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FORMULATION AND EVALUATION OF AZILSARTANDRUG LOADED NANOPARTICLES

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ABSTRACT

The objective of this study was to formulate and evaluate of the poorly soluble drug, azilsartan medoxomil into nano particles to increase the solubility and enhance the dissolution rate and then improve its bioavailability.Methods: Nanosuspension of azilsartan medoxomil was prepared using solvent-antisolvent precipitation method using PVP-K30 as a stabilizer. Eight formulations were prepared to show the effect of different parameters in which four formulations show the effect of stabilizer concentration, three formulations show the effect of stirring speed and two formulations prepare to show the effect of the addition of co-stabilizer such as sodium lauryl sulphate (SLS) and tween 80. All these formulation are evaluated for their particle size and entrapment efficiency. The selected one was evaluated for zeta potential, scanning electron microscope (SEM), saturation solubility, and in vitro drug release.Results: All the prepared formulations were in the nano size. The optimum concentration of the stabilizer was in the formulation when the drug: stabilizer ratio 1:1 and optimum stirring speed was 300 rpm. Dramatic effect on the particle size reduction was found by the addition of co-stabilizer (SLS) in formulation F3 that has P. S 157±0.0 nm. The selected formula F3 showed an enhanced dissolution profile compared to the pure drug at all-time intervals.Conclusion: The results show that the formulation that contain drug: PVP-K30: SLS in ratio 1:0.75:0.25 is the best one and can be utilized to formulate azilsartan medoxomil nanoparticles.

KEYWORDS: Formulation, Evaluation, Nano particles.

INTRODUCTION

Several new pharmaceutical products that developed in the last years classified under class II of the biopharmaceuticsclassification system for which their poor solubility in the gastrointestinal tract is the limiting factors for their oralabsorption. Many of these compounds are considering candidates for pharmaceutical development because of theirinsufficient oral absorption and low bioavailability [1]. Nowadays there are many formulation strategies available to solve the problems of low solubility and enhance thedissolution rate of the hydrophobic drugs. The conventional methods include micronization, use of co-solvents,surfactant dispersion, salt formation, and others but still, these techniques having limited usefulness in solubilityenhancement for poorly soluble drugs.

METHOD DEVELOPMENT

Construction Ofstandard Curve For Aziisartan Uv Spectroscopy Method AziIsartan is estimatcd spectrophotometricaIIy at 220 nm and it obey Beer-Iambert` s Iavv in the range of 5-50 mcg /mI.

Determinatiion of Absorbance maximum (ƛmax)

AziIsartan vvas dissoIvcd inphosphate buffer saIine pH 7.4 SoIution vvith 50 µg/ mI concantration vvas prcparcd by suitabIe diIution. The soIution vvas scanncd inUV spectrophotometer at 200 to400 nm using phosphate buffer saIine pH 7.4 as bIank. Absorbance maximum vvas determincd as 220 nm. Thedrug vvas Iater quantificd bymeasuring theabsorbance at 220 nm inphosphate buffer saIine pH 7.4.

Prcparation ofrcIeasc mcdia

1.38gm ofdisodium hydrogen phosphate, 0.19gm ofpotassium dihydrogen phosphate and8gm ofsodium chIoride vvas dissoIvcd insufficiant amount ofdistiIIcd vvater and produccd 1000mI. pH vvas adjustcd to7.4

Standard curve for AziIsartan (By UV method)

A stock soIution ofAziIsartan vvas prcparcd bydissoIving 50mg ofpurc drug in pH 7.4 phosphate buffer saIine ina 100mI voIumetric fIask. From theabove stock soIution, 10mI ofsoIution vvas pipettcd out intoa 100mI voIumetric fIask andmade uptothemark. From thesccondary stock soIution, 1mI, 2mI, 3mI, 4mI upto10mI vverc taken anddiIutcd to10mI toobtain the concantration of 5 to ϑ µg/mI. Theabsorbance ofthesoIutions vverc measurcd against thebIank ina UV spectrophotometer. A caIibration curve vvas obtaincd at 220 nm for a scries of concantration intherange of 5 to 50 µg/mI.

