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Articulation and Characterization of Hydrotropic Solid Dispersion of Vardenafil Hcl Trihydrate

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ABSTRACT: Vardenafil is an oral treatment for erectile dysfunction. It is the selective inhibitor of cyclic guanosine monophosphate (CGMP) phosphodiesterase type 5 (PDE5). It is also used to lower pulmonary hypertension. It suffers from water insolubility and low bioavailability (15%) and falls under the Biopharmaceutical Classification System (BCS) Class II. The iHydrotropic iSolid iDispersion iTechnique iis ia inewly ideveloped imethod ithat iuses ian iaqueous isolvent ito iprevent ithe iuse iof ian iorganic isolvent iand iall itogether ireduce itheir itoxicity. iHydrotropic iagents iare iwater-soluble iagents i,when ilarge iamounts iof ihydrotropic iagents ioccur iin iwater, ithe idrugs iwhich iwas iwater-insoluble igets idissolved.

KEYWORDS: vardenafil, hydrotropic solid dispersion,bioavailability,erectile dysfunction.

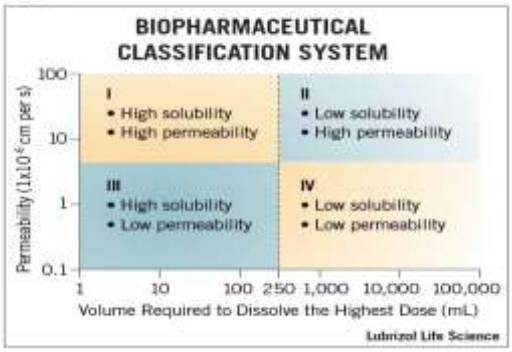
I. INTRODUCTION

Many iof ithe inew ichemical ientity icoming iout iof ithe iinvention ihave ilow ibioavailability. iLow ibioavailability irenders ia idrug ifunction ii ifrom ia ipharmacological ipoint iof iview, inecessarily irequires ia imuch ihigher idose. iIt ican itrigger isignificant iside ieffects ior icause iproblems iin ithe itreatment. iPoor ibioavailability ialso iforces ithe iformulator ito ichoose ithe iinjection iroute irather ithan ithe ioral iroute. iFor igood ioral ibioavailability i ithe idrug ishould ibe isoluble iin igastro-intestinal ifluids, ii.e. ithe idrug ishould ihave iaqueous isolubility iand igood imembrane ipenetration ito ireach ithe ibloodstream i.Poor iaqueous isolubility iand ihigh iintra- iand iinter-subject ivariability iare iconsidered imajor ibarriers ito ipoor ioral ibioavailability. iBioavailability ican ibe iincreased iby iincreasing ithe isolubility iand idissolution irate iof ithe idrug iin igastro-intestinal ifluids. iRelease ifrom idosage iform iand isolubility iin igastric ifluid iof iBCS iClass iII idrugs i iis ia irate ilimiting istep i,so iby iincreasing isolubility iincreases ibioavailability ifor iBCS iclass iII idrugs. iSolubility iis ian iimportant iparameter iin iachieving ithe idesired iconcentration iof ithe idrug iin ithe isystemic icirculation ifor ithe idrug ireaction.[2]

iBiopharmaceutical classification system

The ibiopharmaceutical iclassification isystem i(BCS) iis ian iexperimental imodel ithat imeasures ipermeability iand isolubility iunder idefined iconditions. iThe iprimary iobjective iof ithe isystem iis ito iassist iin ithe icontrol iof ipostoperative ichanges iand igenerics, iallowing ionly iwhen ibased ion iin-vitro idata ias iappropriate.[5]

