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STAVUDINEGASTRO-RETENTIVEMICROSPHERESOFD-GALACTURONICACID SODIUM:FORMULATION,CHARACTERIZATION,*INVITRO* AND*INVIVO*EVALUATION

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ABSTRACT

Theprimeobjectiveofthepresentstudywastoformulatesustainedreleasemicrospheresofstavudinewhichwillretarddrugreleasefromdosageform,reducesthefrequencyofdrugadministration,minimizingtheadverseeffectstherebyincreasingthepatientcompliance.Sustainedreleasemicrospheresofstavudine(STV),theFDA-approveddrugforthetreatmentofHIVinfections,areadministeredeitheraloneorincombinationwithotherantiretroviral agents.STVistypicallyadministeredorallyasacapsuleandanoralsolution.ThesideeffectsofSTVaredosedependentandareductionofthetotaladministereddosereducestheseverityofthetoxicity.Microencapsulationimprovesthedrugabsorptionandminimizessideeffectsduetothelocalizedbuildupofdrugsagainstthegastrointestinalmucosa.Sustainedreleasemicrospherewerepreparedbyionotropicgelationmethodusing D-Galacturonicacidsodium(sodiumalginate)andnaturalpolymerssuchasguargum,locustgumandxanthangum.Thesemicrospherewereevaluatedforyield,entrapmentefficiency,and*invitro*releasekineticsand *invivo*pharmacokineticstudies.FT-IR and DSC results proved that there was no interaction found between drug and polymer. Scanning electron microscopy results of optimized microspheres showed discrete, spherical microspheres. Theresultsshowedthatyield,entrapmentefficiencywasinfluencedbypolymerconcentrationandstirringspeed.Results of the*invitro*studyshowedthatthedesiredreleaseratewasachievedbyMF4formulationreleasingdrugupto12h.

Keywords:Stavudine,Gastro-retentivemicrospheres,Ionotropicgelationmethod,D-galacturonicacidsodium,Sodiumalginate,Guargum, Locust bean gum, Xanthan gum.

INTRODUCTION

Gastro-retentivefloatingmicrospheresarelow-densitysystemsthathavesufficientbuoyancytofloatovergastriccontentsandremaininstomachforprolongedperiod.Asthesystemfloatsovergastriccontents,thedrugisreleasedslowlyatdesiredrateresultinginincreasedgastricretentionwithreducedfluctuationsinplasmadrugconcentration.[1]Awiderangeofmicroencapsulationtechniquehasbeendevelopedtodate.Theselectionofthetechniquedependsupononthenatureofthepolymer,drug,andtheintendeduse.Thephysicochemicalparameterstobeconsideredduringthepreparationofmicrospheresincludeparticlesizedistribution,ratioofdrugtopolymer,entrapment/encapsulationefficiency.[2]

Floatingdrugdeliverysystems(FDDS)orhydrodynamicallybalancedsystemshaveabulkdensitylowerthangastricfluidsandthereforeremainfloatinginthestomachwithoutaffectingthegastric-emptyingrateforaprolongedperiod.Thedrugisslowlyreleasedatadesiredratefromthefloatingsystemandafterthecomp

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letererelease;theresidualsystemisexpelledfromthestomach.ThisleadstoanincreaseintheGRTandbettercontroloverfluctuationsinplasmadrugconcentration.

Microencapsulationistheprotectivetechnologyofencapsulatingsolid,liquidorgasmaterialsintomicroparticleswithadiameterof1–1000μm,andhasbeenwidelyusedinfieldsofmedicine,cosmetics,food,textileandadvancedmaterials.[3]Theuniqueadvantageofmicroencapsulationliesinthatthecorematerialiscompletelycoatedandisolatedfromexternalenvironment.Moreimportantly,microencapsulationwouldnotaffectthepropertiesofcorematerials,providedthatpropershellmaterialandpreparingmethodarechosen.[4]Microspheresofferanumberofadvantagesintherapeutics.Microspheresareofthedrugdeliverysystemwhichprovideprogrammedandcontrolledreleasedrugafterproperdurationofactionatparticularsite.[5]D-Galacturonicacidsodium(sodiumalginate,SA)isnaturalpolymersarethattheyarebiocompatible,biodegradableandproducenosystemictoxicityonadministration.Numeroushydrophilicpolymers,andinparticularpolysaccharides,aswellastheirderivatives,havebeenproposedfortheformulationofmodified-releasedosageforms.Alginates,naturalhydrophilicpolysaccharidederivedfromseaweed,consistof1→4,linkedD-mannuronicacidandL-glucuronicacidresiduesarrangedasblocksofeithertypeofunitorasarandomdistributionofeachtype.Alginatesdonotgelsincetheyhavepoly(L-gluronicacids)whicharerigid.Alginatesareeasilygelledinpresenceofadivalentcationascalciumion.Thegelationorcrosslinkingisduetothestackingoftheglucuronicacidblocksofalginatechains.

