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Research Article

FORMULATION AND EVALUATION OF CONTROLLED RELEASE MICROSPHERES OF LANSOPRAZOLE

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Abstract: The aim of this study was to develop, formulate and evaluate controlled release microspheres of Lansoprazole, using Eudragit S100 and Eudragit L100 polymers in different ratios as release retardant material. Microspheres were prepared by solvent evaporation method using methanol / liquid paraffin system (w/o). The prepared microspheres were characterized for their particle size, drug loading, FT-IR and Scanning Electron Microscopy. The *in vitro* release studies were performed in pH 1.2 and in 7.2 pH phosphate buffer. The prepared microspheres were white, free flowing and spherical in shape. The IR spectra showed stable character of Lansoprazole in mixture of polymers and revealed the absence of drug polymer interactions. The drug loaded microspheres showed 82.83 – 95.49 % of entrapment and release extended up to 12 h. Scanning electron microscopy study revealed that the microspheres have rough surface and spherical in shape. The best-fit release kinetic was achieved with zero order. The release of Lansoprazole was influenced by the drug to polymer ratio, amount of Eudragit S100 and Eudragit L100 combination. The release was found to be erosion controlled.

Key words: Lansoprazole; Eudragit S100; Eudragit L100; Controlled release microspheres.

INTRODUCTION

Lansoprazole, a substituted Benzimidazole compound [IUPAC Name-(*RS*)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1*H*-benzo[*d*]imidazole] is a strong proton pump inhibitor (PPI) having an inhibitory activity on gastric ulcer formation and accelerates the ulcer healing by inhibiting H+/ K+-ATPase production in the parietal cells and suppress the acid secretion.[1-3] As H+/ K+-ATPase system is regarded as acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid pump inhibitor, in that it blocks the final step of acid production. [4]

Lansoprazole widely used in the world for the therapy of gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome etc..[5] Clinically, LPZ is prescribed to elderly patients whose swallow function is reduced with high frequency.[6]

Lansoprazole is unstable in Acid and therefore various formulations are used to maintain proper bioavailability of drugs. Literature reveals that different formulations like Liquid intra-gestric Suspension[7], fast disintegrating tablet [8] , Oro-dispersible tablet[9], Micropellets[10] and enteric coated tablet. The Present study was design to develop a stable, pharmaceutically equivalent, robust and control release microsphere formulation of Lansoprazole.

MATERIALS AND METHODS

Drugs and Instruments

Lansoprazole,, Eudragit-S100, Eudragit - L100, Methanol, Acetone, Liquid Paraffin, Petroleum ether obtained from hetero drug formulation. UV-Visible Spectrophotometer, Electronic Analytical Balance, FTIR,USP dissolution apparatus, Mechanical Stirrer, Stability studies, pH-tutor, Optical microscope obtained Lab.

Preparation of microspheres

Solvent Evaporation method

The microsphere was prepared by using solvent evaporation method. [12-13] To retard the drug release, the drug was coated with Eudragit S100 and Eudragit L100 in different ratio. Microencapsulation was carried out by solvent evaporation technique. A homogenous mixture of the polymers was made in 15 ml methanol. Drug was then added to polymer solution. The resulting mixture was then poured in 50 ml liquid paraffin and stirred continuously at 500-800 rpm for 3 to 4 h until methanol evaporated completely. The

microspheres formed were collected by filtration, washed 4-5 times with petroleum ether and dried at room temperature for 24 h. The microspheres obtained from this technique were found to be spherical and without aggregation and mean particle size was observed.

Table 1: Drug and Polymer combination in different ratio

Formulation Code	Lansoprazole (mg)	Eudragit S100 (mg)	Eudragit L100 (mg)
F1	300	300	-
F2	300	600	-
F3	300	900	-
F4	300	-	300
F5	300	-	600
F6	300	-	900
F7	300	300	300
F8	300	600	300
F9	300	900	900

Evaluation of microspheres

UV-Spectrophotometric method was developed for the determination of Lansoprazole in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) at 283.0 nm. FT-IR spectrum of pure drug, pure polymer and drug-polymer mixture revealed no chemical interaction. Percentage yield for the formulation of F1 to F9 varied from 73.80 % to 85.5 %. Percentage drug entrapment efficiency for the formulation of F1 to F9 varied from 82.83 % to 95.49 %.Particle size for the formulation F1 to F9 varied from 99.96 µm to 527.86 µm. Results of formulation F7 not only closely met to targeted data but also showed the zero order kinetics desired release as well as having good % DEE.