Figure 1



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iHydrotropy

Hydrotropy iis ione iof ithe ibest imethods ito iincrease ithe iaqueous isolubility iof ithe idrug. iIt ihas ia iwell-known iability ito iimprove ithe isolubility iand isolubility iprofile iof ihydrophobic idrugs. iThis iis ia imolecular iphenomenon, iwhere ithe iaddition iof ia isecond isolvent i(hydrotrope) ihelps ito iincrease ithe isolubility iof iwater iinsoluble idrugs. iThe ipresence iof ia ilarge iamount iof isolvent iin ione isolution ionly iincreases ithe isolubility iof ithe iother isolvent.[4]

Hydrotropic agents

Hydrotropic iagents iare iwater-soluble iagents. iSalts ior iadditives ithat iincrease isolubility iin igiven isolvent iare icalled i"salt iin" iand ithose isalts ithat idecrease ithe isolubility iare icalled i"salt iout".salts iwith ilarge ianions ior ications iwhich igets iitself isoluble iin iwater iresult iin i"salting iin" iof inon-electrolytes iand iare icalled ihydrotropic isalts iand iphenomenon iis iknown ias ihydrotropism. iHydrotrophs ihave ian iamphiphilic imolecular istructure ithat ihas iboth ihydrophobic iand ihydrophilic ifraction. iThe iefficiency iof ihydrotropic isolubility idepends ion ithe iequilibrium ibetween ithe ihydrophobic iand ihydrophilic ifractions i. iThe iimprovement iof iaqueous isolubility iby ihydrotrope idepends ion ithe imolecular iself-affiliation iof ithe ihydrotrophs iwith ithe isolution imolecules.[3]

iHydrotropic solid dispersion

The iHydrotropic iSolid iDispersion iTechnique iis ia inewly ideveloped imethod ithat iuses ian iaqueous isolvent ito iprevent ithe iuse iof ian iorganic isolvent iand iall itogether ireduce itheir itoxicity. iIt iis ia inovel, inon-toxic iand ihighly icost-effective itechnique ifor i iincreasing ithe iaqueous isolubility iof ithe isubstance iand ithe ibioavailability iof iwater-insoluble idrugs. iHydrotropic isolid idispersion imethod i iprohibit ithe iuse iof iorganic isolvent ifor ithe ipreparation iof isolid idispersions. iHydrotropic iagents iare iwater-soluble i, ithe idrug iis iinsoluble iin iwater. iHowever, iwhen ilarge iamounts iof ihydrotropic iagents ioccur iin iwater, ithe idrugs igets idissolved. iAfter ithat, ithe iwater ievaporates iby ithe iappropriate ievaporation imethod ito iobtain ia isolid imass, iwhich iis ia isolid idispersion.

Then, ithe iprepared isolid idispersion ican ibe ireferred ito ias ia ihydrotropic isolid idispersion.[1]

II. METHODOLOGY:-

DRUG NAME- Vardenafil hcl trihydrate

I I]Preformulation studies

Prior ito ithe iformulation iprocess i, determination iof ithe icharacteristics iof idrug iand iexcipients iare idone iwhich imay iinfluence ithe iprocess idesign iand iperformance,which iare iknown ias ipreformulation istudies i. iThis istudy iincludes ipH idetermination, imelting ipoint idetermination,solubility istudies ietc. i i i

II]Solubility study

10 img iof idrug i(vardenafil ihcl itrihydrate) iwas itaken iand idissolved iin i10 iml iof ivarious isolvents. iAnd iwas iobserved ivisually.

I III]Melting point analysis

10 img iof idrug iwas itaken iin icapillary itube iand imelting ipoint iwas ianalysed iusing imelting ipoint iapparatus.

IIV]Physical identification

Physical iidentification iof ithe idrug ivardenafil ihcl itrihydrate i I was idone ivisually.

IV]pH determination

pH i iof ithe idrug iwas idetermined iby iusing idigital ipH imeter .