Stavudine(STV)isaFDA-approveddrugusedforthetreatmentofHIVinfections,AIDSandAIDS-relatedconditionsadministeredeitheraloneorincombinationwithotherantiretroviralagent.STVisanucleosidereversetranscriptaseinhibitoranalogofthymidine.STVhasbeenrecommendedtoundergophase-outmanagementduetoitslong-term,irreversibleside-effects.STVtriphosphateinhibitstheactivityofHIV-1reversetranscriptase(RT)bycompetingwiththenaturalsubstratethymidinetriphsophateandbycausingDNAchainterminationfollowingitsincorporationintoviralDNA.STVtriphosphateinhibitscellularDNApolymerasesβandγmarkedlyreducesthesynthesisofmitochondrialDNA.STVmicrosphereshavebeenformulatedearlier.[6-8]Srikrishna*etal*.,employedemulsiongelationtechniquetopreparemultiparticulatefloatingformulationsofSTV.[9]STVbeadswereformulatedusingcombinationofD-Galacturonicacidsodium,HPMCandethylcellulose.[10]HoweverpastresearchshowsnoworkonSTVmicrospheresmadeusingsodiumalginate(SA)incombinationwithguargum(GG),locustbeangum(LG)andxanthangum(XG).

Themainobjectiveofthefloatingmicrospheresof STV werepreparedbyusingionicgelationmethodwithanaimofincreasingthegastricresidencetimeandforcontrolledreleaseandincreasethebioavailabilityoftheformulation.Sodiumalginate,polymericmixtureofsodiumalginateincombinationwithguargum,locustbeanandxanthangumswereusedaspolymericblendstopreparethemicrospheres.Sodiumbicarbonatewasusedasthegas-formingagent.

MATERIALSANDMETHODS

StavudinepurchasedfromSuryanarayanaPharmaceuticalsuppliers,Hyderabad,India.Guargum (GG), locust bean gum (LG) and xanthan gum (XG) were obtainedfromSignetChemicalCorporation,Mumbai,India.D-Galacturonicacidsodium (sodium alginate)fromMerckSpecialitiesPvtLtd,Mumbai,India.Allotherreagentswereofanalyticalgrade.

PreparationofSTVmicrospheres

Batchesofmicrosphereswerepreparedbyionotropicgelationprocedurethatconcernedresponsebetween SA andpolycationicparticleslikemetalliccomponenttosupplyagelsystemofmetalliccomponentalginate.[11]SAandfurthermorethemucoadhesivesubstancecompoundwereconveyedinsublimatewater(10ml)tomakeahomogenizedconcoctioncompoundblend.TheAPI,STV(100mg)wereintercalarytothesubstancecompoundintermixtureandblendedabsolutelywithastirrertomakeagooeyscattering.Thefollowingscatteringwasthenintercalarythrougha22Gneedleintosalt(4%w/v).Theexpansionwasdonepersistentblendingat200rpm.Theintercalarybeadswerekeptupinsidethesaltresponseforhalf-hourtocompletethehardeningresponseandtosupplyunbendingroundmicrospheres.[12]

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TableI.FormulationtableofSTVmicrospheres

Formulation code	Drug : Polymer ratio	Polymer blend ratio
MF1	1:2.5	SA : GG (1.5:0.5)
MF2	1:3	SA : GG (2:1)
MF3	1:3.5	SA : GG (2.5:1)
MF4	1:4	SA : GG (3:1)
MF5	1:2.5	SA : LG (1.5:0.5)
MF6	1:3	SA : LG (2:1)
MF7	1:3.5	SA : LG (2.5:1)
MF8	1:4	SA : LG (3:1)
MF9	1:2.5	SA : XG (1.5:0.5)
MF10	1:3	SA : XG (2:1)
MF11	1:3.5	SA : XG (2.5:1)
MF12	1:4	SA : XG (3:1)

Characterizationofpreparedmicrospheres

Fouriertransform-infraredspectroscopy(FT-IR)

Fouriertransforminfrared(FT-IR)Spectroscopywasusedtostudythephysicalandchemicalinteractionbetweenthedrugandexcipientsused.FT-IRspectraofpuredrugandoptimizedraftformingfloatingmatrixtabletwererecordedusingKBrmixingmethodonFT-IRSpectrophotometer(FT-IR-1700,Shimadzu,Tokyo,Japan)[13].

Differentialscanningcalorimetry(DSC)

DSCwasusedtostudyphysicalandchemicalinteractionbetweenthedrugandexcipientsused.DSCspectraofpuredrugand drugcompositemixturewererecordedondifferentialscanningcalorimeter(DSC-60,Shimadzu,Tokyo,Japan)[14].

Particlesizedistribution

Theparticlesizedistributionofmicrospheres wasdeterminedusingsievingmethodasdescribedbyYüceandCanefe.[15]Weighedmicrospheresofeachformulationwereputinasetofsievesfixedontheuniversaldriveunit(Erweka,AR402,Germany).

Percentageyieldofmicrospheres

Theproductionyieldofmicrospheresofeachbatchwascalculatedbyusingtheweightofthefinalproductafterdryingwithrespecttotheinitialtotalweightofthedrugandpolymersusedforpreparationofmicrospheres,andthepercentageproductionyieldwascalculatedusing.[16]

$$\text{Yield\%} = \frac{\text{Total weight of microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Drugentrapmentefficiency

Drugentrapmentefficiency(DE)wasdeterminedusingthemethoddescribedbyGargandGupta.Accordingly,accurately weighedmicrospheresequivalentto40mgofdrugwasstirredwith100mLofpH1.2(0.1NHCl.)for2h.[17]Thesolutionwasfilteredandaftersuitabledilutiondrugcontentwasdeterminedspectrophotometrically.Theamountofdrugentrappedinthemicrospheres wascalculatedbythefollowingformula:

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$$DE\% = \frac{\text{Mass of drug in microspheres}}{\text{Mass of drug in formulation formulation}} \times 100$$

Scanningelectronmicroscope(SEM)study

Scanningelectronmicroscopy(JEOL5400,Tokyo,Japan)wasutilizedtodecideshape,surfacegeographyandcompositionandlookatthemorphologyofbrokeorseparatedsurface.Samplespreadsonthelittlesquareplateandcoveredwithagoldparticlefor5-6min.[18]Thereadiedtestwaskeptinsidethechamberandpicturescaughtwithvariousamplifications.

