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FORMULATION AND EVALUATION OF RABEPRAZOLE SODIUM AND DOMPERIDONE PELLETS

P. Swathi*
Department of Pharmaceutics, Malla Reddy College of Pharmacy, Hyd.

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ABSTRACT

The aim of present study was to formulate and evaluate Rabeprazole sodium and Domperidone pellets for the treatment of gastro esophageal reflux disease. Modified release drug delivery systems were capable of drug release when and where it requires. In the present study delayed release Rabeprazole sodium pellets were prepared by a drug layering, seal coating and enteric coating by using eudragit L100 55 as enteric coating material different weight gains were developed and evaluated for optimized formula and Sustained release Domperidone pellets were prepared by drug layering, sustained release coating with ethyl cellulose 7 cps as sustained release material. The formulated coated pellets were evaluated for angle repose, bulk density, tapped density, hausener ratio, Carr's index, FTIR, DSC. Moisture content. In vitro release and acid-resistance studies were carried out in simulated gastric fluid and simulated intestinal fluid, respectively. The results indicated that Rabeprazole sodium pellets with seal coat of 10 % (F13) formula and 30% of enteric coat with eudragit L 100 55 (F30) formula showed good acid resistance and drug release. Domperidone pellets with 10 % (F9) and 12 % (F10) formulas of extended release coating with ethyl cellulose were showed required sustained action. The optimized formulations were evaluated for different release kinetics and found that Rabeprazole delayed release pellets were following First order and Korsemeyer-peppas equation Hence the release mechanism was by concentration dependent dissolution process. Domperidone pellets were following First order and Higuchi's equation Hence the release mechanism was by concentration dependent diffusion process. F20 formula of rabeprazole pellets and F10 of formula domperidone pellets were showed required release characteristics were selected and filled in to the capsules.

Corresponding author
Palepu. Swathi
Assistant Professor,
Department of Pharmaceutics,
Mother Teresa Pharmacy College,
Kothur,Sattupally, Dist :Khammam,Telagana-507303.
Swathipalepu1@gmail.com,
8466843335.

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INTRODUCTION

Gastro esophageal reflux disease (GERD) is a common chronic, relapsing condition caused by the combination of excess reflux of gastric juice and impaired clearance of this refluxate from the esophagus. It is one of the most prevalent gastrointestinal disorders affecting all age groups and carries a risk of significant morbidity and possible mortality from resultant complications thus affecting the quality of life of the patient.[1,2]

GERD is commonly due to transient or permanent changes in the barrier between the esophagus and the stomach, which can be due to incompetence of the lower esophageal sphincter (LES), transient LES relaxation, impaired expulsion of gastric refluxate from the esophagus, or association with a hiatal hernia. Reflux of gastric contents can cause esophageal mucosal abnormalities, such as ulcers and peptic strictures, as well as reflux-induced asthma and acid laryngitis. Left untreated esophageal adenocarcinoma can develop in approximately 0.2 - 2.0% of patients with Barrett's esophagus, a complication of GERD.[2-5]

Goals of GERD management include symptom control, promoting mucosal healing, preventing complications and symptom relapse, and improving health-related quality of life. Today, proton pump inhibitors (PPIs) have largely supplanted the H2RAs with superior efficacy in suppression of gastric acid secretion.9 A significant percentage of patients with GERD also have delayed gastric emptying. Prokinetic drugs correct this defect without altering gastric acidity. These agents improve lower esophageal sphincter competence, esophageal clearance and gastric emptying.10 Therefore in GERD patients failing to Rabeprazole alone, combination of Rabeprazole and prokinetic agent may be more useful. [8-12]

A major fact that Rabeprazole sodium is drug of focus for recent years as the patent protection for the Rabeprazole molecule expired in Canada at the end of 2007, As stability of Rabeprazole sodium is poor. In particular it is rapidly decomposed and colored under moist conditions or in an acidic to neutral aqueous solution. A sustained release action of Domperidone is needed. Design of multi particulate pellets dosage form has more advantageous over conventional tablet dosage forms.

