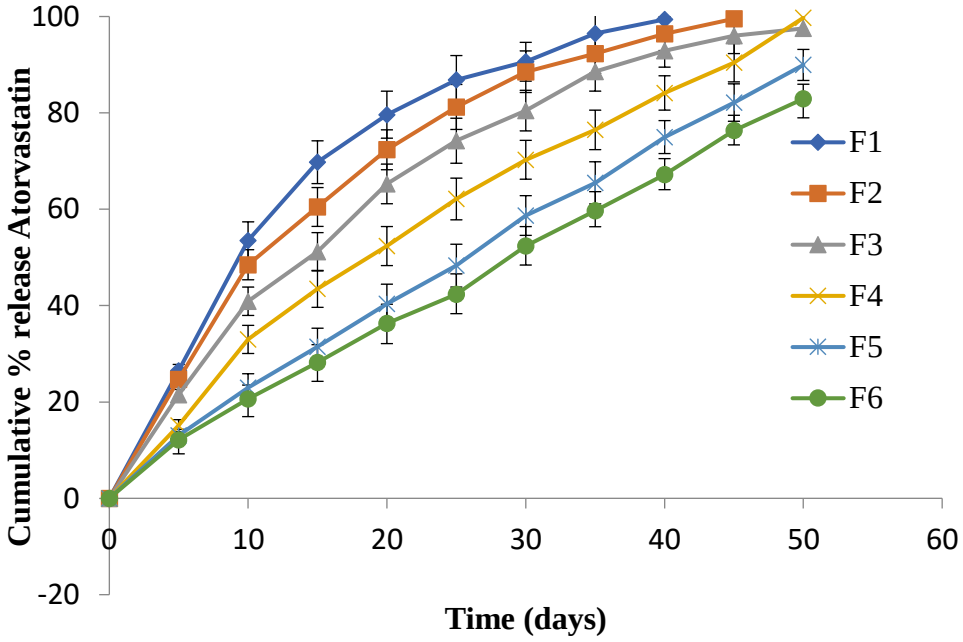

Figure 2: Cumulativeamountofdrugreleasevs time plots of formulationsF1-F6

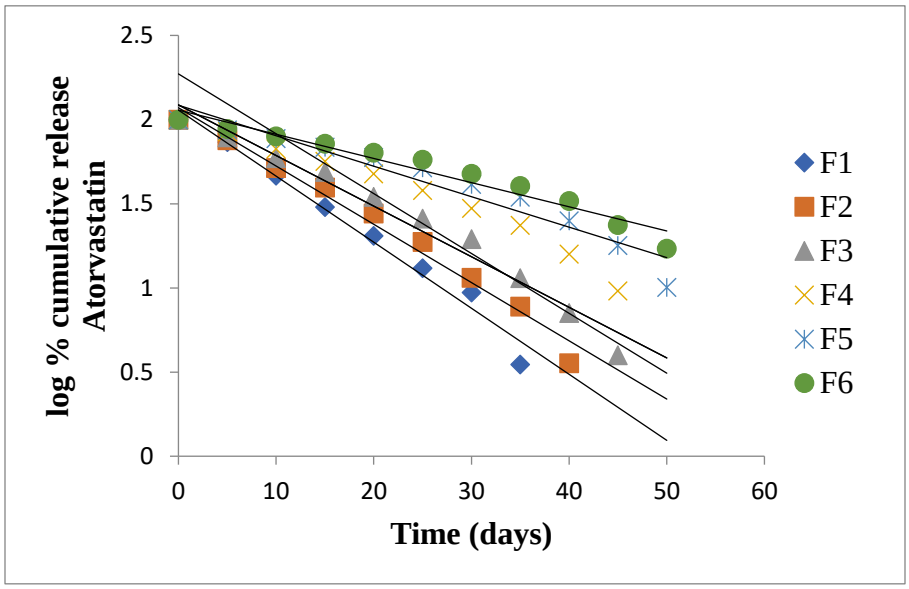

Figure 3:Firstorder release kineticplotsforatorvastatinformulationsF1-F6

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

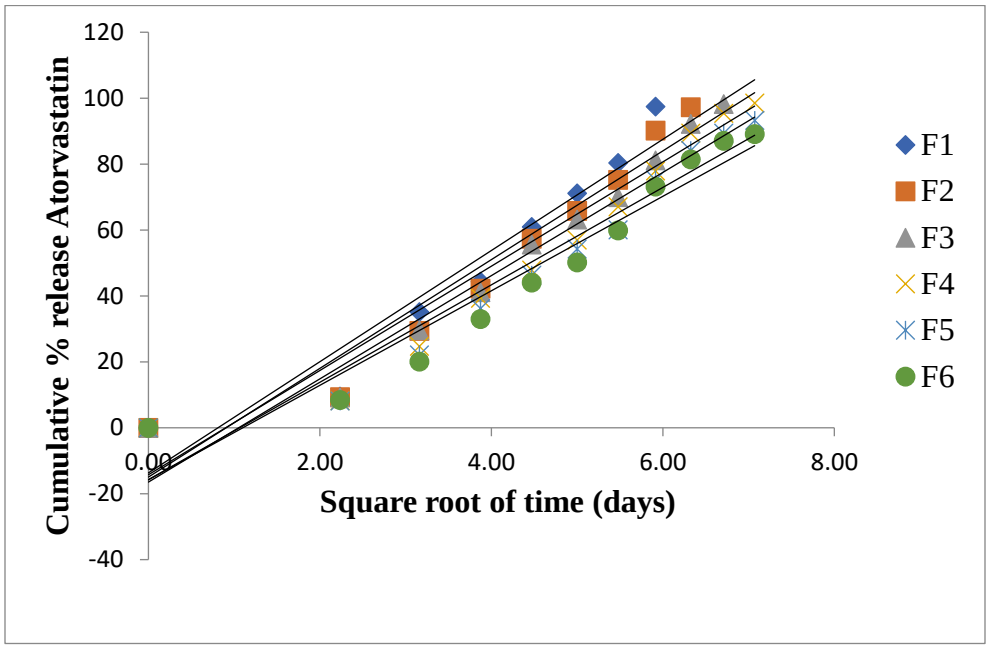