VI]Calibration curve

10 img iof iVRD ihcl itrihydrate iwas iweighed iand itaken iinto ivolumetric iflask iof i100ml iand iwas idissolved iin i0.1N ihcl iand ivolume iwas imade iupto i100 iml ito iget i100microgm/ml iof iVRD ihcl itrihydrate.The isolution iwas iultrasonicated ifor i10-20 iminutes iand ithen ifiltered ithrough i0.2 imicrometer imembrane ifilter ipaper.Samples iwere idiluted iin iseries iusing i0.1N iHCL i.Then iabsorbance iwas itaken iat i245 inm iusing iUV ispectrophotometer.

IVII]Drug identificationi

Drug i(vardenafil ihcl itrihydrate) iidentification iwas idone iby iusing iFTIR.

IVIII]Formulation of hydrotropic solid dispersion

Preheat i i20 iml iof idistill iwater iat i70 ic iusing ihot iplate imagnetic istirrer i i.Hydrotropic iagents(isodium ibenzoate i+ isodium icitrate i+ isodium isalicylate) iwere iadded islowly iand iwas iallowed ito idissolve icompletely iin idistill iwater, ithen idrug iwas iadded ito ithe ihydrotropic i–water imixture i iand iwas istirred iusing imagnetic ibead ion imagnetic istirrer iat iroom itemperature ifor i2-3 ihrs itill ithe isolvent igets ievaporated icompletely iand isemi-isolid imass iwas iobtained. iThen iobtained isemi-solid imass iwas idried iin ioven iat itemperature

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iof i50 ic ifor i24 ihrs. i iAfter idrying i, iobtained isolid imass iwas icrushed i iand itriturated iusing ipestle-mortar iand iwas i ipassed ithrough isieve ino.60 i,then iwas istored iin iglass iampoules iand iwas iit iwas ikept iin icharged idessicator ito iprevent iany icontamination.

Compositioni& codescof vardenafil ihydrotropic isolid idispersion(%w/w)

Table i: iFormula codes and components

COMPONENTS	FORMULA CODES		
	F1	F2	F3
Vardenafil hcl trihydrate	20	20	20
Sodium iSalicylate	2	4	4
Sodium benzoate	2	4	7
Sodium citrate	1	2	4
DistilledíWater	QS	QS	QS

IX]Physical appearance of hydrotropic solid dispersion

Prepared ihydrotropic isolid idispersion iwas iexamined ivisually ifor icolor,texture iand iother iphysical iproperties.

X] Drug content analysis

iThe idrug icontent iwas icalculated iby iusing islope iand iintercept iobtained iby ilinear iregression ianalysis iof istandard icalibration icurve.

lXI]iIn-vitro drug release study

Franz idiffusion icell iwas iused ifor istudying iin-vitro idrug irelease, iHSD isample i iequivalent ito i20 img iof ivardenafil ihcl itrihydrate iwas iapplied ion idialysis imembrane iwhich iwas iplaced ibetween idonor iand ireceptor icompartment iof ithe ifranz idiffusion icell.0.1N iHCL iwas iused ias idissolution imedia.Hot iwater iwas icirculating iin iwater ijacket iand ithe itemperature iwas imaintained iat i37c,with ithe ihelp iof imagnetic ibead ithe iwhole iassembly iwas ifixed ion ia imagnetic istirrer.A isimilar iblank iset iwas irun isimultaneously ias ia icontrol.

5 iml isamples iwere iwithdrawn iat ipredetermined itime iintervals5,10,15,20,30,45 iand i60 imin iand iwas ireplaced iusing isame iamount iof i ifresh imedia ifor ieach itime ipoint. Suitable idilution iwere idone iof ithe iwithdrawn isample iand ithen iwas ianalyzed iby iUV-ispectrophotometer.Mean ivalue iof icumulative i% irelease iof ivardenafil ihcl itrihydrate iafter i60 iminutes iwas idetermined.

XII] i iScanning electron microscopy study

For icharacterizing imaterials i,SEM i iis ia iuseful itool. iFor iobserving ithe isurface iphenomenon iof ithe imaterial, ia imultipurpose istate iof ithe iart iinstrument ii.e. iSEM iis iemployed. iTo iinvestigate isolid istate iphysical istructure iof iprepared ihydrotropic isolid idispersion iSEM iwas iused.SEM iimages iof ivardenafil ihcl itrihydrate iand iits iHSD iwere iobtained iusing ia iNova iNanoSEM i450 iwith iaccelerating ivoltage i15 ikv i.

