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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF NOVEL FIXED DOSE COMBINATION OF S (-) PANTOPRAZOLE AND MOSAPRIDE CITRATE BY TABLET IN CAPSULE APPROACH

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ABSTRACT

Objective: The main objective of the present study was to formulate a fixed dose combination of chirally pure S (-) pantoprazole and mosapride citrate tablets. Since no systematic studies on the design and development of S (-) pantoprazole and mosapride citrate tablets in capsule approach are available in literature, we propose to develop a suitable formulation to characterize *in-vitro* release profile of both the tablets in capsules. Chirally pure S (-) pantoprazole tablets were prepared as delayed release, and mosapride citrate tablets were prepared as immediate release tablets.

Methods: Enteric coating was done on S (-) pantoprazole tablets to modify its release in 6.8 phosphate buffer. *In-vitro* dissolution of the capsule containing both the tablets was performed in two different media, 0.1 N HCl and 6.8 phosphate buffer, respectively. All physico-chemical parameters for both the tablets, as well as the capsules, were evaluated individually and were found well within the specified limits.

Results: Initially dissolution was performed in 0.1 N HCl in which immediate release tablet of mosapride dissolves completely and pantoprazole tablets remains as it is due to enteric coating. The further tablet was placed in 6.8 phosphate buffer in which delayed release tablets of S (-) pantoprazole gives complete release. The drug product was found stable during accelerated stability studies for 6 months at 40°C/75% RH.

Conclusion: A stable and robust formulation of S (-) pantoprazole and mosapride citrate as fixed dose combination was developed and evaluated. Tablet in capsule approach was developed, and results were well within the specified limits.

Keywords: S (-) pantoprazole, Mosapride citrate, Modified release, Fixed-dose combination, Delayed release.

INTRODUCTION [1-12]

Ulcers, crater-like sores, formed in the stomach and duodenum are called gastric and duodenal ulcers, respectively. Stomach and duodenum ulcer are generally referred to as peptic ulcers. *Helicobacter pylori* infection is the major cause of peptic ulcer, since 85-95% of patients with peptic ulcer have this organism. The combined dosage form of any pharmaceuticals is for the synergistic effect or to give longer time effect. In the present study, mosapride citrate and S (-) pantoprazole combination are used as antacid to decrease acidity (excess secretion of acid in the stomach). S-isomer of pantoprazole is known to be more effective and lesser dependent on cytochrome 2C19 than R-isomer of pantoprazole. Pantoprazole, a selective and long-acting proton pump inhibitor, are completely metabolizes through the hepatic cytochrome P (CYP) 450 system by CYP2C19 and CYP3A4 and up to 80% of the inactive metabolites are eliminated through renal excretion. The reduction of therapeutic dosage by chiral purification decreases the metabolic load on the body.

Pantoprazole however is a racemic mixture of S-pantoprazole and R (+) pantoprazole in 1:1 ratio. The pharmacokinetics of R and S isomers of pantoprazole vary widely in extensive and poor metabolizers. Studies have shown that S-pantoprazole is more potent (1.5-1.9 times) and more effective (3-4 times) than the racemate in inhibiting gastric lesions in different pre-clinical models, suggesting that in patients, S-pantoprazole at 50% of the dose of racemate would be at least equivalent in efficacy to racemate. This was further confirmed by results of a multicentric, comparative clinical trial of S-pantoprazole versus racemic pantoprazole in patients with gastroesophageal reflux disease which showed superior efficacy with S (-) pantoprazole 20 mg compared to racemic pantoprazole 40 mg. S (-) pantoprazole would be a potent proton pump inhibitor at half the racemate dose.

Mosapride is a gastroprokinetic agent that acts as a selective 5HT4 agonist. Mosapride is a novel prokinetic agent which seems to exert its action through a high affinity and specificity for the 5-HT4 receptor. The major active metabolite of mosapride, known as M1, additionally acts as a 5HT3 antagonist which accelerates gastric emptying throughout the whole of the gastrointestinal tract in humans, and is used for the treatment of gastritis, GERD, functional dyspepsia, and irritable bowel syndrome. It is recommended to be taken on an empty stomach (i.e. at least 1 hr before food or 2 hrs after food). Pantoprazole, like other proton-pump inhibitors is susceptible to degradation in acidic and neutral media. Thus, the drug degrades when it is exposed to the acid medium, well before reaching the proximal small intestine where the drug is absorbed. Therefore, there is a need for a delivery system which would protect the drug from degradation during its passage through the stomach and take it unaffected to its site of absorption. Delayed release formulations such as enteric coated tablets could accomplish the dual benefits of protecting the drug from the detrimental effects of gastric contents and to deliver the drug to a specific region of the intestine [10]. An enteric coating is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. Enteric refers to the small intestine; therefore, enteric coatings prevent the release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH.