RESULTS&DISCUSSION

Polymer Drug Compatibility

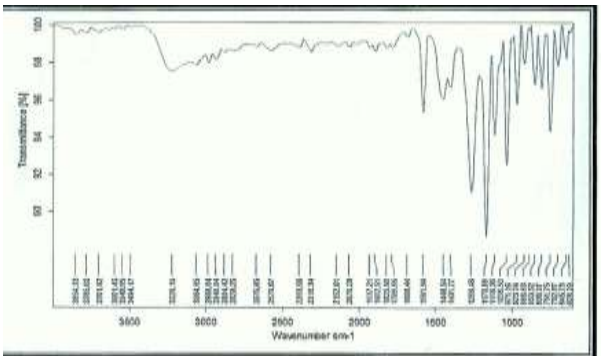


Figure-1: FT-IR Spectrum of pure lansoprazole

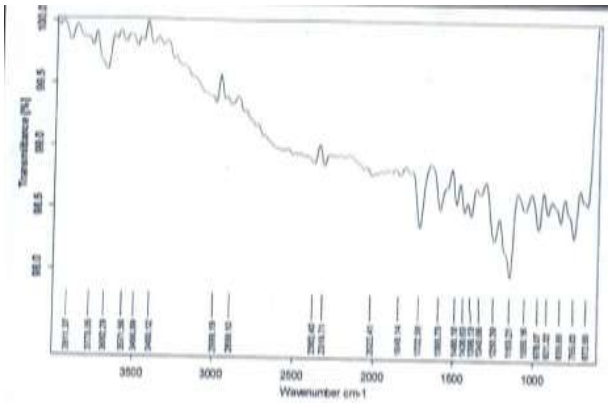


Figure-2: FT-IR Spectrum of pure EudragitS100

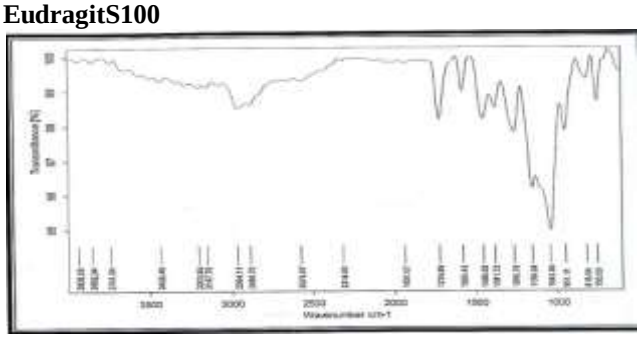


Figure-3: FT-IR Spectrum of pure EudragitS100& Lansoprazole

Table 2 : FT-IR Spectrum of pure Lansoprazole

Band	Wave number (cm-1)
Aromatic C-H	3064
Sp3 C-H	2988
	2940
	2884
	2829
C-O-C bending	1170
C=N streching	1268
CF bending	645
Aromatic OOP	751

FT-IR gave the confirmation about purity of drug, polymer and there was no interaction between drug, and polymers. So, the drug and polymer are compatible.

Solubility study:

Eudragit L100 and S100 will dissolve only above pH 6.8 and 7.0 respectively. Eudragit L100 and Eudragit S100 are soluble in methanol, so methanol was used as solvent and liquid paraffin was used as dispersion medium.

Development of Analytical Methods of Drug

Estimation of Lansoprazole was carried out by UV spectrophotometer at λmax 283.0 nm in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 7.2. The value of regression coefficient in pH 1.2 was found to be 0.995 and in pH 7.2 regression coefficient value was found to be 0.996, which showed linear relationship between concentration and absorbance. The standard calibration curve obeyed Beer's law at the given concentration range of 5 µg/ml to 25 µg/ml in pH 1.2 and pH 7.2. By using this regression co-efficient equation the assay and % CDR were calculated.

Physicochemical Parameters of Various Formulations

The percentage yield was found for F1, F2, F3 batch showed good percentage yield 79.76, 85.33, 80.62, while as the concentration of total amount of polymer (Eudragit L100) was increased, the percentage yield was found for F4, F5, F6 showed 80.21, 85.5, 73.80 respectively. And for the Eudragit S100 and L100 combination i.e. 1:1:1 was 76.6, 1:2:1 was 84.95 and for 1:1:2 was 83.97.

The percentage DEE of Eudragit S100 formulations F1, F2, F3 batches were found to be 95.49 ± 0.26, 92.0 ± 2.68, 85.8 ± 3.87. The percentage DEE of Eudragit L100 formulations F4, F5, F6 batches were found to be 91.16 ± 0.66, 86.0 ± 0.51, 82.83 ± 0.53. The percentage DEE of Eudragit S100 and Eudragit L100 combination formulations F7, F8, F9 batches were found to be 95.16 ± 0.69, 89.16 ± 0.69, 85.16 ± 0.52. Higher drug entrapment was found in formulation F1, F4 and F7

Particle size for the formulation F1 to F9 varied from 99.96 µm to 527.86 µm. Results of formulation F7 not only closely met to targeted data but also showed the zero order kinetics desired release as well as having good % DEE.

Angle of Repose of different formulations was measured according to fixed funnel standing method44,24, from above the given data F7 formulation provides best formulation for CDDS.