Hence the present work aims to formulate delayed release pellets of Rabeprazole sodium and sustained release pellets of Domperiodone by using different polymers and optimization of the formulation.

Pelletization

Pellets :

Pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today.[13-15]

Pellets have to meet the following requirements:

- They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating. The particle size range should be as narrow as possible.
- The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000mm.
- The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.[16-18].

The most common advantages of pelletization are:

- Improved appearance of the product and the core is pharmaceutically elegant.
- Pelletization offers flexibility in dosage form design and development.
- Pellets are less susceptible to dose dumping.
- It reduces localized concentration of Irritative drugs.
- It improves safety and efficacy of a drug.
- Pellets offer reduced variation in gastric emptying rate and transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pellets ensure improved flow properties in formulation development [19,20]

MATERIALS AND METHODS

Materials:

Rabeprazole sodium, Domperidone, L-HPC LH21, Titanium dioxide, Povidone K 30 and Medium chain triglycerides are the gifted samples from Ortin laboratories, Sodium carbonate, Sodium hydroxide, Sodium lauryl Sulphate, are obtained from AVA Chemicals Pvt, Ltd. cellulose Ether K100M, HPMC E5, Propylene glycol, Eudragit L 100 55, Triethyl citrate, Hydroxyl propyl cellulose E5, Ethyl cellulose 7 cpsp and talc are procured from Zeel Pharmaceuticals.

Methods:

Preparation Rabeprazole Pellets

Preparation of Core Pellets

Rabeprazole sodium core pellets were prepared by drug solution layering onto nonpareil seeds in bottom spray fluid-bed processor. Aqueous solution of hypromellose E 5 was prepared by dissolving it in purified water with stirring. Magnesium oxide was added to solution of step 1 with stirring and the solution stirred continuously until it dissolved completely. Rabeprazole sodium was dissolved in solution of step 2 with stirring to get a clear solution. Add binder to the above solution. Nonpareil seeds were charged in a bottom spray fluid-bed processor and drug solution was continuously sprayed over them under an optimized set of process variables to obtain drug pellets. After the completion of drug layering, the pellets were dried in the fluid-bed processor until loss on drying (LOD) of less than 2% w/w was attained. The dried drug pellets were sifted to collect 16 to 20 mesh fraction. Undersize and oversize drug pellets were discarded.

Table 1: Formulation of core pellets.

Formulation code	Non pareil Seeds(g)	Rabeprazole sodium (g)	Sodium carbonate (g)	Sodium hydroxide (g)	Low Substituted Hydroxy propyl cellulose LH21(g)	cellulose Ether K100M (g)	Sodium lauryl Sulphate (g)	HPMC E5 (g)	Purified Water
F1	50	20	40		20		2	4	q.s
F2	50	20		40	20		2	4	q.s
F3	50	20	40		10		2	4	q.s
F4	50	20	40		30		2	4	q.s
F5	50	20	40			10	2	4	q.s
F6	50	20	40			20	2	4	q.s
F7	50	20	40			30	2	4	q.s
F8	50	20	40			40	2	4	q.s

Preparation of Seal-Coated Pellets:

The primary objective of applying seal coat on rabeprazole sodium pellets was to separate the drug layer from the outermost enteric layer which is acidic in nature. Direct contact of acidic enteric layer with the drug would otherwise result in destabilization of drug and generation of impurities. Hypromellose Or HPMCE5 was dispersed and dissolved with stirring in purified water. Titanium dioxide, propylene glycol 6000, was dispersed in the hypromellose solution with stirring to produce the seal coating dispersion.LOD value is critical to stability of drug since higher level of moisture content may lead to destabilization of drug. The dried seal-coated drug pellets were sifted to collect 16 to 20 mesh fractions.

Table 2:Formulation of Barrier Coating.