The combination of S (-) pantoprazole with mosapride is more effective than the combination of racemic pantoprazole and mosapride in providing symptomatic relief to patients. In the present study, S (-) pantoprazole is used in place of racemic pantoprazole. S (-) pantoprazole is more effective at its half dose in comparison with pantoprazole in improving symptoms of heartburn, acid regurgitation, bloating, and equally effective in healing esophagitis and gastric erosions. The relative risk reduction is 15-33%. Combination of S (-) pantoprazole with mosapride and using the tablet is capsule approach is to formulate a single unit dose of a capsule containing both tablets. Mosapride is an immediate release tablet and S (-) pantoprazole is delayed release tablet. Both tablets were filled in hard gelatin capsules. Dissolution of

the capsules was performed in 0.1 N HCl followed by 6.8 phosphate buffer to release mosapride and S (-) pantoprazole, respectively.

METHODS

Materials

S (-) pantoprazole was procured from Emcure Pharmaceuticals, Mosapride Citrate Dihydrate was received from Symed Labs, Mannitol was received from Rouquette Pharma, Povidone K-90 was received from BASF, croscarmellose sodium was received from DFE Pharma, Cross-Povidone was received from Ashland Specialty Ingredients, microcrystalline cellulose was received from FMC Biopolymer, hydroxypropyl methyl cellulose (HPMC) was received from Dow Chemicals, Aerosil and Eudragit were received from Evonik Industries, sodium carbonate dihydrate, calcium stearate, and sodium hydroxide were received from Merck, polyethylene glycol-6000 (PEG-6000) was received from Clariant Produkte, Talc was received from IMERYS Talc, titanium dioxide was received from Kronos Titan, iron oxide yellow and red were received from Koel Colors.

Methods

Preparation of S (-) pantoprazole delayed-release tablets

Accurately weighed quantities of S (-) pantoprazole sodium, croscarmellose sodium and mannitol were shifted from 40# sieve. Sodium carbonate anhydrous was milled through the multimill and passed through 60# sieve. Above sifted materials were transferred in a rapid mixer granulator and mixed. A binder solution of polyvinylpyrrolidone K-90 in purified water was prepared and added to the above mixture to get required wet mass. The wet mass passed through 10 mm screen and dried in fluidized bed dryer (FBD). Polyplasdone XL and croscarmellose sodium were sifted through 40# sieve and mixed with dried granules. Calcium stearate was sifted through 60# sieve and mix with above granules. The lubricated granules were compressed into tablets using appropriate punches.

Table 1: Formulations of S(-) pantoprazole delayed release tablets

Ingredients	Formulation (quantity/tablet in mg)		
	F1	F2	F3
S (-) pantoprazole sodium	10.58	10.58	10.58
Mannitol	34.32	34.32	34.32
Sodium carbonate anhydrous	10.00	10.00	10.00
Purified water	q.s.	q.s.	q.s.
PVPK-90	1.00	1.00	1.00
Polyplasdone XL	7.50	7.50	7.50
Croscarmellose sodium	5.00	5.00	5.00
Calcium stearate	1.6	1.6	1.6
Hypromellose	2.1	2.1	2.1
Isopropyl alcohol	30.66	30.66	30.66
Methylene chloride	20.44	20.44	20.44
Enteric coating			
Eudragit	24.65	24.65	19.71
Sodium hydroxide	0.09	0.09	0.075
Titanium dioxide	0.37	0.37	0.292
Talc	1.87	1.87	1.49
PEG 6000	0.89	0.89	0.71
Iron oxide yellow	0.18	0.18	0.18
Iron oxide red	0.03	0.03	0.03
Purified water	q.s.	q.s.	q.s.

PEG 6000: Polyethylene glycol-6000, PVPK-90: Polyvinylpyrrolidone K-90

Preparation of mosapride citrate dihydrate immediate release tablets

Microcrystalline cellulose was passed through 100# sieve and co-sifted with mosapride through 100# sieve. Croscarmellose sodium sifted through 60# sieve and all above blend was transferred into rapid mixer granulator and mixed. The binder solution was prepared by dissolving HPMC in purified water and granulation was done. Drying of the granulated blend was performed in FBD. After completion of drying dried granules were sifted through 30# sieve. Pre-lubrication was done in a blender by sifting Aerosil through 40# sieve. Magnesium stearate was sifted through 60# sieve and lubrication was done in a blender. The lubricated blend was compressed into tablets.

