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Enhancement of Glimepiride dissolution profile by Solid dispersion method

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Abstract

The drugs can provide relief,type-II diabetes are poorly soluble in nature. So,formulating them is a tedious and difficult task. So, before formulation their solubilityshouldbeenhancedinordertoincreasedrugavailabilityandbioavailabilitysimultaneously.The main aim of this study solid dispersion with polymerhavinghigh Tgvalue(PVPK30)by solventevaporationtechniquehavingbothadvantage,generationofamorphoussystemandformationofsoliddispersionsimultaneously.This activated system prepared with PVP K 30 as carrier, was able toremarkablyincreasethedissolutionprofileandsolubilityofthepoorly solubleGlimepiridascomparedtoothersoliddispersiontechniques.alltheratiosofsoliddispersions were dissolved completely within 20minute, and when observed visually,they were found to be dissolved only within 2 minute. While, on the other hand, noneof the physical mixture andpure drugwere dissolvedcompletely even after60minutes.

Introduction

A system in which excess amount of drug is present more than its saturationsolubilityinthe"mediumatroomtemperatureisreferredtoassoliddispersionwheretheexcessdrugseparatesintheformofcrystalsorinamorphousformiinthevehicleafterseparatingas asolidphaseEarlier the solid dispersions were prepared using urea and sugars which arebelievedtobethefirstcarriers.Thedisadvantageassociatedwiththesesoliddispersionsisthattheyformcrystallinesoliddispersionswhichishighlythermodynamically stable and slows down the release of drug as compared to theamorphousforms.Thesecondgenerationofsoliddispersionsisidentifiedwiththeuseofamorphous carriers. Polymeric carriers are believed to be of highest utility becausethey are amorphous solid dispersions. The drug particle size was reduced appreciablyto molecular size in order to completely dissolve the drug in the water-soluble carrier,toachievebetterwettabilityanddistributionofthedruginthecarriermaterialresulting into the production of amorphous system containing amorphous carriers anddrug.Thedissolutionofcarrierdominates the drugrelease.

Material and method

Material - Glimepiride (drug), Methanol, polyvinylpyrrolidone PVP K30

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Method

PreparationofCalibrationCurveofGlimepiridein DMWater

10mgof drugglimepiridewas accurately weighedandtransferredtoa100mlvolumetric flask. To this, 20 ml of methanol was added to dissolve the drug and thevolume was made up to 100 ml with methanol to prepare a 100 µg/ml solution.Appropriate dilutions were made with demineralized water to obtain 5, 10, 15, 20, 25,and 30, µg/ml solution of drug. The absorbance of the resulting drug solutions wasmeasured spectrophotometrically at 225 nm against the corresponding reagent blank. Thedatawererecordedintable 1andgraphicallyrepresented infigure1.

Table 1: Absorbance data for calibration curve of glimepiride in demineralizedwaterat225nm(n=3)

S.no.	Concentration(µg/ml)	Absorbance(mean ±S.D.)
1	0	0
2	5	0.085±0.001
3	10	0.178±0.003
4	15	0.259±0.005
5	20	0.351± 0.002
6	25	0.430± 0.011
7	30	0.512± 0.008

