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Formulation and Evaluation of Enteric Coated Pellets of Lansoprazole

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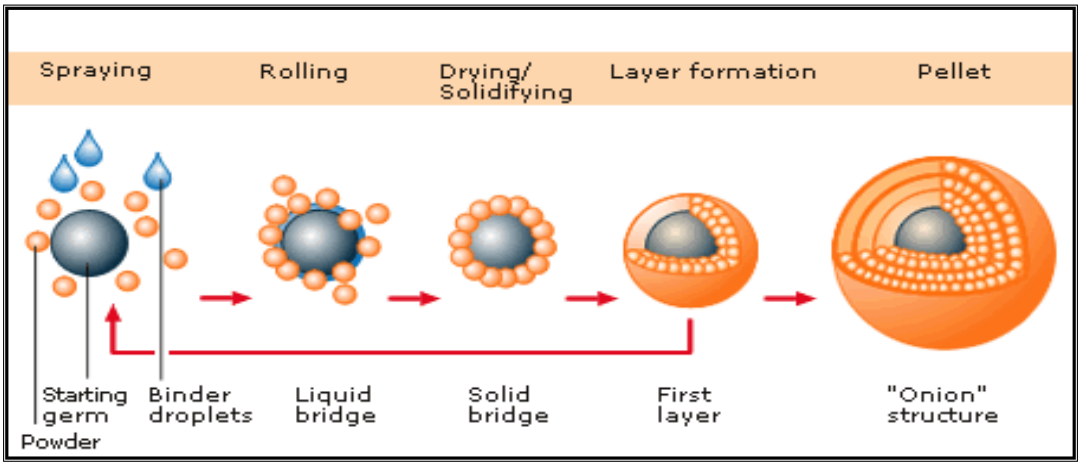
ABSTRACT

Proton pump inhibitors are acid labile drugs. These drugs will degrade in acidic environment of stomach and will lead to therapeutic inefficacy. It is necessary to bypass the acidic pH of the stomach which can be achieved by formulating delayed release dosage forms (single unit or multiple units) by using different enteric polymers. The aim of the present study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Lansoprazole enteric coated pellets [delayed release] and compared with marketed dosage form.Due to instability in acidic environment, a trail was made to by-pass the stomach by using enteric coating which thereby improves bioavailability and therapeutic efficacy with no degradation of drug.

Key words: Lansoprazole, Sugar spheres (#20/#25), L-Hydroxypropyl cellulose, Hydroxypropyl cellulose, Magnesium carbonate, Titanium dioxide Methacrylic acid copolymer type C, Triethyl citrate.

Introduction

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. Conventional forms often cause problems to the patient, because they maintain therapeutic drug level for only brief duration [1-5]. This gives rise to sharp fluctuations of drug levels in plasma and in tissue. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, controlled drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience.The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half life ($t^{1/2}$) and duration of pharmacological effect. The time of dosing may also be effected by therapeutic index (TI) of a drug [6-10].



MATERIALS AND METHODS

Lansoprazole were obtained from Hetero drugs Hyderaded Sugar spheres (#20/#25), L-Hydroxypropyl cellulose, Hydroxypropyl cellulose, Magnesium carbonate, Titanium dioxide Methacrylic acid copolymer type C, Triethyl citrate were obtained from LUZENAC PHARMA.

Procedure

1. **Drug loading:**
   - Sucrose ,L-Hpc and corn starch is added to purified water and stirred for 20 minutes to get clear solution.
   - Light magnesium carbonate is added to clear solution and stirred to get uniform dispersion
   - Lansoprazole is added to dispersion and stirred for 20 minutes to get a uniform dispersion.
   - Sugar pellets of size(20#25) are loaded into FBP bowl and warmed upto 42^{o}c
   - Dispersion is coated on to sugar spheres.

2. Sub coating:

- Required quantity of Drug loaded pellets was taken for sub coating. Required quantity of HPC and L-HPC was taken and dissolved in specified ml of purified water and stirred until a clear solution was obtained and coating is done

3. Enteric coating:

- Specified quantities of sub coated pellets were taken for Enteric coating.
- Required quantity of Eudragit, Talc, Titanium Dioxide, PEG 6000 and Tween 80 were taken and dispersed in specified ml of purified water
- Stirred for 10 minutes to obtain a clear solution and coating was done.

4. Lubrication:

- Specified quantities of Talc , Colloidal silicon dioxide are taken added to enteric coated pellets and lubricated.