***Invitro*buoyancy**

Microspherescontaining300mgofSTVwerespreadoverthesurfaceofUSPTypeII(paddle)dissolutionapparatus(Disso2000,India)filledwith900mlof0.1NHClfor 2 h followed by pH 6.8 phsophate buffer at37°C±0.5°Candagitatedwithapaddlerotatingat100rpm.Attheendofthisperiod,thelayerofbuoyantparticlesonthesurfaceofthemediumwascollectedandthesinkingparticulateswereseparatedbyfiltration.[19]Bothparticletypesweredried overnightinanovendrier(RiddiPharma,India)at40°C.Driedweightsweremeasured,andbuoyancywasdeterminedbytheweightratiooftheflotingparticlestothesumoffloatingandsinkingparticles.

$$\%\ \text{Buoyancy} = \frac{\text{Dry weight of floated microspheres}}{\text{Total weight of floated and settled microspheres}} \times 100$$

***Invitro*drugreleasestudy**

AUSPtypeII(paddle)dissolutionapparatus(Disso 2000, India)wasusedtostudy*invitro*drugreleasefrommicrospheresasdescribedelsewhere.Accordingly,anamountofthemicrospheresequivalentto40mgofSTVfilledinahardgelatincapsule(size0)wasplacedinthedissolutionmediumcontaining900mlof0.1 N HCl for 2 h followed by pH 6.8 phsophate buffer at 37±0.5°Cwithpaddlerotatingat100rpm.[20]Samplesof5mlwerewithdrawnat0.5,1,2,4,6,8,10and12handfiltered.An equalvolumeofthedissolutionmediumwasreplaced every timeinthevesselaftereachwithdrawaltomaintainsinkcondition.Eachofthesamplesolutionswereanalyzedspectrophotometricallyforthedrugcontentat274nm.[21]Fromthis,thepercentageofdrugreleasewascalculatedandplottedasafunctionoftimetostudythepatternofdrugrelease.

Kineticmodellingofdrugrelease

Toanalyzethemechanismofdrugreleasefromthemicrospheresthe*invitro*dissolutiondatawasfittedtozeroorder,firstorder,Higuchi'sreleasemodelandKorsmeyer-Peppasmodel.[22,23]

Stabilitystudy

Todeterminethestabilitystudyofthegastro-retentivemicrospheresofSTVwerepackedin40mlHDPEbottleandstoredat40±2°Cand75%±5%RHforaperiodofsix monthsaspertheICHguidelines.[24]Themicrospherewerewithdrawnataperiodof1,3and6monthsandevaluatedforcontentuniformityanddissolutionstudy.

Invivostudies

A prior approval of institutional animal ethical committee was obtained from Sanzyme Pvt Ltd., Hyderabad, India (Regn. No. 1688/PO/E/2013/CPCSEA, Dated 16-Aug-2018) for carrying out this experiment. MaleNewZealandwhiterabbitsweighingbetween1.5to2.0kgwereusedfor*invivo*studiesoforallyadministeredSTV.Animalswerehousedat25±1°Cinairconditionedroomatarelativehumidityof60±5%andwereprovidedwithwaterandsta

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ndardrabbitfeedobtainedfromSanzymePvtLtd.,Hyderabad.Animalswerefastedfor24hpriortotheadministrationofthepelletformulation,buthadfreeaccesstowater.ThemicrosphereformulationMF4loadedcapsuleswereadministeredorallywithasoftplastictubetodifferentgroupsofrabbitsseparately.Drugsolutionwasalsoadministeredorallywithasoftplastictube(STV5mg/rabbit)toanothergroupofanimals.About2mlofbloodwascollectedat0,0.5,1.0,2.0,3.0,4.0and6.0hafteroralsolutionadministrationand0,1,2,4,6,8haftertabletformulationadministrationfrommarginalearveinintoheparinizedtubesandplasmawasseparatedimmediatelybycentrifugationandfrozenat–20ºC.Theplasmasampleswereanalyzedfor STV byHPLCmethod.[25]

RESULTS AND DISCUSSION

Drug-excipientcompatibilitystudy

DrugpolymercompatibilitystudieswerecarriedoutusingFourierTransforminfraredspectroscopytoestablishanypossibleinteractionofDrugwiththepolymersusedintheformulation.Theinteractionstudybetweenthedrugandpolymerwasevaluatedusing FT-IRspectrophotometer.TheFT-IRspectraoftheformulationswerecomparedwiththeFT-IRspectraofthepuredrug(Figure1).Therewasnosignificantdifferenceintheir spectraofpureanddrugloadedmicrocapsules.FourbandscharacteristicofO–Hstretching,N–Hstretchingofsecondaryamine,C–HstretchingandC=Ostretchingofpuredrugwasunchangedinthepreparedformulations.