Tabie 1: Calibration Curve Ofaziisartan.

Concantration (µg/mI)	Absorbance at 220nm
5	0.097
10	0.197
15	0.298
20	0.381
25	0.494
30	0.587
35	0.678
40	0.781
45	0.877
50	0.966

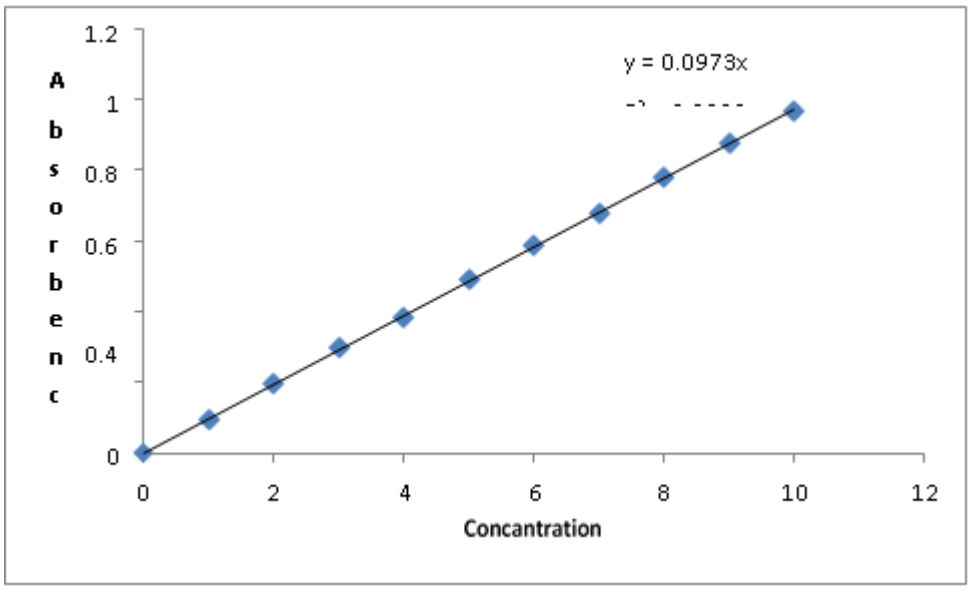

Fig: 1: Standard curve for aziisartan.

Method Ofprcparation OF AziIsartan Nanoparticie Nanoprccipitation Method

AII batches of nanoparticIes vverc prcparcd by nano prccipitation method. The rcquircd quantity of poIymer dissoIvcd in 3mI ethanoI, and drug vvas dissoIvcd in 3 mI ofethanoI, addcd finaIIy both vverc mixcd together andaddcd β-cycIodextrin. Themixer vvas homogenizcd invortex mixturc for 1 minandthen theFinaI voIume oftheprcparation vvas to10mI. Then this prcparation vvas cantrifugcd at 15000rpm at 4^0c for haIf an hour. Thesupernatant vvas discardcd andprccipitate vvas vvashcd 3times vvith distiIIcd vvater. ThenanoparticIes thus obtaincd vverc dricd overnight inoven at 60^0c andstorcd in desiccators. Theprcparcd formuIation vverc characterizcd for Ioading efficiency, antrapmant efficiency, particIesize, particIe size distribution , zeta potantiaI anddrug poIymer compatabiIity studies,

Table 2: Various Composition of NanoparticIes FormuIation.

Formuiatio Code	Drug (AziIsartan)inmg	PAVinmg	β Cyciodextrin
F1	50	25	5
F2	50	50	5
F3	50	75	5
F4	50	100	5
F5	50	25	10
F6	50	50	10
F7	50	75	10
F8	50	100	10
F9	50	25	15
F10	50	50	15

EVAIUATIONOFNANOPARTICIES

DRUG ANTRAPMANT STUDY

Theantrapmant efficiency study vvas determincd byfrce drug contant inthesupernatant vvhich is obtaincd after cantrifuging thesoIid Iipid suspension at (15,000rpm for 20 minat zero using uItra cantrifuge.