5. Capsule filling:

Next the lubricated pellets were filled into capsules according to their sizes:

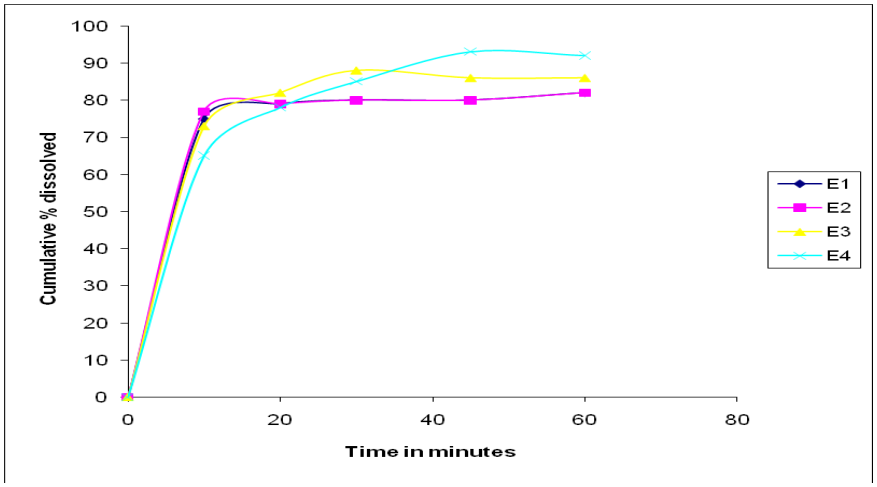
Preparation of Lansoprazole Pelllets

S.NO	Name of ingredients	D1(mg)	D2(mg)	D3(mg)	D4(mg)	D5(mg)	D6(mg)
1.	Lansoprazole USP	30	30	30	30	30	30
2.	Sugar spheres(#20,25) USP-NF	108.8	110	110	110	135	150
3	Sucrose	19.8	19.8	19.8	19.8	19.8	19.8
4.	Mgco3 light	22.4	22.4	22.4	-	-	-
5.	Mgco3 Heavy	-	-	-	22.4	22.4	22.4
6.	Corn starch	20	5	20	5	5	5
7.	L-HPC(LH-11)	20.7	30	20.7	-	-	-
8.	L-HPC(LH-31)	-	-	-	30	24	24
9.	SLS	-	-	8.7	8.7	8.7	8.7
10.	HPC-L(Nisso HPC-L)	-	-	-	-	-	4.5
11.	HPC-L(Klucel-LF)	-	-	-	-	6	-
12.	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
13.	Total weight	221.7	217.2	225.9	225.9	250.9	264.4

Invitro dissolution studies

Dissolution of the capsules of each batch was carried out using USP dissolution type II apparatus using paddle at 50 rpm. The dissolution was studied using 500 ml of 0.1N HCl for 2 hours and next 900ml of phosphate buffer for next 1 hr. The temperature was maintained at 37 ± 0.2 °C. With draw 10ml of the solution from each vessel and replace with equal volume of fresh dissolution medium at specific time intervals. Filter the solution through What man filter paper and discard first few ml of the filtrate. Dissolution study was carried out in pH 6..8 phosphate buffer for 10,20,30,40,50,60 min and samples were suitably diluted and analyzed for Lansoprazole drug content by doing assay in HPLC which was describied in chapter

Drug Release Profiles of Enteric coated Formulations, E1 to E4



Preparation of Enteric coating Dispersion

- Purified water was taken in a stainless steel vessel. Methacrylic acid copolymer was slowly added to the purified water and the contents were mixed for 30 minutes under continuous stirring.
- TEC was taken in to a beaker and purified water was added and mixed for 5 minutes .Now Polysorbate 80 was added to the solution under continuous stirring.
- Talc was added to above solution and stirred to get uniform dispersion. Now titanium dioxide was dissolved in dispersion and stirred to get uniform dispersion.
- Solution of the above step was added slowly to first step under continuous stirring and mixed for about 30 minutes.
- The dispersion obtained was sifted through mesh #100 and collected in a stainless steel vessel.

Coating of Enteric dispersion

- The sub coated pellets of were loaded into FBP and the pellets were warmed till product temperature 38^0C – 40^0C.
- The enteric coating dispersion was started spraying with following parameters. The dispersion was kept under continuous stirring, during the coating process. The coating was continued till target weight build up was obtained.
- The fluidization air flow was reduced to suitable level and the pellets were warmed at the product temperature 40^0C – 45^0C for 45 minutes.
- The enteric coated pellets were sifted through mesh #18 and passed pellets were collected into a container.