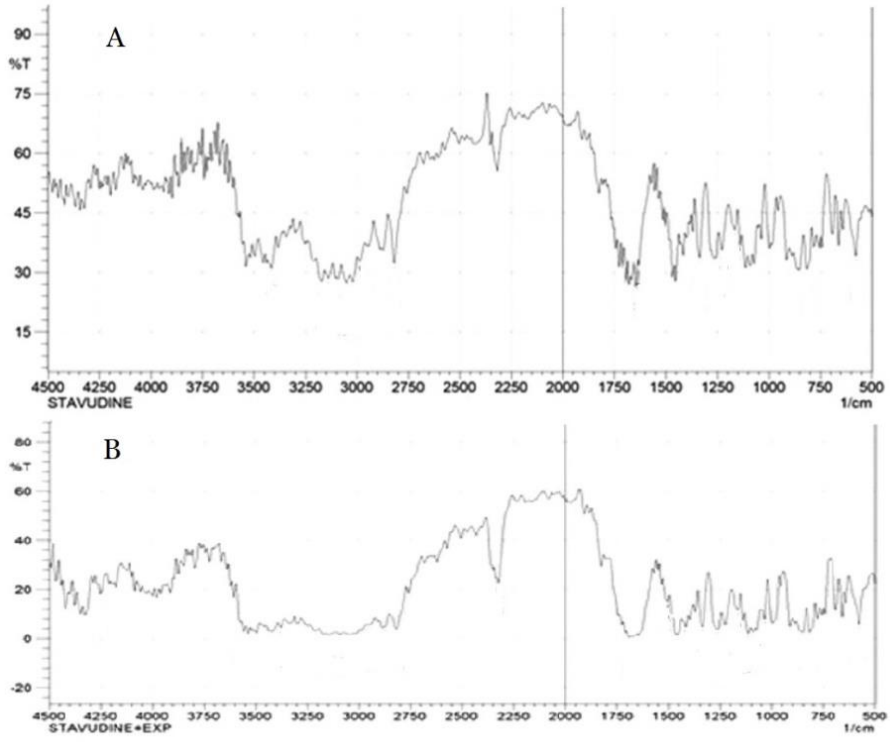

Figure1:FT-IRspectraof(A)puredrugand(B)optimizedformulationMF4

TheDSCthermogramofSTVshowedsharpendothermicpeakat172.1°C,whilethatofformulationMF4showedbroadendothermicpeakat169.36°C (Figure 2).TheDSCthermogramsofadmixtureofSTVwithSAGGinformulationsshowedsharpendothermicpeaksforSTVatthetemperaturessimilartothatofthepeakofSTValone.Thisindicatedthattherewasnodrugexcipientinteractionintheformulations.

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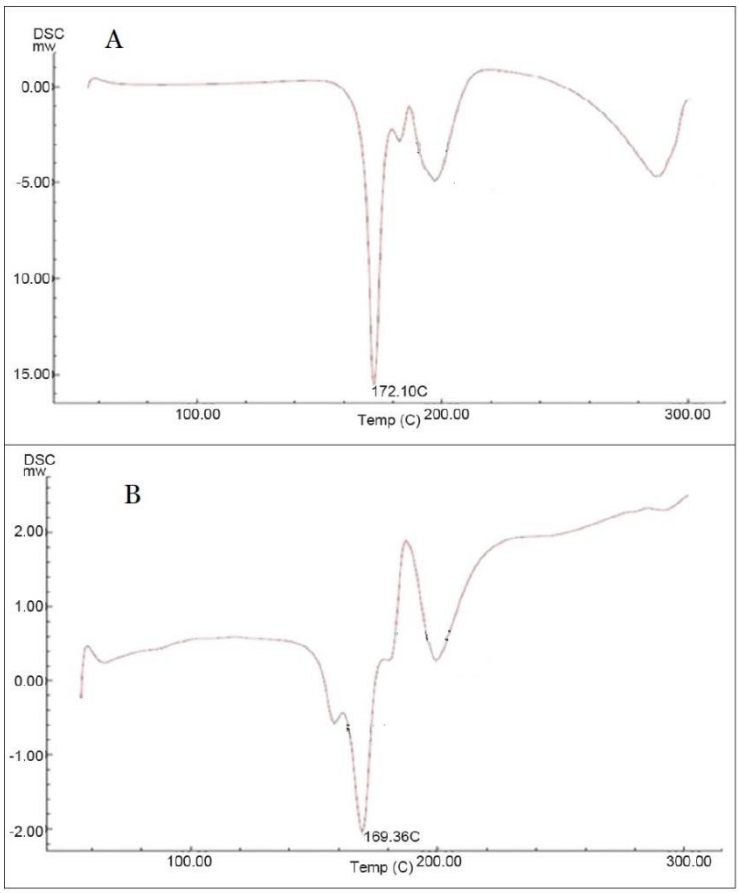

Figure2:DSCthermogramsof(A)STVand(B)optimizedformulation(MF4)

Characterization of prepared microspheres

Scanning electron microscopy and particle size analysis showed that microspheres containing SA and GG as polymer blend had a size range of 512 to 826 µ, microspheres containing SA and LG as polymer blend exhibited a size range between 517 to 834 µ and microspheres containing SA and XG as polymer blend had a size range of 664 to 903 µ (Figure 3). The particle size as well as drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

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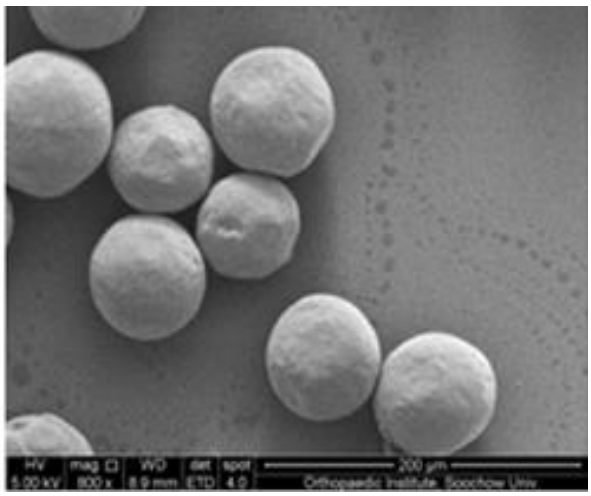