Formulation code	Core pellets	Barrier coating	Enteric coating (30%)
F9 (2%)	135	2.7	41.31
F10 (4%)	135	5.4	42.12
F11 (6%)	135	8.1	42.93
F12 (8%)	135	10.8	43.74
F13 (10%)	135	13.5	44.55
F14 (12%)	135	16.2	45.36
F15 (14%)	135	18.9	46.17

Preparation of Delayed-Release Pellets

Preparation of organic polymer solution dissolve the eudragit polymer in iso propyl alcohol followed by incorporation of plastcizer . This is then followed by drying of the pellets at 40°C for 1 hour to LOD ≤2% w/w and subsequent screening of the dried pellets to collect 14 to 18 mesh fractions.

Table 3:Formulation of enteric coated pellet:

Ingredients	Core pellets(F2)	Barrier coating(10%)	Enteric coating
F16 (10%)	135	13.5	14.85
F17 (15%)	135	13.5	22.2
F18 (20%)	135	13.5	29.7
F19 (25%)	135	13.5	37.1
F20 (30%)	135	13.5	44.5
F21 (35%)	135	13.5	51.8
F22 (40%)	135	13.5	59.4

PREPARATION OF DOMPERIDONE PELLETS

Table 4: Formulation of Domperidone Core Pellet.

Formulation code	Micro crystalline cellulose spheres (gm)	Domperidone (gm)	Hydroxyl propyl cellulose E5 (gm)	Isopropyl alcohol (gm)	Water	Dissolution	Angle of repose
F1	100	30	5	q.s	q.s	96	96.4
F2	100	30	10	q.s	q.s	94	96.5
F3	100	30	15	q.s	q.s	85	97.8
F4	100	30	20	q.s	q.s	70	92

Pellets were prepared in Bottom spray FBC the process parameters were same as preparation of Core Pellets of rabeprazole by following the table 4.

Coating solution preparation

Hydroxy propyl cellulose was dissolved in solvent prepared by mixing 30:70 water ,methnol and separately dissolve the domperidone drug in the same solvent mixture then add both the solutions by vigorous stirring. Dissolve ethyl cellulose and povidone separately in solvent mixture of water and iso propyl alcohol then add medium chain try glyceride to the above solution. Sprayed on the core pellets by fluidized bed coater.

Table 5: Formulation of Extended Release Pellets.

Formulation code	Core	Drug layering	Extended release coating
F5(2%)	100	45	2.9
F6(4%)	100	45	5.8
F7(6%)	100	45	8.7
F8(8%)	100	45	11.6
F9(10%)	100	45	14.5
F10(12%)	100	45	17.4
F11(14%)	100	45	20.3

Evaluation studies

FTIR measurements

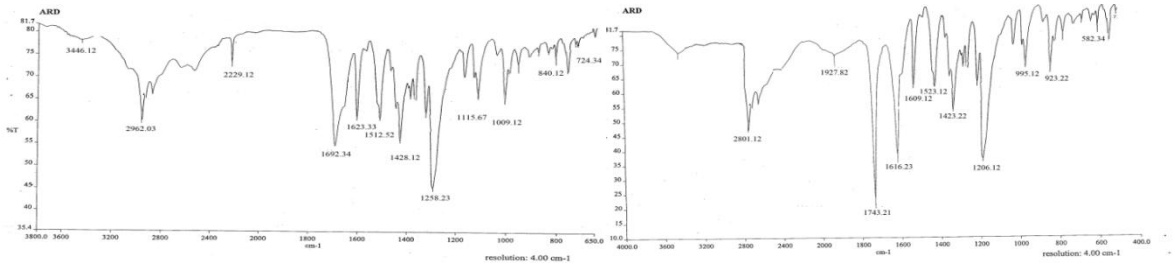

Figure 1: Rabeprazole optimized sample and Rabeprazole sodium pure drug.