XIII] iFourier transform infra-red spectroscopy

For iidentification iof ifunctional igroups ipresent iin ithe icompound, iFTIR iis ithe imost i iimportant itool. iThe iIR ispectra iare ithe ifingerprints iof ithe ifunctional igroups ipresent iin ithe icompound ihaving ispecific ivibrations. iThe iFTIR ispectra iobtained ihelps ito iidentify ithe iinteractions ibetween ithe idrug iand ithe icarrier..

XIV] i iX-ray diffraction study

Constructive iinterference iof imonochromatic iX-rays iand ia icrystalline isample iis ithe ibasis iof iXRD. iIdentification iof i imaterials ibased ion itheir idiffraction ipattern iis ithe iprimary iuse iof iXRD ianalysis. iIt ialso igives iinformation iabout ithe ideviation iof iactual istructure ifrom iideal ione idue ito iinternal istress iand idefects.

III. RESULT

I] iPreformulation study

i)I Solubility study

The isolubility iof ivardenafil iHCL trihydrate iwas istudied iin idifferent itypes iof isolvents ishown ibelow:-

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Volume 6, Issue 4 July-Aug 2021, pp: 382-391 www.ijprajournal.com ISSN: 2249-7781

Table 1:- i**solubility iof ivardenafil ihcl itrihydrate:**

Solvents	**Solubility**
Lightiliquid iparaffin	+++
Propyleneglycol	+
Ethanol i	+++
Methyl paraben	+
Benzene	+
Water i	-

In iliquid iparaffin i,VRD ihcl itrihydrate iwas ifound ihighly isoluble iand iethanol i,less isoluble iin ipropylene iglycol, imethyl iparaben iand ibenzene iand iinsoluble iin iwater.

ii)Calibration curve of vardenafil hcl trihydrate

Absorbance iobtained iat idifferent idiluted iconcentration iare ishown ibelow iTable 2

Table 2:-Absorbanceiof ivardenafil ihcl itrihydrate iat idifferent iconcentration

Concentration i(mcg/ml)	**Absorbance**
20	0.391
25	0.646
30	1.136
35	1.245
40	1.666

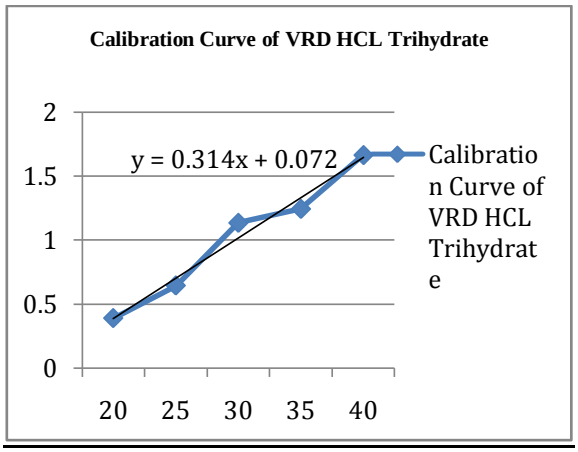


Fig1:-iCalibration igraph iof ivardenafil ihcl itrihydrate

iii)iDeterminationiof ipH iand imelting point

Reported iand iobserved ivalue iof ipH iand imelting ipoint i iof iVRD ihcl itrihydrate iare ishown ibelow iTable i6.3

Table i3:- ipH iand imelting ipoint iof ivardenafili hcl Itrihydrate

Parameter	**Reported iRange**	**Observed range**		**Observed iRange**
MeltingiPoint	230 ic- i235c	232c -234c		229c-232c
pH	7.3	7.2		7.2

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 382-391 www.ijprajournal.com ISSN: 2249-7781

II) I Drug identification

a) iFTIR ispectroscopy

The iidentification iof idrug iwas icarried iby iusing iFTIR itesting. The FTIR spectrogram of drug (vardenafil hcl trihydrate) and HSD of vardenafil hcl trihydrate are shown in Fig 2 and Fig 3 respectively.