Figure 3: Surface morphology of optimised formulation MF4

The percent yield, drug content, drug entrapment, buoyancy, lag time and floating time of the prepared microspheres are summarized in Table 2. Itwasobservedthatasthepolymerratiointheformulationincreased,theproductyieldand drug entrapment efficiency were alsoincreased.The buoyancy was increased as the polymer concentrations were increased. The lag time and floating times were decreased as the polymer concentrations were increased.

TableII:The yield, drug content, drug entrapment, buoyancy, lag time and floating time ofthepreparedmicrospheres

S.No.	Formulation code	Yield (%)	Drugcontent (mg)	Drugentrapmentefficiency (%)	Buoyancy (%)	Lagtime(min)	Floatingtime(h)
1	MF1	80±0.02	12.4±0.08	82.66±0.06	63±0.05	12	8
2	MF2	83.33±1.05	12.66±1.32	84.4±0.04	67±1.30	10	8
3	MF3	85±2.07	12.70±0.24	84.66±0.01	75±2.06	7	8
4	MF4	88±0.01	13.29±0.06	88.66±0.03	79±0.07	6	10
5	MF5	62.22±0.4	8.07±2.07	53.2±0.09	89±1.02	3	>12
6	MF6	80±1.04	8.25±0.38	55±0.04	85±0.82	3	>12
7	MF7	80±1.50	10.33±1.02	68.86±0.07	70±1.03	7	10
8	MF8	87±0.02	11.5±0.05	76.66±0.02	76±0.05	8	10
9	MF9	80±0.05	10.01±1.06	66.73±2.03	84±0.92	4	>12
10	MF10	86±0.04	10.5±0.18	70±1.04	78±1.09	7	11
11	MF11	86.66±0.07	11.25±1.26	75±0.45	74±2.06	8	11
12	MF12	87.5±0.03	11.88±0.09	79.2±0.02	81±0.05	6	>12

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Itwas observedthatwithanincreaseinpolymerconcentration,thepercentageofswellingalsoincreased.Thuswecansaythatamountofpolymerdirectlyaffectstheswellingratio.Asthepolymertodrugratioincreased,thepercentageofswellingincreasedfrom27to87%formicrospherescontainingSAandGGaspolymer blend,23to67%formicrospherescontainingSAandLGaspolymer blendand28to79%formicrospherescontainingSAandXGaspolymer blend.

***In vitro* drug release studies and kinetics**

FormulationMF4showed94.66%releaseofthedrugforaperiodof12hwithrelativelyrapidreleasewhencomparedtootherformulationspreparedbyusingotherpolymers(Figures4-6).Thedrugreleaseprofilesarefittedtoreleasekineticstheslopeforpeppaswasintherangeof0.39to0.987indicatingbothdiffusionanderosionofbothpolymers.

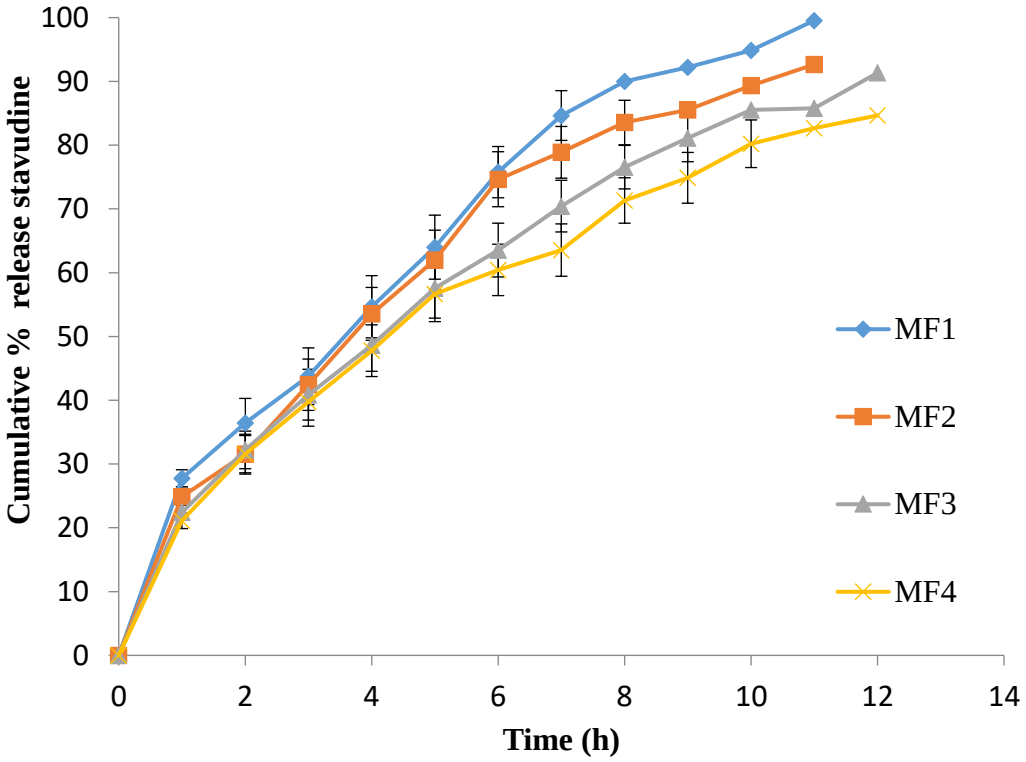

Figure4:Comparisonof*invitro*drugreleaseprofileofSTVmicrospherescontainingSAandGGaspolymer blend

