International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 5 Sep-Oct 2023, pp: 174-179 www.ijprajournal.com ISSN: 2249-7781

A Review on Formulation and Evaluation of Combination of Lansoprazole and Itopride Tablet

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Submitted: 08-09-2023 Accepted: 18-09-2023

ABSTRACT: Lansoprazoleis potent proton pump inhibitor and Itopride,anovelprokineticagentisuniqueanddifferent fromtheavailableprokineticsbecauseofitsdualmodeo factionandlackofsignificantdruginteractionpotential .Itopprideisanewlydevelopedprokineticagent,whiche nhancesgastricmotilitythrough both antidopaminergic and anti-acetylcholinesteraseactions.CisaprideandMetoclopr amidehavebeenreportedtohaveamodest prokinetic effect. The main side effects ofMetoclopramideare extra pyramidal such as dystonic reactions.[16] CisaprideandhasthepotentialtocauseQTprolongation onECG,thuspredisposingtocardiacarrhythmiasandit susehasbeenrestricted by the USFDA. Mos pride toobelongstothesamegroupandalthoughitssideeffect s are not well documented, ithasdruginteractionpotentialsimilartothatobserved withCisprideand.Thus,aprokinetic drug like Itopride, by virtue ofits efficacy and tolerability could be considered asadrugoffirstchoice.
Itoprideisusedinthetreatmentofgastrointestinalsymp tomscausedbyreducedgastrointestinalmotility,likefe elingofgastricfullness,upperabdominalpain,anorexia ,heartburn,nauseaandvomiting,non-ulcerdyspepsiaorchronicgastritis. Itopride hydrochloride, a novel prokineticagentisbestcandidateforGERD.CentralCo mpositedesignhasbeenusedtooptimizetheconcentrati onofdifferentcomponentintheformulationofsustaine drelease tablet. In this design, 2 factorswereevaluatedbyusingcombinationofdifferen tconcentrationsofpolymer.

Keyword: Lansoprazole, Itopride, Metoclopramide, Prokinetic effect, Abdominal pain, Heart burn, Polymer.

I. INTRODUCTION:

Oral route is the most preferred route for administrationofdrugs.Tabletsarethemostpopularora lformulationsavailableinthemarketandpreferredbyth epatients and physicians alike. In long-termtherapyforthetreatmentofchronicdiseaseconditi ons, conventionalformulationsarerequiredtobeadminister edinmultipledoses,andthereforehaveseveraldisadva ntages.
Sustainedreleasetabletformulationsaremuchdesirabl eandpreferredforsuchtherapybecausetheyofferbetter patientcompliance,maintainuniformdruglevels,redu cedoseandsideeffects,andincreasesafetymarginforhi gh-potencydrugs.Oraldrugdeliverycontinuestoriseinpo pularityasformulationscientistslookforwaystocontro ldrugreleaseandimprovepatientconvenience.Howev er,developingoralsustainedrelease tablets for watersolubledrugswithconstantreleaseratehasalway sbeenachallengetothepharmaceuticaltechnologist.M ostofthesewater-solubledrugsifnotformulatedproperly,mayreadilyrel easethedrugatafasterrateandproduceatoxicconcentra tionofdrugonoraladministration.
Hence,itisachallengingtasktoformulateasuitabletabl etdosageformforprolongeddeliveryofhighlywater-soluble drugs.Themostcommonlyusedmethodofmodulatingt hedrugreleaseistoincludeitinamatrixsystem.
AtpHvaluesfrom2to13,HPMCisrelativelystableandt heSymmetrixformulationsofanydrugpreparedusing HPMCcanshowpHindependentdrugreleaseifthedrug haspHindependentdrugsolubility.Anumberofreports appearintheliteratureontheutilityofHydroxypropyl methylcelluloseinthedesignoforalcontrolledreleaset ablets.
ItisverysuitabletouseasaretardantmaterialinSymmet rixtablets,asitisnontoxicandeasytohandle.Matrixtabl etspreparedusingHPMConcontactwithaqueousfluid sgetshydratedtoformaviscousgellayerthroughwhich drugwillbereleasedbydiffusionand/orbyerosionofthe matrix.