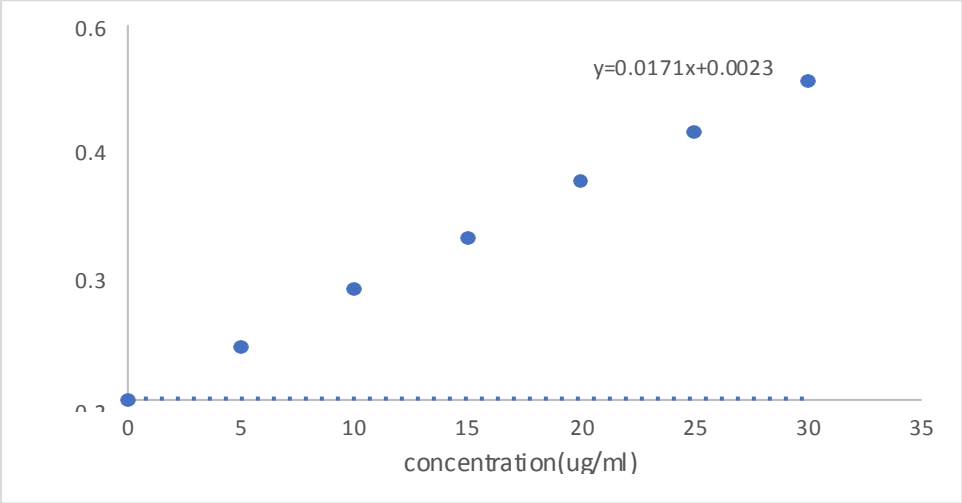

Fig.1:Calibrationcurveofglimepiride

Determination of Interference of Solubilizers in theSpectrophotometricEstimationof glimepiride

Excipients:PolyvinylpyrrolidoneK30wasusedforth einterferencestudy.Fordetermination of interference of solubilizers in the spectrophotometric estimation ofglimepiride, the absorbance of the standard solutions of glimepiride was determined indemineralized water alone and in the presence of the excipients. The absorbance wasrecorded against respective reagent blanks at 225 nm and results are shown below intable2.

Table2:Drugsolubilizersinterferencestudiesinthespectrophotometricestimationofglimepiride

Drug	Solubilizer	Drugconc.(µg/ml)	Solubilizerconc.(mg/ml)	avelength(nm)	Absorbanceagainstrespective reagentblank
Glimepiride	-	30	-	225	0.512
Glimepiride	PVP K30	30	50	225	0.739

Determinationofsolubility

The solubility determination of glimepiridewas carried out in DM water Theexcess drug was added to 30 ml of water containedin a 50 ml glass bottle andbottlewas sealed with closure. The bottle was shaken for 12 hrsonmechanical bathshaker (Khera Instrument Pvt. Ltd., Delhi, India) and allowed to equilibrate for 24 hrsundisturbed. The solution containing drug were filtered through Whatman filter papergrade no.41. Aliquot of the filtrate were suitably diluted with DM water and thedilution wasanalysed on UV-Visible spectrophotometer (Shimadzu 1700).The resultispresentedintable3

Table3:Solubilityofglimepiride

S.No.	Solvent	Solubility%(w/v)
1.	Demineralizedwater	0.0852

DeterminationofPartitionCoefficient

Partition coefficient is a measurement of drug's lipophilicity and its ability tocross cell membrane. Partition co-efficient was determined as ratio of concentration ofdrug inoctanoltotheconcentrationofdrug inDMwaterand itslog valuewastakenforlog P.Partition coefficient of glimepiride was determined at 37 ±0.5ºC by taking 20 ml of octanol which was saturated with 20 ml of DM water by moderate stirring withexternally driven magnetic stirrer for 6 hours. After stirring the system remainedundisturbedforhalfanhour.Accuratelyweighed20mgofdrugwasaddedtothissolutionandwasmoderatelyshakenonwristactionmechanicalstirrerforabout3hours.Itturnsobservedthatnosuspendedparticleswerepresentundissolved.Twolayerswereseparated through separating funnel and the amount of glimepiride dissolved in eachphasewasdeterminedbymeasuringtheabsorbanceofwaterat225nmagainst reagentblankonadoublebeamUVvisiblespectrophotometer(Shimadzu-1700).Afterdeterminingthe concentrationofdrug in waterphase,theconcentrationofdrug inoctanolphase was calculated by subtracting the amount of drug present in aqueous phase from 20mg.

pHDependentSolubilityProfileofglimepiride

For determination of pH dependent solubility, buffer solutions of pH 1.2 to pH10were prepared. Solubility studiesindifferentpH medias were carriedoutbyadding an excess amount of drug in 10 ml of respective medium contained in 20 mlglass vials and keeping the sealed vials containing this solution on a bath shaker(Khera

Instrument Pvt. Ltd., Delhi, India) at room temperature for 24 hrs, so thatequilibriumsolubility can beachievedandsolution wereequilibratedfor12 hrs(undisturbed). The solutions were filtered through Whatman filter paper grade no.41.Filtrates were suitably diluted with respective buffer solutions and absorbance of thesolutions were measured at225nm againstreagentblank on a double beam UV-visible spectrophotometer (Shimadzu 1700). The solubilities at different pH are shownintable4.