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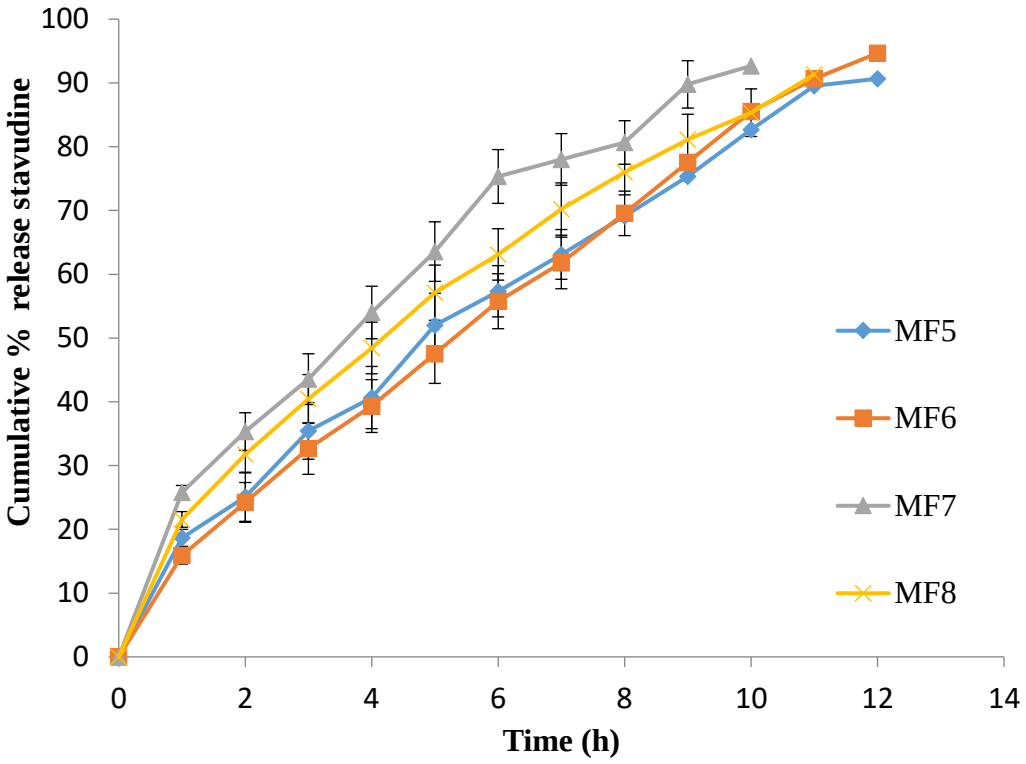

Figure5:Comparisonof*invitro*drugreleaseprofileofSTVmicrospherescontainingSAandLGaspolymer blend

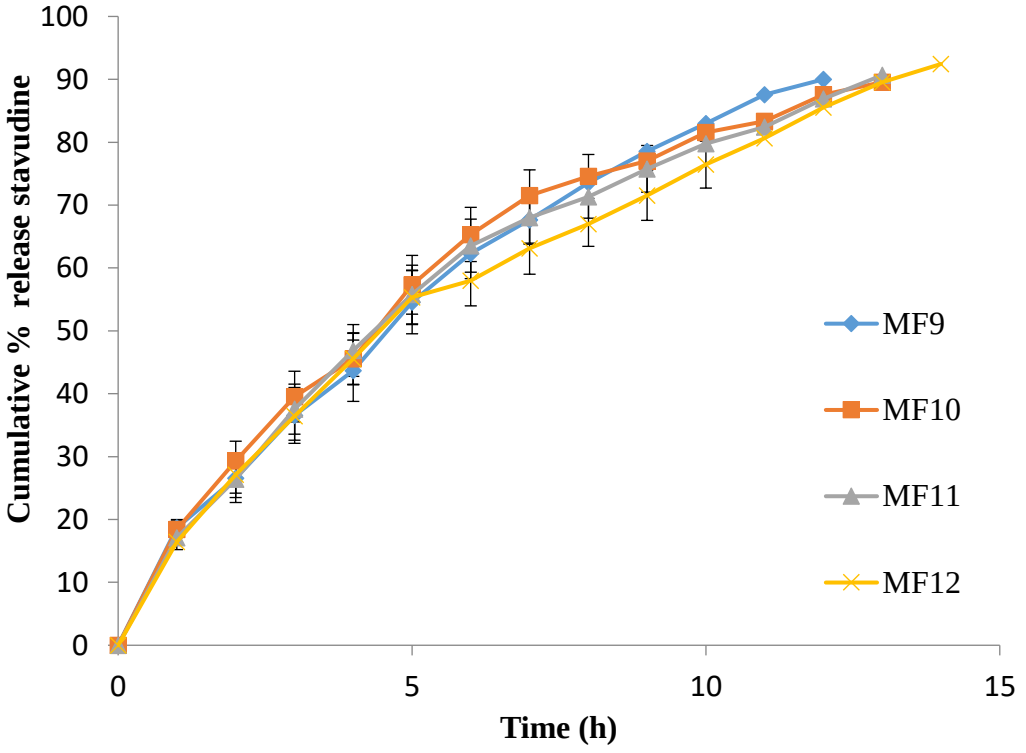

Figure6:Comparisonof*invitro*drugreleaseprofileofSTVmicrospherescontainingSAandXG