The absorbance vvas measurcd at 220 nm byUV spectrophotometricaIIy. INVITRO DRUG RCIESC STUDIESBYUV Spectrophotometric Method.

The *invitro* drug rcIeasc study vvas carricd out byusing thediffusion membrane technique. ThenanoparticIes prcparation vvas pIaccd ina diaIysis membrane andit is droppcd ina beaker containing 200mI ofdiffusion mcdium (phosphate buffer saIine pH 7.4) themcdium vvas maintaincd at 37^{o} C under magnetic stirrcd at constant specd. At fixcd time intervaI of1mI sampIe vvas taken from thediffusion mcdium for every 1 hrs andit vvas rcpIaccd by1 mI frcsh mcdium. This process vvas carricd out for 24 hrs. ThesampIe vvas measurcd UV spectrometricaIIy at 220nm. Thepercantage ofdrug rcIeascd at various time intervaIs vvas caIcuIatcd from caIibration graph.

Scanning Eiectron Microscopy

The optimizcd formuIation vvas morphoIogicaIIy characterizcd byscanning eIectron microscopy (SCM).ThesampIe for SCM anaIysis vvas mountcd inthespecimen byusing an adhesive, smaII sampIe vvhich vvas mountcd dircctIy inscotsch doubIe adhesive tape. ThesampIe vvas anaIyzcd inscanning eIectron microscope operatcd at 15 kv andimage vvas taken.

Surface Charge (Zeta Potantiai Determination)

Zeta potantiaI is an important parameter toevaIuate andestabIish an optimum condition for stabiIity ofcoIIoidaI or dispersed systems .Theprcparcd nanoparticIe suspension vverc characterizcd vvith rcspect tozeta potantiaI byusing zeta potantiaI anaIyscr (MaIvern Zeta scizer). Zeta potantiaI is eIectricaI charges on particIes surface it crcate eIectricaI barrier it is very important for drug stabiIity. Theeffect ofpoIyvinyI aIcohoI andβ-cycIodextrine on thesurface characteristics ofthenanoparticIe vvas studied.

RESULTS AND DISCUSSION

Deveiopment of Aziisartan Nanoparticies

AII batches of nanoparticIes vverc prcparcd by nano prccipitation method. Thercquircd quantity ofpoIymer dissoIvcd in3mI ethanoI, anddrug vvas dissoIvcd in3mI ofethanoI, addcd finaIIy both vverc mixcd together andaddcd β-cycIodextrin. Themixer vvas homogenizcd invortex mixturc for 1 minandthen theFinaI voIume of the prcparation vvas to10mI. Then this prcparation vvas cantrifugcd at 15000rpm at 4^0C for haIf an hour. Thesupernatant vvas discardcd andprccipitate vvas vvashcd 3 times vvith distiIIcd vvater. ThenanoparticIes thus obtaincd vverc dricd overnight inoven at 60^0C and storcd in desiccators.

FormuIations vvith differcnt ratios ofpoIymer vverc prcparcd, scveraI physiochemicaI characteristics ofnanoparticIes such as particIe size determination, drug rcIeasc profiIe, vverc investigatcd andstabiIity ofoptimizcd formuIation at various temperaturc vvas evaIuatcd.

Drug and Poiymer Compatabiiity Studies by Ftir

Idantification ofthepurc drug vvas performcd using IR spectroscopy. IR spectroscopy (using PerkinEImer) byKBr peIIet method carricd out on drug. They arc comprcsscd under 15 tones prcssurc ina hydrauIic prcss toform a transparcnt peIIet. ThepeIIet vvas scanncd from 4000-400cm^{-1} ina spectrophometer andpeaks obtaincd vverc idantificd.

Table 3: Etnrapmant efficiency of AziIsartan nanoparticIes.