Table4:pHsolubilityprofileofglimepiride

S.No.	BufferpH	Solubility(%w/v)	Inference
1	1.2	0.246	Slightlysoluble
2	2	0.106	Slightlysoluble
3	2.8	0.100	Slightlysoluble
4	4	0.032	Veryslightlysoluble
5	5	0.017	Veryslightlysoluble
6	7	0.042	Veryslightlysoluble
7	8	0.119	Slightlysoluble
8	9	0.328	Slightlysoluble
9	10	0.366	Slightlysoluble

DrugSolubilizersIncompatibilityStudies

The differentformulation components involved in the development of theproposed formulations were physically mixed with drug in 1:1 ratio and filled in glassvials properly, capped and sealed. The vials of each sample were kept either at roomtemperature, or in refrigerator or in thermostatically controlled oven maintained at40ºCforonemonthperiod.Aftereveryweek(forone month),thevialswerewithdrawn and the changes in physical appearance (if any) and color of the contentswere observed.Theobservationswererecordedintableno. 5.

S.NO.	Drugsolubilizer(1:1 blend)	InitialObserva-tion	Refrigeratedcondition (2-8ºC)				oomtemperature(25º)				Thermostaticallycontrolledoven (40°C)			
			1w	2w	3w	4w	1w	2w	3w	4w	1w	2w	3w	4w
1.	glimepiride	White Powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
2.	glimepiride + Polyvinylpyrrolidone K30	WhitePowder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

NC=NoChange,W=Week

Formulation DevelopmentofSolidDispersionofGlimepiride

Solventevaporationmethodwasusedforthepreparationof SDs.Fivedifferentdrug:carrierratios(1:1,1:2,1:3,1:4,and1:5)wereusedinTable6.GMPandPVPK30 wereweighedaccordingtotheseweighedratios.Forpreparationofsoliddispersions,firstlydrugwasdissolvedinsolvent(methanol). Then a polymer (PVP K30) was dissolved in that solvent with continuousstirring using mechanical stirrer. This solvent was allowed to evaporate on hot platewith stirring at 45±5ºC. The process of evaporation was continued till constant weightwas obtained. The solid dispersions were kept in desiccator for 24 h, then pulverizedand passed through 100 # sieve. The resultant powders were stored in a desiccatoruntilfurtherinvestigation.Dissolution of the solubilizers was facilitated by agitation of teflon coatedmagnetic bead on a high speed magnetic stirrer. After complete dissolution of carrier,accuratelyweighedquantityofdrugwasdissolvedintheabovesolutionandtemperature was maintained in the range of 45-50ºC so as to facilitate the evaporationof solvent. As evaporation proceeded, speed of bead automatically decreased and itstopped stirring when most of the water was evaporated, thus indicating the formationofsoliddispersion(wet).The wet solid dispersions thus obtained were spread on several watch glassesand the watch glasses were kept in hot air dry oven maintained at 50 ± 2ºC so thatremaining moisture could also be evaporated easily and a constant weight with nofurther weight loss (due to evaporation) could be obtained. After complete drying,solid dispersions were crushed using a glass pestle mortar and passed through sieve #100andwerefinallystoredinanairtightglassbottle.Same procedure was utilized to prepare solid dispersions in the ratio of

1:2,1:3,1:4,and1:5usingappropriatequantityofcarri er(table 6)

Table6:Compositionofglimepiride-PVPK30soliddispersions

S.no.	FormulationNumber	Drug:CarrierRatio
1	SD1	1:1
2	SD2	1:2
3	SD3	1:3
4	SD4	1:4
5	SD5	1:5

FormulationofPhysicalMixtures

Physical mixture of drug and polymers PVP K30 in 1: 1 ratio (PM) was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier for 5 minutesin glass mortal, which was then passed through mess number 40 and stored in a desiccator respectivelySame procedure was utilized to prepare physical mixture in the ratio of 1:2, 1:3, 1:4, and 1:5 using appropriate quantity of carrier (table 7).