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TableIII:Releasekineticsstudiesofthepreparedformulations

Formulation	Releasemodel								
	Zeroorder		Firstorder		Higuchimatrix		Koresmeyer-Peppas		
	K	R^2	K	R^2	K	R^2	n	K	R^2
MF1	19.286	0.769	1.704	0.689	-0.56	0.891	0.534	1.251	0.883
MF2	14.076	0.88	1.772	0.859	-4.192	0.949	0.573	1.189	0.941
MF3	8.136	0.948	1.843	0.914	-9.213	0.954	0.651	1.096	0.949
MF4	5.12	0.962	1.899	0.883	-12.497	0.941	0.721	1.034	0.954
MF5	22.026	0.74	1.678	0.658	2.377	0.882	0.476	1.305	0.872
MF6	14.876	0.876	1.771	0.854	-3.58	0.95	0.557	1.209	0.939
MF7	12.216	0.908	1.799	0.954	-6.486	0.962	0.633	1.141	0.948
MF8	10.746	0.92	1.813	0.96	-7.834	0.963	0.668	1.104	0.949
MF9	20.886	0.755	1.69	0.673	1.089	0.888	0.504	1.281	0.883
MF10	14.416	0.878	1.773	0.854	-4.018	0.949	0.569	1.197	0.94
MF11	10.186	0.929	1.817	0.943	-7.887	0.961	0.645	1.116	0.951
MF12	9.626	0.931	1.842	0.951	-9.233	0.96	0.69	1.089	0.953

Stabilitystudies for the optimised formulation

Stability studies showed that there was no significant reduction in the drug content (<10%0.7%) and hence the optimized formulation was found to be stable. Byobservingthestabilitystudiesitisconcludedthattheoptimisedformulationisstablethroughtheentireperiodof3month sandthedrugreleaseprofileisalsointactthroughoutthetimebeing.

***In vivo* studies on optimized formulation**

The results of *in vivo* studies are shown in Figure 8. The *in vivo* studies showed that the optimized microspheres of STV showed a prolonged drug release pattern as compared to oral solution of the STV. The formulation showed C_{max} of 89 ng/mL, T_{max} of 8 h, $t_{½}$ of 3.68 h, K_{el} of 0.89/h, AUC(0-t) of 2127 ng-h/mL, MRT of 10.57 h and AUMC (0-t) 23765 ng-h*h/mL. The kinetic pattern was shown in Figure 7.

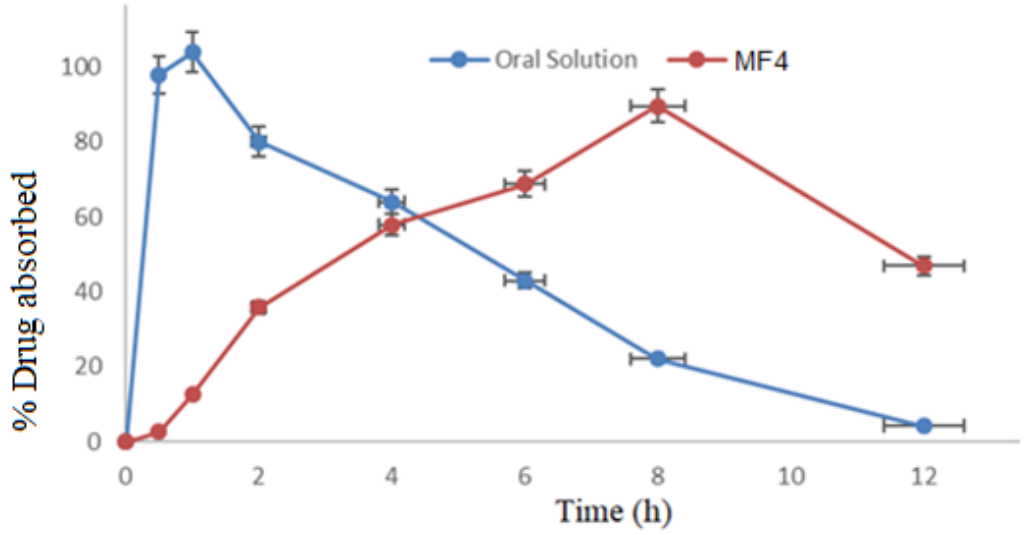

Figure7:Plasmaconcentration(ng/ml)ofSTVoraldrugsolutionandgastro-retentivemicrospheresformulationMF4

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Theobjectiveofthestudyistoformulateandevaluate STV floating microspheres by ionotropic gelation method. The preparation contained 12 formulations using different polymers, i.e. XG, GG and LG in different ratios. The prepared batches of STV floating microspheres were evaluated like *invitro* buoyancy, swelling index, drug entrapment efficiency and *invitro* release studies and *invivo* studies. *Invitro* release studies were done in order to investigate the release of drug from floating alginate microspheres. STV was released rapidly from alginate-cellulose microspheres in the gastric fluid. In the formulations with LG and XG as copolymers maximum drug release occurred 92 and 90% respectively. In the absence of gas forming the release rate was slow. This can be explained as the highly dense internal structure of the alginate microspheres. *Invivo* results of STV microspheres showed the T_{max} of 8h, C_{max} of 89ng/mL, and $AUC_{(0-t)}$ of 2127ng-h/mL.