Preparation of coating solution

Seal coating: Hypromellose was added to isopropyl alcohol under continuous stirring. Methylene chloride was slowly added in the above solution, and stirring was continued for 45 minutes. The solution was filtered through 200# nylon cloth, and the prepared solution was applied to the tablets. Polymer coating: Sodium hydroxide pellets were dissolved in purified water, titanium dioxide, iron oxide yellow, and iron oxide red were passed through nylon cloth with purified water. Under continuous stirring talc and PEG-6000 was added to it. Eudragit was mixed with sodium hydroxide solution and then this solution was added to talc and PEG-6000 solution. Filter the solution through nylon cloth and apply the enteric coated solution on seal coated tablets.

Pre-formulation study

Pre-formulation studies were performed prior to formulation development. A pre-formulation study establishes a basis for understanding the physico-chemical properties of the drug molecule. During the development of a solid dosage form, assessment of possible incompatibilities between a drug and different excipients is an important part of the pre-formulation stage prior to large scale development trials. Excipients are required to facilitate administration, to promote consistent release and bioavailability of the drug, and to protect the active ingredients from the environment. Drug excipient compatibility study of the present formulation was performed and evaluated.

Table 2: Formulation of mosapride Citrate immediate release tablets

Ingredients	Formulation (quantity/tablet in mg)						
	F1	F2	F3	F4	F5	F6	F7
Mosapride citrate dihydrate	5.30	5.00	5.00	5.00	5.00	5.00	5.00
Microcrystalline cellulose	60.70	-	-	61.00	54.00	59.00	59.00
Lactose monohydrate	-	61.00	58.00	-	-	-	-
Croscarmellose sodium	2.00	2.00	2.00	2.00	2.00	2.00	2.00
HPMC	-	-	-	-	2.00	2.00	2.00
PVP K-30	-	-	2.00	-	-	-	-
Microcrystalline cellulose	-	-	-	-	5.00	-	-
Aerosil	1.00	1.00	2.00	1.00	1.50	1.50	1.50
Talc							
Magnesium stearate	1.00	1.00	1.00	1.00	0.50	0.50	0.50
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