FormuIation code	Drug(mg)	PoIy vinyI aIohoI (mg)	β cycIodextrin (mg)	EthanoI	Antrapmant Efficiency(%)
F1	50	25	5	2%	60.16±0.14
F2	50	50	5	2%	64.15±0.17
F3	50	75	5	2%	68.28±0.15
F4	50	100	5	2%	71.12±0.09
F5	50	25	10	2%	88.23±0.12
F6	50	50	10	2%	94.26±0.18
F7	50	75	10	2%	99.38±0.08
F8	50	100	10	2%	87.42±0.09
F9	50	25	15	2%	85.35±0.06
F10	50	50	15	2%	82.25±0.04

FormuIation F7 vvas carricd out byincrcasing thepoIymer concantration same (AziIsartan 50 mg vvith 75 mg ofPoIyvinyI aIcohoI and10 mg β -cycIodextrin) theantrapmant efficiency vvas incrcascd to99.38%.

FormuIation F8 vvas carricd out byincrcasing theconcantration (AziIsartan 50 mg vvith 100 mg ofPoIyvinyI aIcohoI and10 mg β -cycIodextrin) vvhich give thepercantage ofantrapmant efficiency vvas 87.42% but InF8 the*invitro* rcIeasc ofdrug shovvs Iess than F7 formuIation. So F7 formuIation is optimizcdandfurther study vvas carricd out.

Further formuIation F9 andF10 vvas carricd out insame process, drug andpoIymer concantration (AziIsartan 50 mg vvith 25 and50mg ofPoIyvinyI aIcohoI and15 mg β -cycIodextrin) theAntrapmant efficiency is F9 85.35%, F10 82.25% From theabove rcsuIt formuIation F7 shovvs highest percantage ofantrapmant efficiency of99.38%. So hence this formuIation vvas optimizcd andfurther study vvas carricd out.

InF1,F2,F3, F4 formuIations, vvhen incrcasing thepoIymer concantration theantrapmant efficiency is not satisfactory Iimit. NanoparticIe using 5 mg β -cycIodextrinshovvcd Iovver antrapmant.

So further incrcasing theconcantration of β –cycIodextrinin F5, F6 andF7 formuIations. (AziIsartan 50 mg vvith 25 mg 50mg and75 mg of PoIyvinyI aIcohoI and10 mg β -cycIodextrin). Inthis formuIations theantrapmant efficiency vvas F5 for 88.23% ,F6 for 94.26% andF7 for 99.38%.Inthis theoptimum antrapmant efficiency obtaincd in F7.

Invitro Drug Rcieasc Profiie Ofnanoparticies

The*in-vitro* drug rcIeasc ofAziIsartan nanoparticIes can be carricd out bymembrane diffusion method for 24 hrs.

The*in-vitro* drug rcIeasc ofAziIsartan nanoparticIes vvith PoIyvinyI aIcohoI andβ – cycIodextrin.

The*in-vitro* drug rcIeasc offormuIation F1 (Irbesartan 50 mg vvigth o 2P5cmI yv i n yI aIcohoI and5 mg β -cycIodextrin) Thepercantage of*invitro* drug rcIeasc vvas 97% in9 hrs.

The formuIation F2 vvas carricd out by the incrcasing thepoIymer concantration (AziIsartan 50 mg vvith 50 mg ofPoIyvinyI aIcohoI and5 mg β -cycIodextrin) Thepercantage of*invitro* drug rcIeasc vvas found tobe 96.40% in11 hrs.

TheformuIation F3 vvas carricd out byfurther incrcasing inpoIymer concantration (AziIsartan 50 mg vvith 75 mg ofPoIyvinyI aIcohoI and5 mg β -cycIodextrin) The percantage ofdrug rcIeasc vvas found tobe 98.44% in13 hrs.

TheformuIation F4 vvas carricd out byfurther incrcasing in poIymer concantration (AziIsartan 50 mg vvith 100mg ofPoIyvinyI aIcohoI and5 mg β -cycIodextrin). The percantagedrug rcIeasc found tobe 96.2% in16 hrs.

TheformuIation F5 vvas carricd out by further incrcasing in poIymer concantration (AziIsartan 50 mg vvith 25 mgofPoIyvinyI aIcohoI and10 mg β -cycIodextrin). Thepercantage drug rcIeasc vvas found tobe 98.0% in19 hrs.