Table7:Compositionofglimepiride-PVPK30physicalmixture

S.no.	FormulationNumber	Drug:CarrierRatio
1	PM1	1:1
2	PM2	1:2
3	PM3	1:3
4	PM4	1:4
5	PM5	1:5

DeterminationofDrugContentofSolidDispersion sandPhysicalMixtures

Powdered solid dispersion or physical mixture equivalentto10 mg of drugwas accurately weighed and transferred to a 1000 ml volumetric flask, and volumewas made up to 1000 ml with demineralized water. Absorbance of this solution wasmeasured at 225 nm against corresponding reagent blank. Results of the analysis areshowninthetable8.

Table8: Drugcontent ofsolid dispersionsandphysicalmixtureofglimepiride

S.No.	Drug:Solubilizers	Drug content(% w/v)	
		Soliddispersion	Physicalmixture
1	1:1	98%	99.95%
2	1:2	99.93%	98.65%
3	1:3	100.21%	100%
4	1:4	101.2%	101.3%
5	1:5	100.3%	100.2%

DissolutionRateStudies

Dissolution tests are one of the most widely used tests in quality control ofdosage forms. Dissolution tests become especially important when dissolution is theratelimitingstepasinthe case ofB.C.S.classIIorB.C.S.classIV drugs.

Procedure

Solid dispersion or physical mixture equivalent to 10 mg of glimepiride weretestedindissolutionratestudiesusingU.S.P.XXIV(typeII)dissolutiontestapparatus(ModelTDT6P,ElectrolabMumbai,India)withpaddletorotateat50r.p.m. Nine hundred ml of demineralized water was taken as dissolution medium withtemperature of 37±0.5°C.Atdefinitetimeintervals,10ml of thesampleswaswithdrawnandwereanalyzedfordrug content.Withdrawnsampleswerealsoreplaced with fresh dissolution medium. Calculations for the amount of drug weredoneusingrespectiveregressionequationsandtheresultsofthedissolutionstudiesare shownintable9,10,11,12, and 13.

Table 9: Dissolution rate studies of solid dispersion, physical mixture (ratio 1:1)anddrug

S.no.	Time (min)	SD(1:1)	PM(1:1)	Bulk drug
		% CDD	% CDD	% CDD
1	2	41.76	29.43	24.03
2	5	55.69	37.21	29.45
3	10	62.71	44.67	34.81
4	15	86.36	47.84	37.62
5	20	92.73	49.61	41.04
6	30	96.18	53.77	47.25
7	45	99.96	64.49	53.97

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8	60	99.62	77.83	55.16

CAD=Cumulativeamountdissolved;%CDD=%cumulativedrugdissolved;SD =Soliddispersion;PM= Physicalmixture.

Fig.2: Cumulative% drugdissolvedv/stimeplotofsoliddispersion, physicalmixture (ratio1:1) andbulkdrug