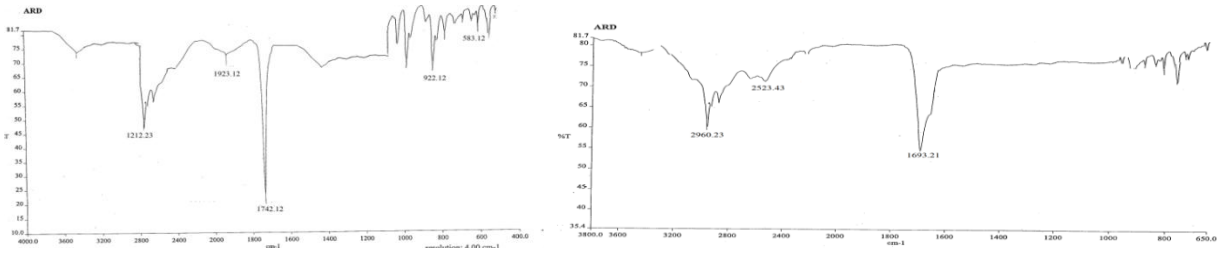

Figure 2:Domperidone optimized sample and Domperidonene Pure Drug.

FT-IR spectra of Rabeprazole alone and its combination with excipients are shown in the Figure1. FTIR spectra of the pure rabeprazole and the drug excipients mixture showed characteristic bands at 2801.12 cm^{-1}, 1743.21 cm^{-1}, 1423.22cm^{-1}, 1206.12 cm^{-1} and 923.22 cm^{-1} due to functional groups, indicating the chemical stability of rabeprazole in the chosen polymeric mixture. This also indicates that rabeprazole is not involved in any chemical reactions with the excipients used.

FT-IR spectra of domperidone alone and its combination with excipients are shown in the Figur 2. FTIR spectra of the pure domperidone and the drug excipients mixture showed characteristic bands at 2962.03 cm^{-1}, 1692.34 cm^{-1}, 1428.12 cm^{-1}, 1115.67 cm^{-1} and 724.34 cm^{-1} due to functional groups, indicating the chemical stability of domperidone in the chosen polymeric mixture. This also indicates that domperidone is not involved in any chemical reactions with the excipients used.

CHARACTERIZATION OF RABEPRAZOLE SODIUM PELLETS

Table 6: Pre formulation studies of core pellets.

Formulation code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	23.5± 0.08	0.78± 0.01	0.82±0.01	16.8	1.05
F2	42.1± 0.14	0.78± 0.01	0.82±0.01	16.6	1.04
F3	22.6±1.36	0.78± 0.01	0.82±0.01	16.9	1.06
F4	22.8±0.15	0.78± 0.01	0.82±0.01	16.8	1.05
F5	34.2±0.63	0.78± 0.01	0.82±0.01	16.6	1.04
F6	36.3±0.04	0.78± 0.01	0.82±0.01	16.9	1.06
F7	32.4±0.06	0.78± 0.01	0.82±0.01	16.6	1.04
F8	33.8±0.06	0.78± 0.01	0.82±0.01	16.8	1.04

Table 7:Dissolution profile of core pellets.

Formulations	10 min	20 min	30min	45min
F1	84	92	96	99
F2	87	90	98	100
F3	95	98	100	101
F4	76	85	90	94
F5	90	94	99	101
F6	90	96	98	101
F7	87	95	98	101
F8	82	90	96	100

Based on the analysis performed and differences occurred in values of angle of repose, percentage moisture content ,dissolution F1 formulation was fixed for the core pellet preparation as shown in table 6 and 7.

Table 8:Characterization of Barrier Coating.

Formulation code	Assay
F9 (2%)	67.5
F10 (4%)	75.2
F11 (6%)	83.6
F12 (8%)	92.3
F13 (10%)	96.20
F14 (12%)	97
F15 (14%)	97

Seal coating was done on to the optimized core pellet formulae (F1) and fixed enteric coat formula used and different percentage weight gains were developed and evaluated based on the assay values F13 formulation was fixed for the seal coat.