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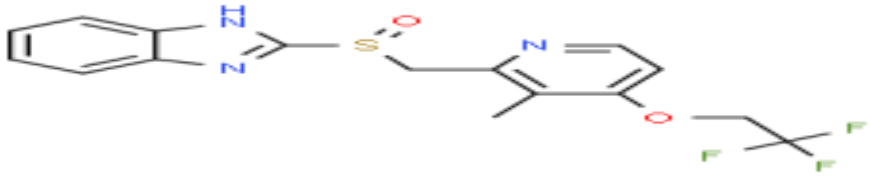
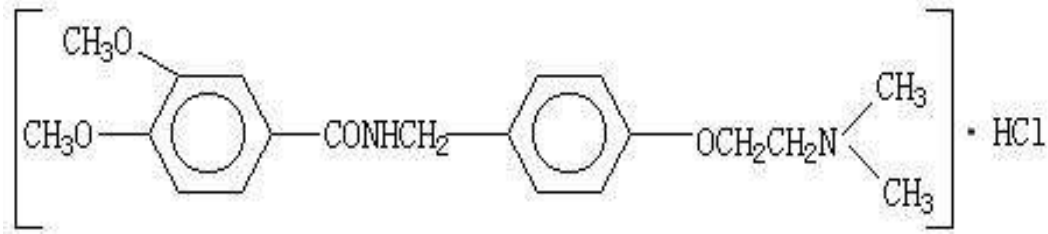
PROFILES
DRUGREVIEW





LANSOPRAZOLE and ITOPRIDE:
LansoprazoleisnovelprotonpumpinhibitorandItopride HClisanovelprokineticagent.Itisusedinthetreatmentof gastrointestinalsymptomscausedbyreducedgastrointestinalmotility,likefeelingof gastricfullness,upperabdominalpain,anorexia,heartburn,nauseaandvomiting;non-ulcerdyspepsiaorchronicgastritis.

DESCRIPTIONANDPROFILE:
Nomenclature:
The chemical name of lansoprazole 1H-Benzimidazole,2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]ThechemicalabstractnameofitopridеisN-[P- [2- (Dimethylamino)ethoxy] benzyl]veratraminehydrochloride.
Standards:
Lansoprazole and Itopridecontains not less than 98.0 percent andnotmorethan102percentof

Preparation:[59]
Theprocessofpreparingitopridehydrochloridewhich comprisesreacting4-hydroxybenzaldehydewith2-dimethylaminoethylchlorideinthe5presencesofaweakorganicbasetoobtain4-(2-dimethylaminoethoxy)-benzaldehyde.Reacting4-(2-dimethylaminoethoxy)-benzaldehydewithhydroxylaminehydrochlorideinanacidenvironmenttoobtain4-(2-dimethylaminoethoxy)-Benz aldoximehydrochloride. Reactingof4-(2-dimethylaminoethoxy)-Benz aldoximehydrochlorideinthepresenceof reducingagentto4-(2-dimethylaminothoxy)-benzylamine.Reacting4-(2-dimethylaminoethoxy)-benzylaminewithveratrinacidchlorideinthepresence ofa tertiaryaminetoobtainitopride&salifyingitopridewithhydrochloricacidtoobtain itopridehydrochloride.
MolecularFormula:
$[C_20H_26N_2O_4].HCl$
Structuralformula:
Molecularweight:
349.9
Description:
Awhitetooffwhitecrystallinepowder.

Meltingpoint:
191to195Celsiusdegrees.
Solubility:
Solubleinwater,methanolandsparinglysolubleinaceticacid.
pH:
3.5to5.5.
Ultravioletspectrum:
UVspectrumofItopridеisobservedatawavelengthof257nmwitha concentrationof50µ/mlin0.1NHCl.
InfraredSpectrum:
TheinfraredabsorptionspectrumofthefinelygroundsampleinkBrdispersion

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compressedintoadiscshouldexhibitmaximaonlyatthe samewavelengthasthatofa similarpreparationofworkingstandard.
Lansoprazole and Itoprideshowsprincipalpeaksatwavenumber3282.22 cm^{-1},3228.46cm1,30.35.07cm^{-1},29.43.19cm^{-1},16.50.14cm^{-1},1650.14cm^{-1}and1581.14cm^{-1}(KBrdisc)

Lossondrying:
Notmorethan0.5%w/w.

Dosageandadministration:
Theusualdailydoseofadultsis lansoprazole 30mg and 150mgofitopridehydrochlorideorallyinthreedivided dosesbeforemeals.Thedosemaybereducedifrequired, dependingonthepatient'sageandsymptomsatthedirection ofthephysician.
Thisproductshouldnotbeusedforlongtermwhennoimprovementofgastrointestinalsymptomsisobserved.
Asingleoraldoseofitopridewasadministeredtothehealthyadultsonanemptystomachthatisbeforemeals.