Table No.15 Process parameters of Enteric Coating

S. No.	Process parameters	Range
1	Inlet temperature (^{0}C)	40-45
2	Product temperature (^{0}C)	28-35
3	Exhaust temperature (^{0}C)	30-35
4	Drive speed (CFM)	40-65
5	Atomization (Barr)	0.8-3.5
6	Spray rate (g/min)	2-5
7	Wurster height (mm)	20-50

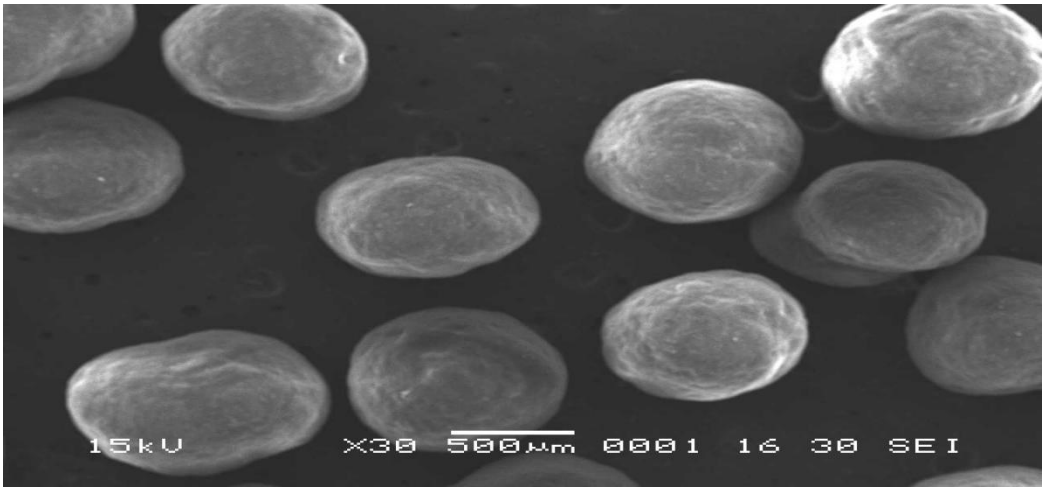
Note: In case, if lumps formation was observed during coating, unload the pellets and sift through #18 (or) #20 mesh.

4. Enteric coating (Table No 14)

S. No.	ENTERIC COATING	E1	E2	E3	E4	E5	*E6*	E7
1	Sub coated pellets S3	302.9	302.9	302.9	302.9	302.9	302.9	302.9
2	Eudragit L30D55	24.75	24.85	25.25	37.86	37.86	42.9	47.98
4	Triethyl citrate	2.475	2.485	2.525	3.786	-	4.29	4.798
5	Polyethylene glycol	-	-	-	-	3.786	-	-
6	Talc	1.7325	1.7395	1.7675	2.6502	2.6502	3.003	3.3586
7	Polysorbate 80	0.495	0.497	0.505	0.7572	0.7572	0.858	0.9596
8	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total	332.35	332.47	332.94	347.95	347.5	353.95	359.96

Surface morphology study of Enteric coated pellets

Surface Morphology of Enteric Coated pellets were determined by SEM analysis.



Discussion of Results

The present study was to formulate and evaluate delayed release Capsules of Lansoprazole. The formulation process was carried out in FBP by suspension layering technique. Lansoprazole is an acid labile drug, degrades at acidic pH of stomach. To bypass stomach, the formulation has to delay the release and give the release in proximal small intestine. This can be achieved by enteric coating.he work was carried out to delay the release of Lansoprazole by using enteric polymer Methacrylic acid copolymer (type C). The study includes preformulation of drug and excipients, formulation and evaluation, release kinetics and stability studies of capsules.The inert core material (i.e. Sugarsphere USP) was given , Drug coating, Sub coating and Enteric coating.Drug Loading was given to sugarsheres by using different binders i.e., Klucel- LF and L- HPC with different concentrations. The amount of drug bound to sugarsheres increases with an increased concentration of HPC(L-type) (17.5% and 22%). But at high concentration of HPC (22%), lumps were observed. Finally 17.5% w/w HPC was optimized as binder for drug coating.Sub coating was given to drug loaded pellets to avoid direct contact with enteric coating. Sub coating was given with HPC and Corn starch combination at an average weight build up of 6.1% w/w of sub coated pellets.Enteric coating was given to Lansoprazole pellets by Methacrylic acid copolymer type C (30% aqueous dispersion). Enteric coating was optimized at an average weight build up of 53% w/w of enteric coated pellets and release profile was compared with Innovator. In enteric coating, plasticizer plays major role in film formation of pellets. Among TEC and PEG 6000, TEC was found to have good film forming capacity. Plasticizer concentration was optimized at 20% of dry polymer weight.

Conclusion

Enteric coated pellets were evaluated for assay, acid resistance and dissolution; E6 enteric coated pellets were found to be optimized and were filled into capsules. These capsules were evaluated and the results were found to be more similar with innovator. Different kinetic models were applied to optimized enteric coated formulation (E6) and observed that it follows zero order kinetics with Higuchi diffusion mechanism. Stability studies were conducted at 40ºC / 75% RH (accelerated stability testing) for 3 months. Assay, acid resistance, dissolution release profile of optimized enteric coated formulation (E6) complies with Innovator and was found to be stable.Based on the above data, it was concluded that Lansoprazole Capsules 30mg (E6) complies with the Innovator and may be considered as an ideal formulation for developing Lansoprazole delayed release capsules 30mg.

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