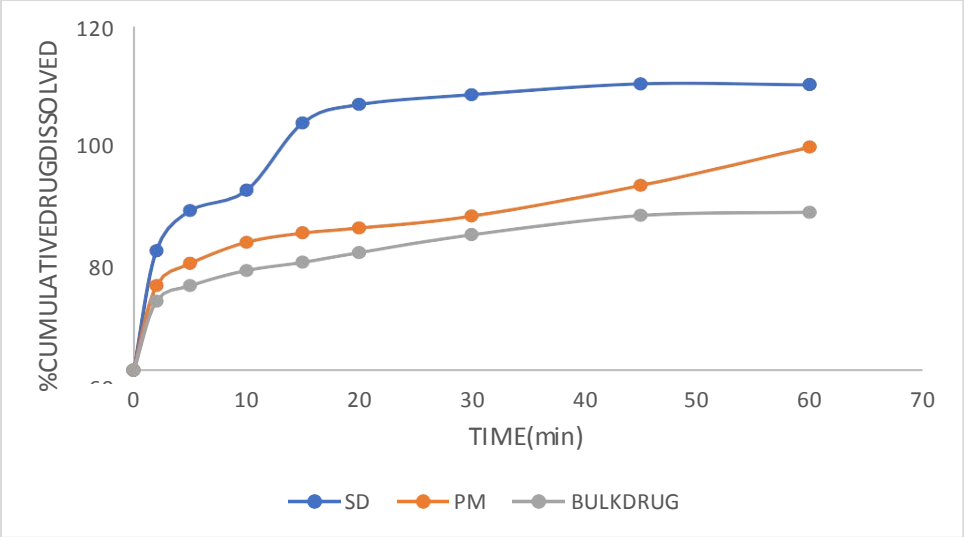

Table 10: Dissolution rate studies of solid dispersion, physical mixture (ratio 1:2)anddrug

S.no.	Time (min)	SD(1:2)	PM(1:2)	Bulkdrug
		% CDD	% CDD	% CDD
1	2	42.39	29.52	24.08
2	5	54.73	37.33	29.61
3	10	62.41	44.94	33.99
4	15	86.94	48.40	36.91

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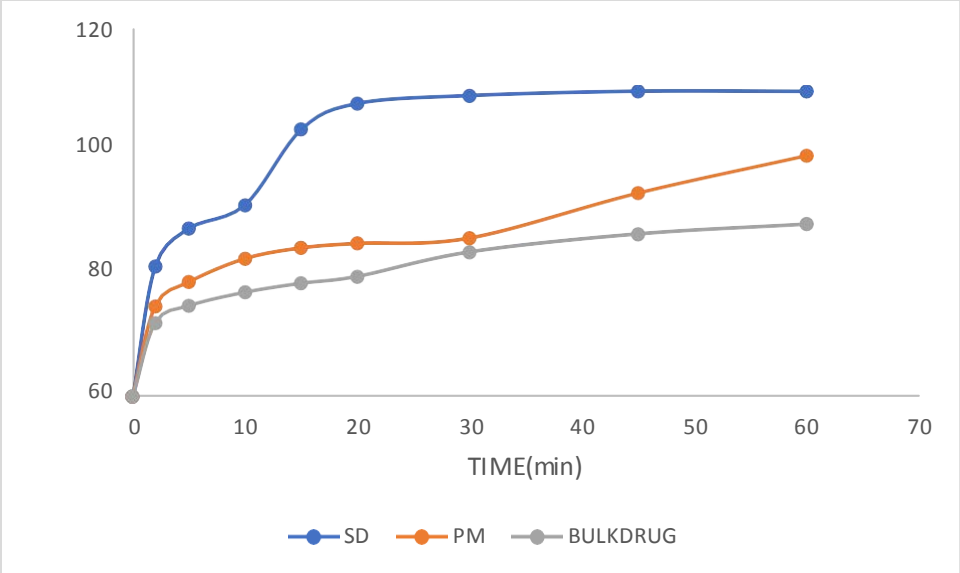
5	20	95.40	49.87	39.14
6	30	97.98	51.62	47.12



7	45	99.40	66.26	52.98
8	60	99.35	78.42	56.16

CAD=Cumulativeamountdissolved;%CDD=%cumulativedrugdissolved;SD =Soliddispersion;PM= Physicalmixture.

Fig.3: Cumulative % drug dissolved v/s time plot of solid dispersion, physical mixture(ratio1:2) andbulkdrug

Table11:Dissolutionratestudiesofsoliddispersion,physicalmixture(ratio1:3)anddrug

S.no.	Time (min)	SD(1:3)	PM(1:3)	Bulkdrug
		%CDD	%CDD	%CDD
1	2	41.20	29.32	25.13
2	5	56.48	37.59	29.69

3	10	61.82	45.20	35.21
4	15	87.83	48.05	38.64
5	20	94.51	51.06	42.03
6	30	96.73	52.22	48.23
7	45	99.04	70.69	54.98
8	60	99.63	79.93	56.21

CAD=Cumulativeamountdissolved;%CDD=%cumulativedrugdissolved;SD=Soliddispersion;PM=Physicalmixture.