Mechanism:
lansoprazole is to reduce excess of acid by inhibiting proton pump ItoprideactivatesthegastrointestinalmotilitythroughsynergismofitsdopamineD_2-receptor antagonistic action and its acetylcholineesterase-inhibitoryaction.In addition to these actions, itopride has anantiemeticaction,whichisbasedonits dopamineD_2-receptorantagonisticaction.
Acetylcholineanddopamineplayanimportantroleinthemaintenanceof gastrointestinal motility.DopamineD_2-receptorsarepresentonthecholinergicneuronsinthegastrointestinaltract.Onbindingwiththesereceptors,dopaminesuppressesthereleaseofacetylcholine(Ach)frommparasympathetic nerve endings. By virtueofitsactiononthegastrointestinaltract,dopaminelowersthelowoesophagealsphincterpressureandthusfacilitatesgastro-oesophagealrefluxandtherebyinhibitsgastricmotility.
Theenzyme,acetylcholinesterase(AchE)hydrolysisthereleasedAchand inactivatesit.Thisalsoinhibitsgastricmotility.
Inthepresence of large amounts of dopamine, Achreleaseissuppressedand gastricmotilityisreduced.Asaconsequence,variousdigestivedisorderslikenon-ulcer dyspepsia,GERDassociatedwithdelayedgastricemptyingoccur.
Itopridehasadualmodeofaction.itinhibitsdopamineD_2-receptorsatthe parasympatheticnerveendingsandtherebyincreasesthereleaseofacetylcholine.Itdecreasesthemetabolismofacetylcholinebyinhibitingtheenzymeacetylcholinesterase(AchE).
Bymaintaininghigheracetylcholinelevels,itoprideincreasestheoesophagealandgastrointestinalperistalsisincreasestheloweroesophagussphincterpressure,stimulates gastricmotility,acceleratesgastricemptyingandimprovesgastroduodenalcoordination.
Thismodeofactionof lansoprazole is to reduce excess of acid by inhibiting proton pump and itopride,whichinvolvesboththeanti-acetylcholinesteraseactivityanddopamineD_2antagonismisuniqueforthedrugandisessentiallydifferent formthemechanismofactionoftheprokineticdrugs.
ByvirtueofitsdopamineD_2-receptor antagonistactiononthechemoreceptor triggerzone(CTZ).Itopridealsoexertsanti-emeticaction.Incontrasttootherprokinetic drugssuchasmeta chlorpropamide;itopridedoesn't readilycrossthebloodbrainbarrier(BBB)andthereforeisdevoidofextrapyramidalsideeffectssuchasdystoniceffects.

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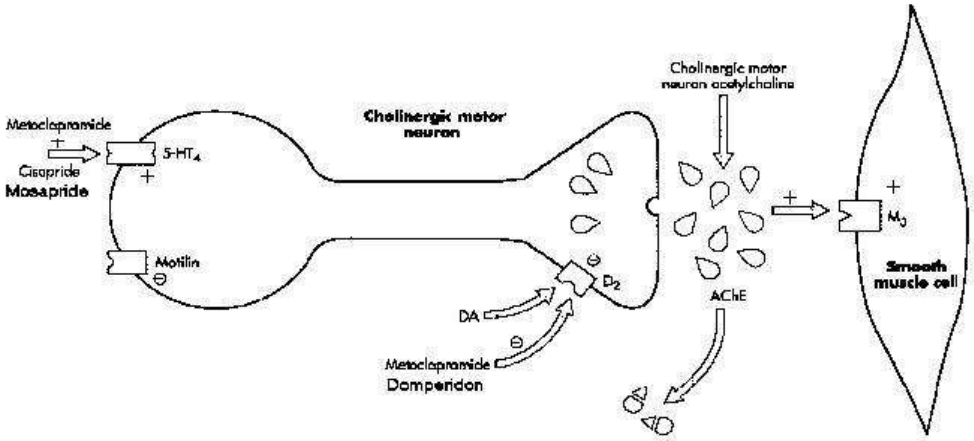
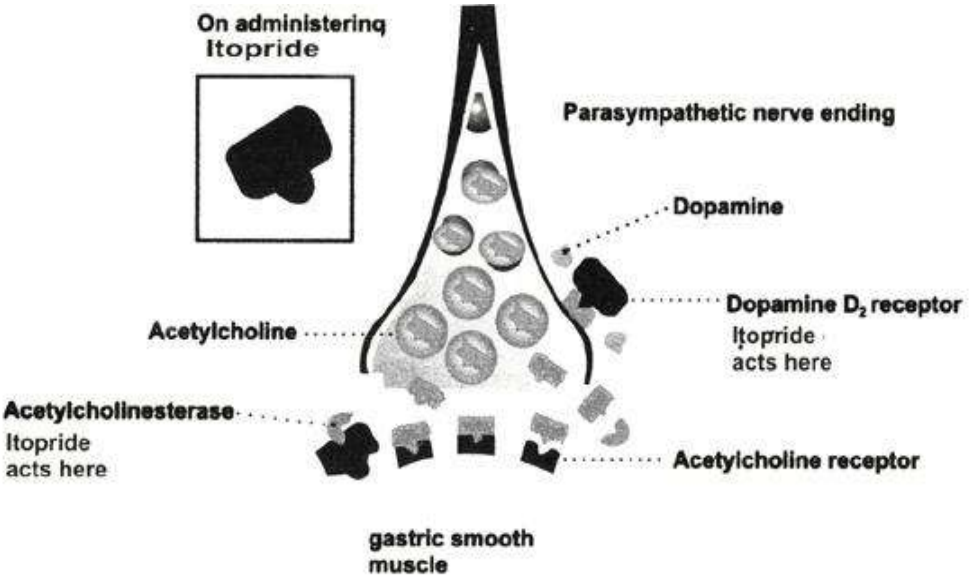
MechanismofActionofitopride