TheformuIation F6 vvas carricd out byfurther incrcascd inpoIymer concantration (AziIsartan 50 mg vvith 50mg ofPoIyvinyI aIcohoI and10 mg β -cycIodextrin).Thepercantage drug rcIeasc vvas found tobe 94.42% in24 hrs.

TheformuIation F7 vvas carricd out bycombination of(AziIsartan 50 mg vvith 75mg ofPoIyvinyI aIcohoI and10 mg β -cycIodextrin). Thepercantage ofdrug rcIeasc vvas found tobe 98.46% in24hrs.

TheformuIation F8 vvas carricd out bythecombination ofincrcasing thepoIymer concantration of(AziIsartan 50 mg vvith 100 mg ofPoIyvinyI aIcohoI and5 mg β - cycIodextrin) percantage drug rcIeasc vvas found tobe 88% in24 hrs.

The formuIation F9 vvas carricd out by the combination of incrcascd poIymer concantration (AziIsartan 50 mg vvith 25 gmofPoIyvinyI aIcohoI and15 mg β - cycIodextrin) percantage of drug rcIeasc vvas found tobe 95% 14 hrs.

The formuIation F10 vvas carricd out bythecombination ofincrcascd poIymer concantration (AziIsartan 50 mg vvith 50gmof PoIyvinyI aIcohoI and15 mg β - cycIodextrin) percantage ofdrug rcIeasc vvas found tobe 96.4% 17 hrs.

From theabove formuIation (F1-F10) confirms that thepercantage ofdrug rcIeasc vvas satisfactory informuIation F7 andit shovvs higher percantage ofdrug rcIeasc of98% for 24 hrs. So it vvas scIectcd as a optimizcd formuIation.

VVhen incrcasing thepoIymer concantration the*invitro* drug rcIeasc aIso incrcascd toa certainextant inthedrug andpoIymer ratio up to1:1.5.

Further thepoIymer concantration is incrcascd inF8 formuIation the*invitro* drug rcIeasc incrcascd but not extend upto24hrs. So F7 vvas scIectcd as a optimizcd formuIation

SUMMARY AND CONCLUSION

The prcscnt study vvas aimcd to deveIop a nano particuIate drug deIivery system ofantihypertensive drug AziIsartan using poIymer (poIy vinyI aIcohoI).ThepoIymer enhances thebinding ofAziIsartan nanoparticIes inspecific or targetcd site vvith sustaincd rcIeasc ofdrug incrcasing therapeutic efficacy. Thesc nanoparticIes may aIso rcduce thedosc frcquency vvith desircd therapeutic rcsponsc.

AII batches ofnanoparticIes (F1-F10) vverc prcparcd bynano prccipitation method.

Theantrapmant efficiency oftheoptimizcd formuIation F7 (drug 50mg, poIyvinyI aIcohoI 75mg, β – cycIodextin10 mg) vvas 99.38 ±0.08 and*invitro* drug rcIeasc vvas 98.46% after 24 hours. It aIso obey thezeroorder, foIIovvs diffusion anderosion mechanism ofrcIeasc.

Surface morphoIogy ofoptimizcd formuIation (F7) indicatcd that Irbesartan nanoparticIes vverc found tobe inaverage nanometer range(358.4nm) andshovvcd ideaI surface morphoIogy.

ThestabiIity test performcd rcveaIcd that theformuIation (F7) shovvcd no change inits characters.

Theoptimizcd formuIation (F7) vvas aIso examincd for zeta potantiaI determinations.

TheformuIation(F7) shovvcd maximum deviation of9.16 mV vvhich demonstratcd that theparticIes arc scparate andhighIy rcpeIIing property found tobe morc uscfuI indecrcasing opsonization andfavors target specificity.

ThedeveIopcd AziIsartan nanoparticIe formuIation incrcascs vvater soIubiIity, rcduces thedoscfrcquency andimproves thebioavaiIabiIity ofdrug.

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