Figure 4:HiguchikineticplotsforatorvastatinformulationsF1-F6

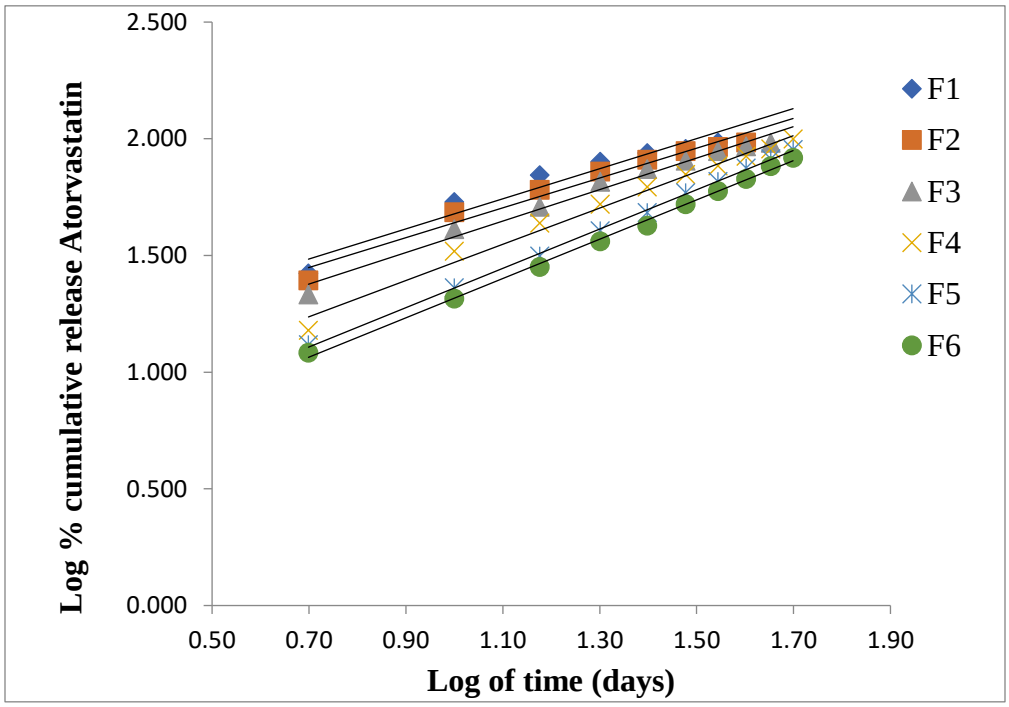

Figure 5:KorsmeyerPeppasplotsforatorvastatinformulationsF1-F6

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table III: Dissolution kinetic values obtained from different plots of formulations F1-F6 showing regression equations and correlation coefficients

Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas
F1	y = 3.1219x + 34.634 R^2 = 0.5336	y = -0.0629x + 1.8389 R^2 = 0.9397	y = 20.327x + 15.057 R^2 = 0.7902	y = 0.5215x + 1.4529 R^2 = 0.7228
F2	y = 1.0248x + 37.74 R^2 = 0.5774	y = -0.0211x + 1.804 R^2 = 0.9404	y = 10.233x + 24.249 R^2 = 0.7641	y = 0.3538x + 1.4464 R^2 = 0.7082
F3	y = 0.6459x + 35.444 R^2 = 0.6661	y = -0.0122x + 1.8258 R^2 = 0.9454	y = 7.8733x + 22.913 R^2 = 0.8298	y = 0.3333x + 1.3816 R^2 = 0.7745
F4	y = 0.5728x + 31.544 R^2 = 0.7245	y = -0.0105x + 1.8644 R^2 = 0.958	y = 7.4903x + 18.771 R^2 = 0.8763	y = 0.3658x + 1.2839 R^2 = 0.8231
F5	y = 0.4111x + 21.439 R^2 = 0.8512	y = -0.0059x + 1.9432 R^2 = 0.9365	y = 6.3154x + 8.7724 R^2 = 0.9608	y = 0.4633x + 0.9656 R^2 = 0.876
F6	y = 0.3756x + 17.208 R^2 = 0.904	y = -0.0048x + 1.9665 R^2 = 0.9555	y = 5.9664x + 4.988 R^2 = 0.9823	y = 0.5209x + 0.796 R^2 = 0.8658

Aspartofinitialplan,itwasproposedtocontinuethe dissolution studiesuntil90%of cumulative amount of thedrugreleasewasachieved.Itwasinferredthatthereleaseofthedrugfromthepolymerwassustainedfor aprolongedperiodwhichwasnotanticipatedatthebeginningofthestudy.A 90%ofthedrugwasreleasedin30daysforthe formulationF1whichwasconsideredasthefastestamongtheformulationsprepared.FormulationsF5andF6did notachievedesireddrug release(90%) evenafter50days.Basedonthemaximumamountofcumulativedrug releaseandextentofsustainability, theformulationF4showedthebestreleaseprofile ascomparedtothe formulationsF1,F2andF3.Basedontheregressionvalues,thereleasekineticswerepredicted.Regressionvaluesofgreaterthan0.9shouldbeconsideredtoestimatethereleasephemoneon.Itwasinterpretedthatalltheformulationsfollowedfirstorderdrug release kineticswhichmeans thatthereleasewasdirectlyproportionaltotheconcentrationthedrugcontent.Also,an increaseintheconcentrationofthepolymerledtosustainthedrugrelease.Only,the\formulationsF5toF6haveregressionvalu esofhigherthan0.9forHiguchimodel.Henceitcouldbeinferredthattformulations F5andF6followedfirstorder \releasekineticsalongwithFickiandiffisuionmechanism.Asforall theformulations,whenKorsmeyer-Peppasequations wereplotted,theobtainedregressionvalueswerelessthan0.9.Henceitwasinferredthatthereleasekineticsfollowedfirstorder releasekineticsandnon-Fickiandiffusionmechanisms.However,fortheformulationsF5andF6onlythefirstorderkineticscouldbeconfirmed.Theset woformulationscorrelatesbothHiguchiandKorsmeyerPeppasmodelsandhencetheirdiffusionmechanisms(Fickianornon -Fickian)cannotbeestimated.

Conclusion

Basedontheliteraturereview,PLGAwasusedfortheformulationandevaluationofcontrolled release atorvastatinin situgelstoseethefeasibilityofintrapocket-controlleddelivery,forthetreatmentofperiodontitis.Drug-excipientcompatibilitystudieswereperformedandbasedontheresultswithFTIRspectroscopy,itwasevidentthattheselecte dpolymerwascompatiblewithatorvastatinandhencecontinuedforformulationandevaluationstudies.A total of six formulationswerepreparedandtheirphysicochemicalevaluationssuchasvisualappearance,pH,sol-geltransitiontemperatures,gellingtime,spreadabilityandsyringeability,viscositiesweredetermined.Also,the drug releasekineticsandtheirmechanismswerestudiedusingzeroorder,firstorder,Higuchi,KorsmeyerandPeppasmodels.Itwas identifiedthatalltheformulationsshowedgoodphysicalappearancebyformingclearsolutionswhenprepared.The pHofalltheformulationswereinbetween5.9to6.1indicatingthattheywereslightlyacidictoneutralandcouldbeadministered totheoralcavity.Basedongellingproperties,spreadability and syringeability andviscosityprofiles, the formulationF4showedbetterprofilecomparedtotherestoftheformulations.Invitrodrugreleasestudiesrevealedthattheform ulationsfollowedfirstorderkineticswithnonFickiandiffusionmechanism.Sustainedandprolongedreleasewasachievedfor alltheformulations.FormulationsF5 and F6hadprolongeddrug releaseofupto50days.However,consideringallthe physicochemicalparametersandin vitroreleaseprofilesintoaccounttheoptimizedformulationswasconsidered to beF4.Thisformulationisfurtherproposedtobe consideredforin vivostudies.

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ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

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