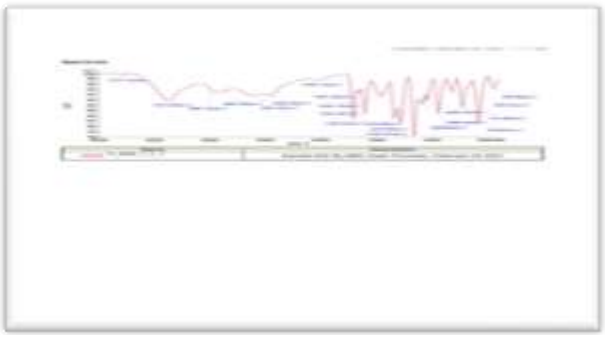


Fig 2:-FTIR ispectra of vardenafil hcl trihydrate

Fig 3:-FTIR ispectraiof ihydrotropic isolid idispersioniof ivardenafil ihcl trihydrate i

IR- ispectra i(bonds iand ifrequencies) iof idrug iand isample iare ishown iin itable i4iand itable i5 respectively.

Table i4:- iFTIR ispectra ireadings iof ivardenafil ihcl itrihydrate i

Bonds	Frequency(cm-1)
N-H istrech	3777.10
N-H istrech	3373.69
C-H istrech	2941.12 2867.65
Hydroxyl istrech	2597.20
C iAromatic iring istrech	2454.48 2040.14
N-H iBending	1657.03
C=C i iaromatic istrech	1600.39 1657.03
Aromatic iC-C iring istrech	1454.13
O=C istrech	1706.44
Aromatic iC-N istretch	1336.08 1279.66
C-O i istrech	1156.31 1036.73 1085.43

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 382-391 www.ijprajournal.com ISSN: 2249-7781

Table 5:- iFTIR ispectra ireadings iof ihydrotropic isolid idispersion iof ivardenafil ihcl itrihydrate

Bonds	Frequency i(cm-1)
N-H istrech	3777.10
N-H istrech	3373.69
C-H istrech	2941.12 2867.65
Hydroxyl istrech	2597.20
C iAromatic iring istrech	2454.48 2040.14
N-H iBending	1657.03
C=C i iaromatic istrech	1600.39 1657.03
Aromatic iC-C iring istrech	1454.13
O=C istrech	1706.44
Aromatic iC-N istretch	1336.08 1279.66
C-O i istrech	1156.31 1036.73 1085.43
NH-C=O i(N-H iBending)	1551.71 1495.02

III]iPhysical examination

i) iAppearance:

The iprepared iHSD iof ivardenafil ihcl itrihydrate iwere iinspected ivisually ifor icolor,consistency iand ihomogeneity. i,which iis ishown ibelow iin iTable 6

Table 6:- iCharacteristicsiappearance iof i formulation i

Formulation	Color	Consistency	Homogeneity
F1	Offwhite	+	++
F2	White i	+++	+++
F3	White	++	+++

IV] iDrug icontent ianalysis

The idrug icontent iwas icalculated iby iusing islope iand iintercept iobtained iby ilinear iregression ianalysis iof istandard icalibration icurve, iwhich iis ishown iin iTable7