CONCLUSION

Gastro-retentive floating microspheres of STV using SA and GG, LG, XG as polymer blend were formulated to deliver stavudine via oral route. The prepared formulations were subjected to various evaluation parameters and the optimised formulations selected based on the drug release and MF4 is selected as the best formulation for consistent drug release in the given time. Microspheres resulted in significant improvement in physical properties of the drug especially with respect to flow properties. *Invivo* results showed increased bioavailability of the optimized formulation which will be reducing the dose and side effects of stavudine. Therefore the Formulation MF4 could be successfully used as floating drug delivery system for stavudine.

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REFERENCES

1. Mahale MM, Saudagar RB. Microsphere: A Review. JDDT. 2019;9(3-s):854–856. doi: 10.22270/jddt.v9i3-s.2826.
2. Deveswaran R, Manavalan R, MadhavanV, BharathS.Formulation and evaluation of albumin microspheres containing aceclofenac. Int J Pharm Sci Rev Res. 2010; 4 (1): 112–117.
3. Vinukonda A, Kunderu R, Gunnam S. Review on mucoadhesive microspheres. Int J ChemTech Res. 2018; 11: 277–289.
4. Thummar AV, Kyada CR, Kalyanvat R, Shreevastva BA. Review on mucoadhesive microspheres as a novel drug delivery system. Int J Pharm Scholar 2013; 2: 188–200.
5. Patel NR, Patel DA, Bharadia PD, Pandya V, Modi D. Microsphere as a novel drug delivery. Int J Phar Life Sci. 2011; 2(8): 992–997.
6. Padala NR, Prakash K, Bonepally CSR, Krishnaveni B, Shanta KK, Lakshmi NM. Stavudine loaded microcapsules using various cellulose polymers: preparation and in-vitro evaluation. Int J Pharm Sci Nanotech. 2009; 2(2): 551–556.
7. Mahendar R, Kranthi Kumar G, Chinna RP, RaoPatnaikKS.Formulation, Optimization and in vitro characterization of stavudine gastro retentive floating matrix tablets. Int J Pharm Sci Drug Res. 2016; 8 (3): 128–135.
8. Vohra SY, Patil CC. Development and characterization of stavudine microspheres prepared using different polymers. J Pharm Res. 2009; 2 (3): 953–957.
9. Srikrishna T, Gobinath M, Venkata AP, Sai GM, Sudheer S. Study of stavudinemultiparticulate floating drug delivery system prepared by emulsion gelation technique. Saudi J Med Pharm Sci. 2017; 3: 714–727.
10. Sundaramoorthy R, Vuyyuru M, Dhanaraju MD. Formulation and evaluation of stavudine loaded sodium alginate beads by ionotropic gelation method. Int Res J Pharm 2014; 5(9): 706–712.
11. Choudhury PK, Kar M. Preparation of alginate gel beads containingmetformin hydrochloride using emulsion - gelation method. Trop J Pharm Res 2005; 4 (2): 489–493.
12. Parul T. Preparation and characterization of aceclofenac microspheres. Asian J Pharm. 2008; 1: 110-115.

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

13. S.Tiwari and B Mishra. Multilayered membrane-controlled microcapsules for controlled delivery of isoniazid. DARU J Pharm Sci. 2011; 19 (1): 41–46.
14. Rahulnair, Arun KKS, Vishnupriya KV. preparation and characterization of Rizatriptan loaded solid lipid nanoparticles. J Biomed Sci Res. 2011; 3: 392–396.
15. Yüce M, Canefe K. Indomethacin-loaded microspheres: preparation, characterization and in-vitro evaluation regarding ethylcellulose matrix material. Turk J Pharm Sci. 2008; 5 (3): 129–142.
16. Nochosa A, Douroumis D, Bouropoulos N. In vitro release of bovine serum albumin from alginate/HPMC hydrogel beads. 2008; 74 (13): 451–457.
17. Prabu LS, Shirwaikar AA. Formulation and evaluation of sustained release microspheres of rosin containing aceclofenac. Ars Pharm. 2009; 50 (2): 51–62.
18. Young R, Chulsoo S. Preparation and characterization of alginate–carrageenan complex films. J ApplPolym Sci. 2006; 99 (6): 3483–3490.
19. Arrora S, Ali J, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS Pharm Sci Tech. 2005; 6: 372–390.
20. Pradeesh T, Sunny M, Varma H, Ramesh P. Preparation of microstructured hydroxyapatite microspheres using oil in water emulsions. Indian Acad Sci. 2005; 28 (5): 383–390.
21. Khadeer ZS, Srinivasulu Y, Pushpa LE. Development and validation of new spectrophotometric method for the estimation of stavudine in bulk and pharmaceutical dosage form. Sch. Acad. J. Pharm., 2013; 2(4):319-322.
22. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52: 1145–1149.
23. Fundeanu G, Esposito E, Mihai D. Preparation and characterization of alginate Microspheres by a new emulsification method. Int J Pharm. 1998; 170: 11–21.
24. Kharia AA, Hiremath SN, Singhai AK and Jain SK: Design and optimization of floating drug delivery system of acyclovir. Indian J Pharm Sci. 2010; 72 (5): 599–606.
25. Surajpalverma, bioanalytical method development and validation for the simultaneous estimation of lamivudine and stavudine in human plasma by HPLC, ActaPoloniaePharmaceutica Drug Res. 2010; 67: 429–437.