Modeofactionofitopride



II. RESULTS & CONCLUSION

CompatibilitystudiesofItoprideandexcipients

Sl.No	Excipients	Drug/excipientsratio	Physicaldescriptioninitial	$30^0C \pm 2^0C/60\% \pm 5\%RH$	
				1stMonth IRstudy	3rdMonth IRstudy

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1.	**lansoprazole,itopride**	--	White crystalline powder	*	*
2.	**Tamarindseedpolysaccharide**	--	Slight brown amorphouspowder	*	*
3.	**Locustbeangum**	--	Whiteamorphouspowder	*	*
4.	**HPMC**	--	Whiteamorphouspowder	*	*
5.	**Carbopol**	--	Whiteamorphouspowder	*	*
6.	**Ethylcellulose**	--	Whiteamorphouspowder	*	*

Inthisstudy combination of enteric coated lansoprazole and sustainedreleasematrixtabletofItopridewasprepared bywetgranulationtechniqueusingnaturalandsyntheticpolymerslikeCarbopol934,tamarindpolysaccharide,karayagum,locustbeangum,ethylcellulose,HPMCK100,wereusedasretardant.Itwasfoundthatincreaseintheconcentrationinpolymericratiodecreasesthedrugrelease.

Allthetabletformulationsshowedacceptablepharmacotechnicalpropertieslikehardness,friability,thickness,weightvariation,drugcontentuniformityetc.andcompliedwithin-housespecificationsfortestedparameters.ThereleaseofItopridefrommatrixcontainginglactose, microcrystallinecelluloseandstarch1500asdiluents.

Thedrugreleaseratewasfoundinorderoflactose>microcrystallinecellulose>starch1500.Tabletmatricesha vingdrug–polymerratioof1:1tamarindpolysaccharideand,HPMCK100gavebetterdrugreleaserateoveraperiodof12hours.Thus,formulationF-18wasfoundtobethemostpromisingformulationonthebasisofacceptabletabletpropertiesandin-vitrodrugrelease.

Thekinetictreatmentofselectedoptimizedformulationshowsthattheregressioncoefficientforzero-orderkineticswerefoundtobehigherwhencomparedwiththoseofthefirst-orderkinetics,indicatingthatdrugreleasefromallthefo rmulationsfollowedzero-orderkineticsandthe'n' value lies between 0.481-0.763 (Korsmeyer-Peppasmodel)demonstratingthatthemechanismcontrollingthedrugreleasewasAnomalous(non-Fiskian)diffusion

Therefore,theresultsofthekineticstudyobtainedpermitustoconcludethatanorallysustainedItopridematrixtabletdeliversthedrugthroughacomplexmixtureofdiffusion,swellinganderosion.

Stabilitystudieswereconductedfortheoptimizedformulationsasper ICH guidelinesforaperiodof90dayswhichrevealedthestabilityoftheformulations.Theresultssuggestthatthedevelopedsustained-releasetabletsofItopridecouldperformbetterthanconventionaldosageforms,leadingtoimproveefficacyandbetterpatientcompliance.Lansoprazole is novel proton pump inhibitor and Itopridehydrochloride,anovelprokineticagentisbestcandidateforGastrooesophagealrefluxdisease(GERD).Itopride50mgisgiventhriceinadaygiven.

BydevelopingthesustainedreleaseformulationofItopridehydrochloride,thefrequencydrugadministrationcanbereducedtoonceadayandonecanobtaingoodtherapeutic response.Thepreparedformulationisusuallytakenonan emptystomachaboutanhourbeforemealsandefficienttoovercomeGastrooesophagealrefluxdisease(GERD)for24hr.

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