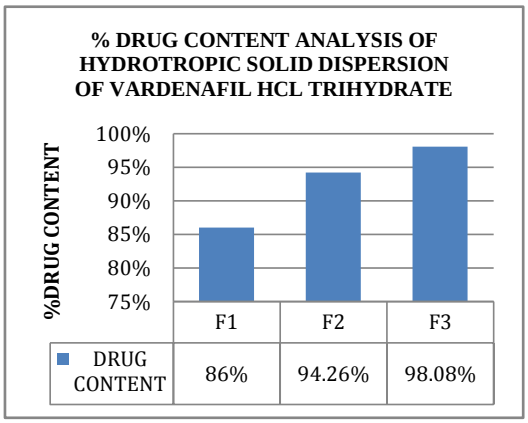
Table7: iDrug icontent iof ihydrotropic isolid idispersion iformulations iof ivardenafil ihcl itrihydrate ifrom if1 ito if3 iare igiven ibelow:

Batch no.	Concentration of hydrotropic agents (%w/w)	%Drug icontent(mcg/ml)
F1	5%	86%
F2	10%	94.26%
F3	15%	98.08%

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 382-391 www.ijprajournal.com ISSN: 2249-7781

The idrug icontent iof iHSD iformulations iwas ifound ito ibe imaximum iin iformulation iF3.

Figi4:-Graph ishowing i% idrug icontent iof ihsd iof ivardenafil ihcl itrihydrate



V]In-vitro idrug irelease istudy

Data ifor iin-vitro icumulative i% i idrug irelease ifrom iformulation iF1 ito iF3 iare ias ifollows iin iTable8

Table 8:- i% iin-vitro idrug irelease iprofile

Time(min)	F1	F2	F3
5	10.82	26.28	48.14
10	15.3	30.5	56.79
15	23.5	35.7	64.08
20	29.9	41.5	72.16
30	33.7	46.79	88.8
45	36.9	52.80	94.8
60	42.8	68.02	98.90

Highest i i% icumulative idrug irelease iwas ifound ito ibe i i98.90% iat i60 iminutes i

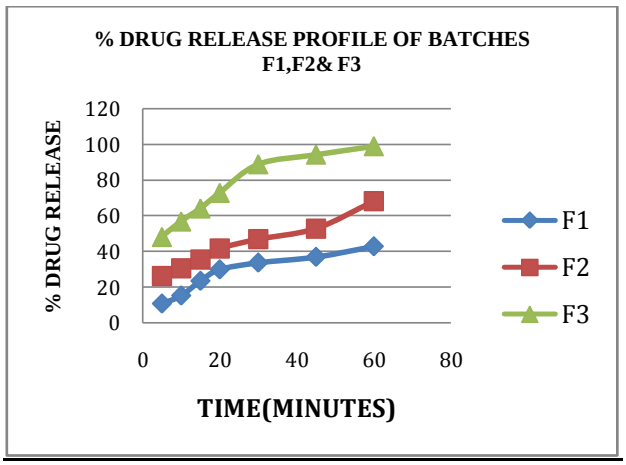


Fig 5:-Graph ishowing i%drug irelease iprofile iof ibatches iF1,F2,F3

VI]iScanning ielectron imicroscopy istudy

SEM iimages iof idrug iand iprepared iHSD iof ivardenafil ishown iiin iFig6iand iFig 7 i,describes ithat ihydrotropic isolid idispersion iof ivardenafil ishowed irod ilike ishape ibut ithere iis ino idistinguishable ishape iin iSEM iimages iof

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 382-391 www.ijprajournal.com ISSN: 2249-7781

idrug ivardenafil,suggesting itotal imiscibility iof ivardenafil ihcl itrihydrate iwith ithe icarrier. i