Table 9:Characterization of enteric coated pellet.

Formulation Code	CDR in 0.1N HCL	CDR in Tris buffer pH at 45 min	Assay
F16 (10%)	30%	96.5	97.1
F17 (15%)	25%	97.5	97
F18 (20%)	15%	98.6	96.7
F19 (25%)	8%	92.4	97
F20 (30%)	4%	98.5	97
F21 (35%)	2%	95.2	97
F22 (40%)	2%	83.7	96.4

The enteric coat was optimized by performing the acid resistance test the formulation which released very less amount in the acidic media was selected and assay and dissolution in buffer media were performed.Optimization of enteric coat was done by using F1 core formula and F13 seal coat formula and based on the analysis concluded that F20 and F21 formulations were suitable for the preparation.

EVALUATION OF DOMPERIDONE PELLETS

Table 10:Preformulation Studies Domperidone Core Pellets.

Formulation code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	22.3	0.82	0.86	16.8	1.05
F2	23.4	0.83	0.85	16.8	1.04
F3	21.3	0.83	0.87	16.3	1.04
F4	22.2	0.82	0.85	16.7	1.05

Extended release coating was done on to the **F3** formula of core pellets then developed different weight gains of extended release pellets as shown in table 10.

Table 11: Dissolution profile of domperidone:

Time	F5	F6	F7	F8	F9	F10	F11
Acid stage							
0.5hr	60	54	48	43	35	23.4	15.9
1 hr	75.2	68.4	65.4	56.6	49.4	44.5	31,2
Buffer stage							
2nd hr	80.2	78.3	76.7	67.5	58.4	49.2	58.6
3rd hr	89.6	84.3	79.6	73.4	88.9	75.6	65.4
4th hr	94.3	89.7	86.5	76.8	91.1	85.4	74.9
5th hr	97.3	96.4	94.5	74.3	93.2	87.5	75.2
6th hr	98	97.8	97	85.4	94.6	92.4	78.3
7th hr	98	98	97	92	97.5	93.4	82.3

Based on the evaluation parameters F9,F10 formulations were found to be best formulations as shown in the table 11.

Kinetic Studies:

Rabeprazole delayed release pellets were following First order and Korsemeyer-peppas equation Hence the relese mechanism was by concentration dependent dissolution process.

Domperidone pellets were following First order and Higuchi's equation Hence the release mechanism was by concentration dependent diffusion process.

CONCLUSIONS

Preformulation studies were performed before formulation development the drug and excipients werefound to be compatable. Rabeprazole sodium and Domperidone pellets were prepared by using different excipients for rabeprazole sodium pellets F1 formulation (containg sodium carbonate as alkalizing material and L-HPC as polymer) for core pellets,F13 formulation (with 10 % 0f seal coat) for seal coat and F20 formulation (with 30 % of eudragit coating) for enteric coating were optimized respectively based on diferent preformulation and evaluation parameters and for domperidone pellets F3 formulation(with hydroxyl propyl polymer at a concentration of 15 5 W/V) for core ,F9,F10 formulation (with 10 % and 12 % sustained release coating with ethyl cellulose 7 cps) for sustained release coating were optimized respectively.

Optimized formuloins were studied for different release kinetics Based on the regression values analyzed for different order of reactions Rabeprazole delayed release pellets were following First order and Korsemeyer-peppas equation Hence the release mechanism was by concentration dependent dissolution process.

Based on the regression values analyzed for different order of reactions Domperidone pellets were following First order and Higuchi's equation Hence the release mechanism was by concentration dependent diffusion process.

F20 formulation (with 10 % seal coat and 30% delayed release coat) of rabeprazole pellets and F10 formulation (with 12 % sustained release coat with ethylcellulose 7 cps) of domperidone pellets were selected and filled in to the capsules.

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