Fig.4: Cumulative% drugdissolvedv/stimeplotofsoliddispersion,physicalmixture(ratio1:3) andbulkdrug

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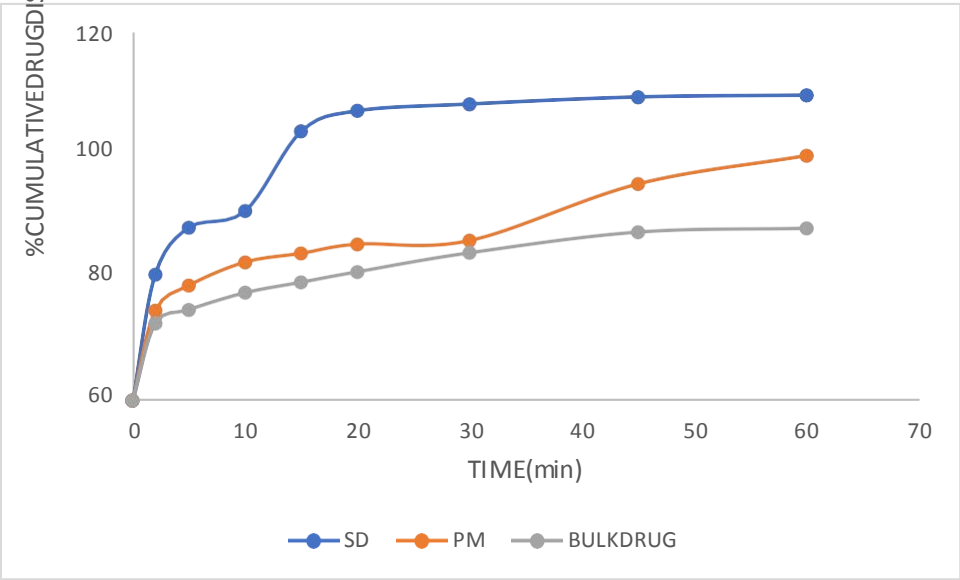
Table12::Dissolutionratestudiesofsoliddispersion,physicalmixture(ratio1:4)anddrug

S.no.	Time (min)	SD (1:4)	PM(1:4)	Bulk drug
		% CDD	% CDD	% CDD
1	2	45.20	32.62	25.13



2	5	58.88	39.63	29.69
3	10	69.22	47.28	35.21
4	15	91.83	50.78	38.64
5	20	93.41	55.53	42.03
6	30	97.33	62.29	48.23
7	45	99.12	78.62	54.98
8	60	99.78	81.33	56.21

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CAD=Cumulativeamountdissolved;%CDD=%cumulativedrugdissolved;SD =Soliddispersion;PM= Physicalmixture.