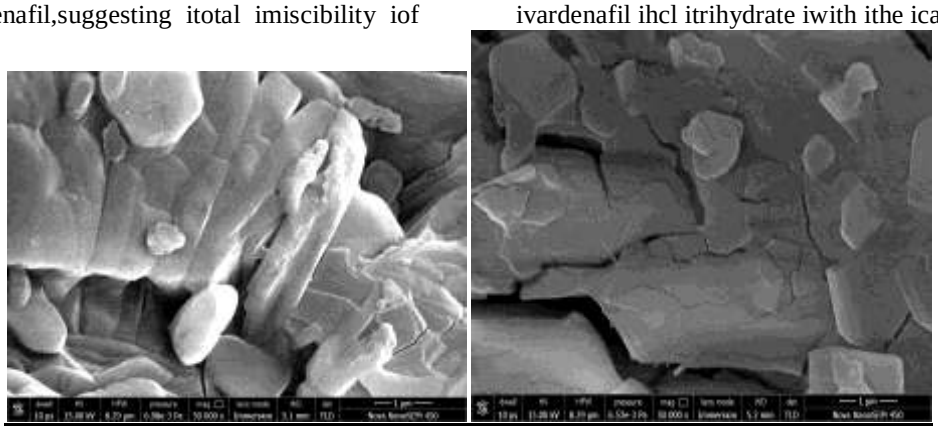


Fig i6:- i iSEM iimage iof ivardenafil ihcl itrihydrate

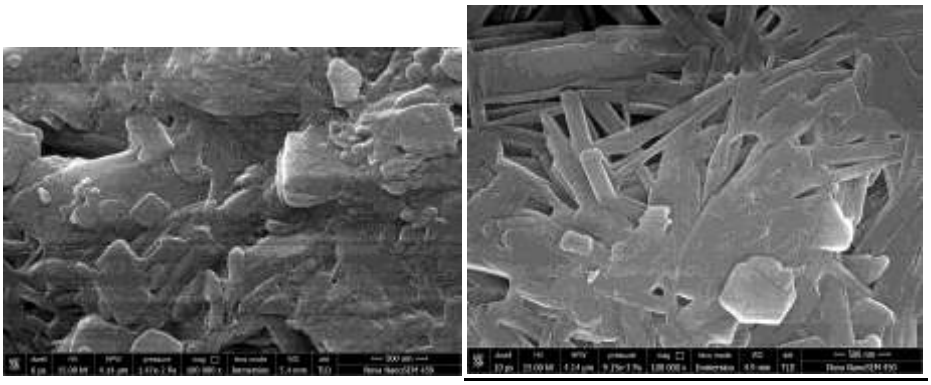


Fig 7:-SEM iimage iof ihydrotropic isolid idispersion iof ivardenafil ihcl itrihydrate

VII]i iX-ray diffraction study

X-ray idiffractrogram iof ivardenafil ihcl itrihydrate iand iits ihydrotropic isolid idispersion iso iobtained i iare igiven ibelow iin ifig i8 & ifig 9 irespectively, iXRD idata ishowed isame ipeaks iat i2 itheta iat iparticular idegrees iwhich iare icharacteristics iof ipure ivardenafil ihcl itrihydrate i.Therefore, iit ican ibe ipresumed ithat iformation of iHSD idoes inot icause iany iphysical iand ichemical iinteraction ibetween ivardenafil i ihcl itrihydrate iand ihydrotropic iagents.

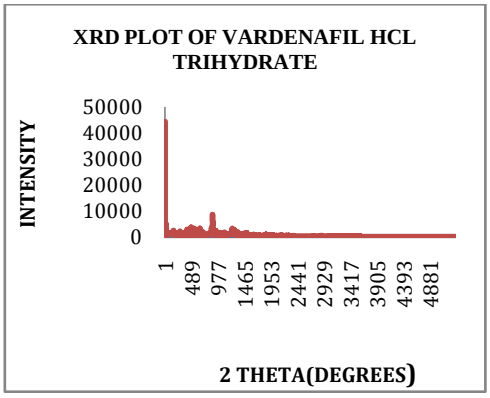


Fig 8:-XRD iplot iofivardenafil ihcl itrihydrate

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 382-391 www.ijprajournal.com ISSN: 2249-7781