HPMC: Hydroxy propyl methyl cellulose, PVP K-30: Polyvinylpyrrolidone K-30

Table 3: Drug-excipients compatibility study

Sample name	Stage	Sulfone impurity (%)	Sulfide impurity (%)	Single max (%)	Total impurities (%)
S(-) pantoprazole sodium (API)	Initial (2-8°C)	0.00	0.00	0.01	0.03
	55°C closed 15 days	0.01	0.00	0.01	0.04
	40°C/75% RH closed 1 M	0.01	0.00	0.01	0.03
	40°C/75% RH open 1 M	0.00	0.00	0.01	0.02
S(-) pantoprazole sodium+mannitol	Initial (2-8°C)	0.00	0.00	0.01	0.03
	55°C closed 15 days	0.01	0.01	0.06	0.16
	40°C/75% RH closed 1 M	0.01	0.00	0.01	0.03
	40°C/75% RH open 1 M	0.00	0.00	0.01	0.02
S(-) pantoprazole sodium+sodium carbonate	Initial (2-8°C)	0.00	0.00	0.01	0.03
	55°C closed 15 days	0.01	0.00	0.01	0.04
	40°C/75% RH closed 1 M	0.01	0.00	0.01	0.03
	40°C/75% RH open 1 M	0.00	0.00	0.01	0.02
S(-) pantoprazole sodium+PVP K-30	Initial (2-8°C)	0.02	0.00	0.01	0.05
	55°C closed 15 days	0.02	0.00	0.01	0.14
	40°C/75% RH closed 1 M	0.02	0.00	0.01	0.04
	40°C/75% RH open 1 M	0.03	0.01	0.08	0.26
S(-) pantoprazole sodium+croscarmellose sodium	Initial (2-8°C)	0.01	0.00	0.01	0.04
	55°C closed 15 days	0.03	0.13	0.09	1.83
	40°C/75% RH closed 1 M	0.01	0.03	0.10	0.31
	40°C/75% RH open 1 M	0.00	0.04	0.12	0.44
S(-) pantoprazole sodium+crospovidone	Initial (2-8 0C)	0.01	0.00	0.01	0.05
	55°C closed 15 days	0.01	0.00	0.03	0.09
	40°C/75% RH closed 1 M	0.01	0.00	0.01	0.03
	40°C/75% RH open 1 M	0.01	0.01	0.04	0.11
S(-) pantoprazole sodium+calcium stearate	Initial (2-8 0C)	0.00	0.00	0.01	0.03
	55°C closed 15 days	0.01	0.00	0.03	0.08
	40°C/75% RH closed 1 M	0.01	0.00	0.01	0.03
	40°C/75% RH open 1 M	0.01	0.00	0.01	0.03
S(-) pantoprazole sodium+hypromellose	Initial (2-8 0C)	0.01	0.00	0.01	0.04
	55°C closed 15 days	0.01	0.00	0.03	0.14
	40°C/75% RH closed 1 M	0.02	0.00	0.01	0.04
	40°C/75% RH open 1 M	0.01	0.00	0.01	0.03
Mosapride citrate dehydrate (API)	Initial (2-8°C)			0.06	0.09
	55°C closed 15 days			0.06	0.10
	40°C/75% RH closed 1 M			0.06	0.11
	40°C/75% RH open 1 M			0.09	0.14
Mosapride citrate dehydrate+microcrystalline cellulose	Initial (2-8°C)			0.06	0.15
	55°C Closed 15 days			0.06	0.10
	40°C/75% RH closed 1 M			0.05	0.10
	40°C/75% RH open 1 M			0.05	0.10
Mosapride citrate dehydrate+lactose	Initial (2-8°C)			0.06	0.10
	55°C closed 15 days			0.15	0.25
	40°C/75% RH closed 1 M			0.14	0.25
	40°C/75% RH open 1 M			0.06	0.09
Mosapride citrate dehydrate+aerosil	Initial (2-8°C)			0.06	0.10
	55°C closed 15 days			0.10	0.46
	40°C/75% RH closed 1 M			0.14	0.24
	40°C/75% RH open 1 M			0.12	0.20
Mosapride citrate dehydrate+magnesium stearate	Initial (2-8 0C)			0.06	0.10
	55°C closed 15 days			0.14	0.30
	40°C/75% RH closed 1 M			0.12	0.26
	40°C/75% RH open 1 M			0.05	0.11
Mosapride citrate dehydrate+microcrystalline cellulose	Initial (2-8°C)			0.06	0.10
	55°C closed 15 days			0.14	0.24
	40°C/75% RH closed 1 M			0.12	0.22
	40°C/75% RH open 1 M			0.06	0.12
Mosapride citrate dehydrate+HPMC	Initial (2-8°C)			0.06	0.11
	55°C closed 15 days			0.13	0.25
	40°C/75% RH closed 1 M			0.13	0.24
	40°C/75% RH open 1 M			0.05	0.08
Mosapride citrate dehydrate+opadry white	Initial (2-8°C)			0.06	0.10
	55°C closed 15 days			0.12	0.31
	40°C/75% RH closed 1 M			0.11	0.34
	40°C/75% RH open 1 M			0.06	0.22
Mosapride citrate dehydrate+croscarmellose sodium	Initial (2-8 0C)			0.06	0.10
	55°C closed 15 days			0.13	0.21
	40°C/75% RH closed 1 M			0.11	0.27
	40°C/75% RH open 1 M			0.05	0.13
Mosapride citrate dehydrate+PVP K-30	Initial (2-8°C)			0.06	0.10
	55°C closed 15 days			0.14	0.27
	40°C/75% RH closed 1 M			0.13	0.23
	40°C/75% RH open 1 M			0.12	0.26
Mosapride citrate dehydrate+talc	Initial (2-8°C)			0.06	0.09
	55°C closed 15 days			0.14	0.23
	40°C/75% RH closed 1 M			0.13	0.24
	40°C/75% RH open 1 M			0.06	0.11