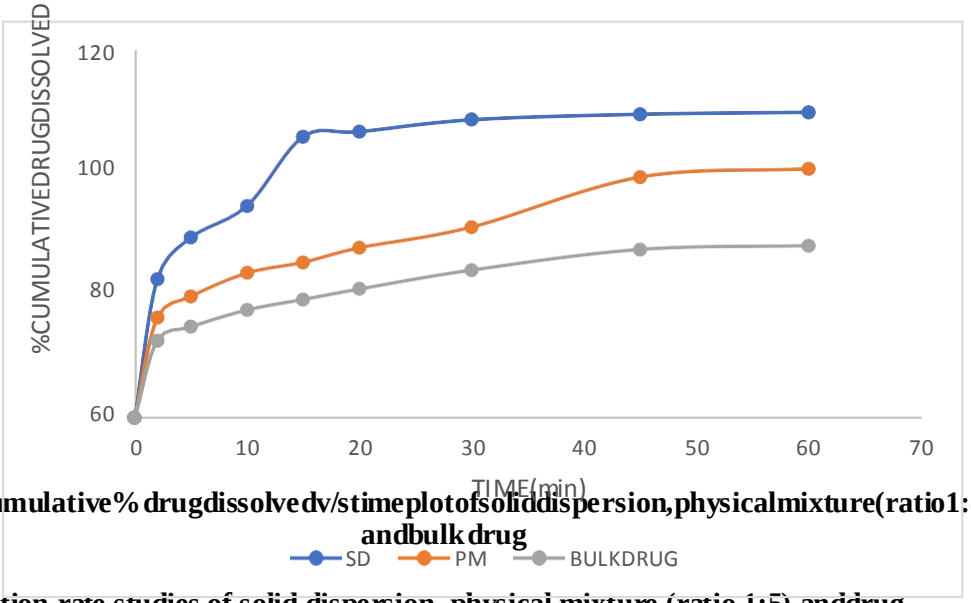

Fig.5: Cumulative% drugdissolvedv/stimeplotofsoliddispersion,physicalmixture(ratio1:4) andbulk drug

Table13: Dissolution rate studies of solid dispersion, physical mixture (ratio 1:5) anddrug

S.no.	Time (min)	SD(1:5) %CDD	PM(1:5) %CDD	Bulk drug %CDD
1	2	48.23	34.12	25.13
2	5	61.88	42.23	29.69
3	10	72.05	49.34	35.21
4	15	93.23	52.28	38.64
5	20	94.09	58.23	42.03
6	30	97.89	68.29	48.23

7	45	99.35	82.32	54.98
8	60	99.83	85.02	56.21

CAD=Cumulativeamountdissolved;%CDD=%cumulativedrugdissolved;SD =Soliddispersion;PM= Physicalmixture.

Conclusion

Fromtheabovestudies,itisevidentthatalltheratiosofs oliddispersions were dissolved completely within 20minute, and when observed visually,they were found to be dissolved only within 2 minute. While, on the other hand, noneof the physical mixture andpure drugwere dissolvedcompletely even after60minutes.

The aim of the present research study was to formulate of solid dispersionusing solventevaporation method thatcan be used to enhance the solubility of apoorly water-soluble drug. The main aim of this study solid dispersion with polymerhavinghigh Tgvalue(PVPK30)by solventevaporation techniquehavingbothadvantage,generationofamor phoussystemandformationofsoliddispersionsimult aneously. This activated system prepared with PVP K 30 as carrier, was able toremarkablyincreasethedissolutionprofileandsolu bilityofthepoorlysolubleGlimepiride ascomparedtoothersoliddispersiontechniques.

In the present study, poorly water-soluble drug, glimepiride, was the drug ofchoice. It was incorporated into solid dispersion using random combination of carrier.Theexcesssolventwasevaporatedfromthisso lutionandsoliddispersionwasobtainedwhichwaslate rdriedcompletely,pulverizedandpacked.

For identification and characterization of drug, spectrophotometric analysis,FTIR spectroscopy, differential scanning calorimetry study were carried out. The drugcompliedwiththe results reportedintheliterature.

The calibration curve of the drug was prepared in the aqueous solution. Thelinearity of the calibration curve showed that the Beer Lambert's law was obeyed inthe concentrationrangeof10-50µg/mlattheλ maxof225nminDMwater.

Preformulation study was carried and solubility of drug in water was carriedout. Aqueous solubility of drug was found to be 0.0852mg/ml. Drug excipient physicalcompatibility study was done observing any physical changes in the blends of drugand excipient for 1 month. UV interference study for drug estimation was also donetaking drug concentration 20µg/ml and excipientconcentration 1000µg/ml againstDM water. These studies showed no physical incompatibility between the drug andexcipients.Solubilisersdidnotinterfereinthespec trophotometricanalysisofglimepiride at225nm.

Different solid dispersions were prepared with different drug and carrier ratio.Prepared solid dispersions were compared for dissolution studies with pure drug andphysical mixture. Solid dispersions containing drug, polymer in various ratios showedverygooddrugreleaseprofile.

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