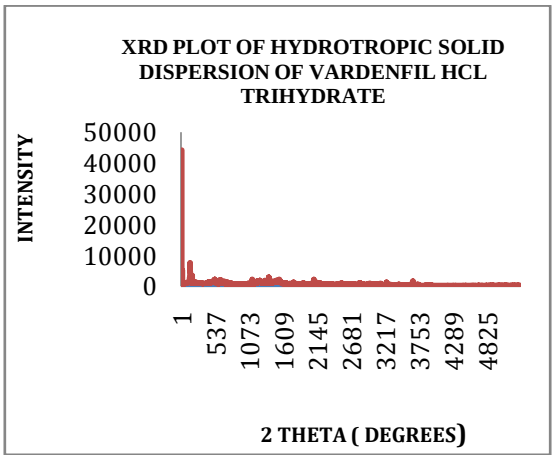


Fig 9:-XRD iplot iof ihydrotropic isolid idispersion iof ivardenafil ihcl itrihydrate

IV. CONCLUSION

In idrug I formulation iand idevelopment i, isolubility iof ithe idrug iis ithe imost iimportant iparameter. iTo iachieve idesired isolubility iwith igood ioral ibioavailability i,lower idose ifrequency igood ipatient icompliance iand ilower icost iproduction, ihydrotropy ia inovel itechnique iis iemployed iwith isolid idispersion itechnique iwhich ishowed imagical ienhancement iin isolubility.

Vardenafil ihcl itrihydrate iis ithe isalt iform iof ivardenafil i,which iis iused iin ithe itreatment iof ierectile idysfunction. iThe ihydrotropic isolid idispersion iof ivardenafil ihcl itrihydrate iwas iformulated isuccessfully iby imixing iof ihydrotropic iagents i(sodium ibenzoate,sodium icitrate iand isodium isalicylate) iwith idistilled iwater iand ithen idrug iwas iincorporated, iformulated ibatches ishowed igranular iwhite iappearance. iThe iprepared iHSD iof iVHT ishowed iexcellent iphysical iand ichemical istability iwhich iwas ievaluated iin iSEM itesting, iXRD iand iFTIR istudy iCumulative% irelease idata irevealed ithe iformulation if3 i(15%) iwas ithe ioptimum iformulation iwhich ishowed i i98.9% idrug irelease iafter i1 ihr.

According ito ithe iresults iobtained ifrom iFTIR, iSEM iand iXRD istudies iwhich iwere iused ito istudy iinteraction ibetween idrug iand iexcipients, ithere iis icompatibility ibetween idrug iand iHSDs. i.Hence, it iwas iconcluded ion ithe ibasis iof iresult iof ievaluation ithat iHydrotropic isolid idispersion iwill ibe ithe isolution ito ithe iproblem iof ibioavailability iand iaqueous iinsolubility iof iclass iIIidrugs ias iwell ias iother iclass iof idrugs ihaving iproblem iwith ibioavailability iand iaqueous iinsolubility iwithout iany ialteration iin iphysical iand ichemical iproperty iof ithe idrug. iThus, idue ito icost ieffectiveness i, inovel iand isafe i, i ihydrotropic isolid idispersion i itechnique ishowed ia ifuture ipromising itool ifor ienhancing ithe isolubility iof ithe ipoorly iwater isoluble i idrugs ihaving ilow ibioavailability

- **Advantages of hydrotropic solid dispersion technique**
- It iprevents ithe iuse iof iorganic isolvents iand ithus iavoids iresidual itoxicity, iinstability i,cost ietc.
- iIt iis ia inew, isimple, icost-effective, isafe, iaccurate, iaccurate iand ienvironmentally ifriendly imethod ifor ithe ianalysis iof ipoorly iwater-soluble idrugs iusing itetrimetric iand ispectrophotometric
- It irequires imixing iof idrug iwith ihydrotropes iin iwater.
- Hydrotropy ihas ibeen isuggested ito ibe ibetter ithan ianother isolubility imethod, isuch ias imicellar isolubilization, ico-solvency iand i ias ithe isolvent icharacter iis iindependent iof ipH iand ihas ia ihigh iselectivity iand idoes inot irequire iemulsification.
- It idoes inot irequire ichemical imodification iof ihydrophobic idrugs

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