HPMC: Hydroxy propyl methyl cellulose, PVP K-30: Polyvinylpyrrolidone K-30

RESULTS

In the present study, we made an attempt to deliver S (-) pantoprazole in a sustained manner using delayed-release tablets and mosapride as immediate release tablets. Both tablets were filled in a hard gelatin capsule. In the present study, approach of tablets in the capsule was followed. Both tablets were prepared individually and filled in the single capsule shell. There is no study available on the formulation of chirally pure S (-) pantoprazole combined with mosapride in a capsule dosage form. A series of experiments were performed during pre-formulation studies to select suitable excipients. Evaluations of physical parameters such as friability, hardness, thickness, weight variation, and disintegration time were carried out, and results were satisfactory for final formulation. The dissolution method was developed for both tablets. 0.1 N HCl for mosapride followed by 6.8 phosphate buffer S (-) pantoprazole tablets, respectively. The combination of different excipient was used to formulate S (-) pantoprazole enteric coated tablet for delayed release. Seal coating was applied on core tablets before enteric coating. Mosapride citrate tablets release the drug in an immediate release manner in 0.1 N HCl. After dissolving the immediate release tablet and capsule in 0.1 N HCl S (-) pantoprazole tablets were sifted to 6.8 phosphate buffer medium for delayed release pattern. Dissolution data were plotted as a bar diagram for all formulations of mosapride and S (-) pantoprazole. The accelerated stability study was performed on capsules for at 40°C/75% RH 3M, and results were found well within the specified limits.

Table 4: Post compression parameters of both the tablets (Coated)

Formulations	S (-) pantoprazole delayed-release tablets		
	Weight (mg)	Thickness (mm)	Hardness (kp)
F1	82±5	3.25±0.2	10.00±3
F2	82±5	3.35±0.2	9.80±3
F3	83±5	3.85±0.2	9.70±3

Mosapride citrate immediate release tablets (Uncoated)				
Formulations	**Weight (mg)**	**Thickness (mm)**	**Hardness (kp)**	**Disintegration time (seconds)**
F1	70±5	2.74±0.2	4.50±3	25
F2	71±5	3.27±0.2	3.80±3	20
F3	70±5	3.09±0.2	7.00±3	234
F4	70±5	3.25±0.2	13.00±3	39
F5	71±5	3.57±0.2	8.00±3	23
F6	72±5	3.50±0.2	7.50±3	20
F7	72±5	3.50±0.2	7.50±3	20

Table 5: % drug release of S (-) pantoprazole and mosapride citrate capsules

Formulations	S (-) pantoprazole delayed release in pH 6.8 phosphate buffer
	% Drug release in 45 minutes
F1	94.5
F2	95.9
F3	96.3

Mosapride citrate immediate release 0.01N HCl	
Formulations	**% Drug release in 45 minutes**
F2	100.9
F3	103.4
F4	99.1
F5	97.4
F6	95.9
F7	103.2

Table 6: Stability results: of final Formulations

Conditions	Related substance			
	Sulfone impurity (%)	Sulfide impurity (%)	Single max (%)	Total impurities (%)
Initial	0.03	BLQ	0.01	0.1
55°C 15 days	0.04	BLQ	0.08	0.3
55°C 1 M	0.05	0.02	0.12	0.5
40°C/75% RH 1 M	0.03	BLQ	0.02	0.1
40°C/75% RH 3 M	0.05	0.01	0.06	0.2

DISCUSSION

Chirality can introduce marked selectivity and specificity into the way the drug is handled by the body and how the compound interacts with the receptor or enzyme binding sites in some cases. Chiral molecules have increased receptor selectivity and potency, reduced adverse effects (in many cases), greater pharmacological effects (in many cases), reduced dosage - less metabolic load on body, decreased potential for drug - drug interactions (in many cases), decreased inter-individual variability in response commonly due to polymorphic metabolism (in some cases), an improved safety margin (high therapeutic index). In the present research work, chirally pure S (-) pantoprazole was used in place of racemic pantoprazole. S (-) pantoprazole could be metabolized by alternative pathways like CYP3A4 and sulfotransferases clinically more effective than the racemate. The combination of pantoprazole with mosapride was developed earlier but the formulation of chirally pure S (-) pantoprazole with mosapride and using the tablet in capsule approach is a new approach. Both tablets were formulated individually to avoid the incompatibility and to differentiate the manner of release as one is delayed release and another is immediate release tablet, respectively. Two different dissolution media was used to release the drug in a predefined manner. All the related studies were performed to evaluate the tablet and capsule. The finally stability study was carried out to evaluate the stability of the formulation and results indicate that the product was stable.

CONCLUSION

Based on the study results it can be concluded that a stable fixed dose combination of S (-) pantoprazole and mosapride citrate capsules was formulated. All the parameters of both the tablets either immediate release or delayed release were evaluated and found satisfactory. The % drug release of both tablets from the capsule was observed and found well within the specified limits. Stability results indicate that the formulation was stable and robust.

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