Table 3: Physicochemical parameters of formulations F1 to F9.

Formulation Code	Percentage Yield*(%)	Percentage DEE*(%) ± SD	Particle Size*(µm)	Angle of Repose*(θ) ± SD	Flow Properties
F1	79.76	95.49±0.70	481.35	22.96° ± 1.33	Excellent
F2	85.33	92.0 ± 1.32	146.85	25.31° ± 1.21	Good
F3	80.62	85.8 ± 2.96	325.72	22.06° ± 0.14	Excellent
F4	80.21	91.16 ± 1.04	203.11	17.35° ± 1.46	Excellent
F5	85.5	86.0 ± 2.78	99.96	32.41° ± 0.72	passable
F6	73.80	82.83 ± 3.75	527.86	21.80° ± 0.07	Excellent
F7	76.6	95.16 ± 1.25	489.98	25.16° ± 1.47	Good
F8	84.95	89.16 ± 1.25	424.9	24.94° ± 1.29	Excellent
F9	83.97	85.16 ± 1.75	206.24	21.93° ± 0.67	Excellent

***All readings are mean of three readings.**

Scanning Electron Microscopy

SEM micrographs and typical surface morphology of the formulations are shown in Which shows spherical in shape and surface appearance is rough.

***In-Vitro* Drug Release of Various Formulations**

Table 4 : *In vitro* drug release data of formulations F1, F2 and F3.

Time (h)	% Cumulative Drug Release ± SD		
	F1	F2	F3
1	3.80 ± 0.27	3.38 ± 0.51	2.62 ± 0.18
2	6.00 ± 0.32	5.72 ± 0.50	4.27 ± 0.36
3	35.68 ± 0.71	17.36 ± 0.83	15.69 ± 0.92
4	46.93 ± 0.40	23.96± 1.00	21.09± 1.25
5	62.50 ± 0.30	32.40 ± 0.85	29.06 ± 1.49
6	76.55 ± 0.32	43.83± 1.52	40.78± 1.37
7	84.73 ± 0.55	55.63 ± 2.04	51.46 ± 1.60
8	88.49 ± 0.55	63.19± 2.72	58.74± 1.74
9	91.82 ± 0.55	74.84 ± 2.86	69.27 ± 1.02
10	97.77 ± 0.48	82.30± 1.46	79.90 ± 1.10
11	-	92.46 ± 1.35	84.59± 1.34
12	-	94.36 ± 0.14	89.10 ± 0.62

Table 5: *In vitro* drug release data of formulations F4, F5 and F6.

Time (h)	% Cumulative Drug Release ± SD		
	F4	F5	F6
1	4.71 ± 0.23	3.80 ± 0.59	2.62 ± 0.18
2	9.63 ± 0.56	6.15 ± 0.91	5.54 ± 0.32
3	26.89 ± 0.83	19.26 ± 1.35	19.20 ± 0.90
4	38.95 ± 0.99	25.38 ± 1.44	26.27 ± 0.84
5	50.37 ± 1.01	34.32 ± 1.22	35.92 ± 1.21
6	64.16 ± 1.47	43.17 ± 1.23	43.67 ± 1.08
7	76.62 ± 1.09	54.16 ± 1.31	54.27 ± 0.70
8	88.15± 1.00	62.26 ± 1.47	63.67 ± 0.78
9	91.43 ± 1.02	71.56 ± 1.56	71.62 ± 1.31
10	97.57 ± 0.72	82.90 ± 1.33	76.36± 1.12
11	-	89.05± 0.80	82.48 ± 0.88
12	-	90.03± 0.46	83.87 ± 0.50

Table 6 : *In vitro* drug release data of formulations F7, F8 and F9.

Time (h)	% Cumulative Drug Release ± SD		
	F7	F8	F9
1	2.71 ± 0.18	2.41 ± 0.13	2.14 ± 0.27
2	6.62 ± 0.45	5.54 ± 0.27	5.35 ± 0.63
3	25.97 ± 0.71	18.55 ± 0.67	16.70 ± 0.84
4	36.87 ± 1.06	25.76 ± 0.83	24.75 ± 0.99
5	48.18 ± 1.06	34.51 ± 0.61	33.84 ± 0.84
6	58.60 ± 1.60	43.85 ± 0.84	42.18 ± 0.92
7	67.88 ± 1.00	55.75 ± 0.78	53.62 ± 1.02
8	78.05 ± 1.70	62.76 ± 0.54	60.47 ± 1.08
9	85.68 ± 1.17	71.36 ± 0.70	69.35 ± 1.16
10	91.35 ± 1.10	79.55 ± 0.63	76.93 ± 1.39
11	94.34 ± 0.73	86.59 ± 0.70	82.45 ± 1.02
12	98.15 ± 0.97	88.70 ± 0.71	84.50 ± 1.03

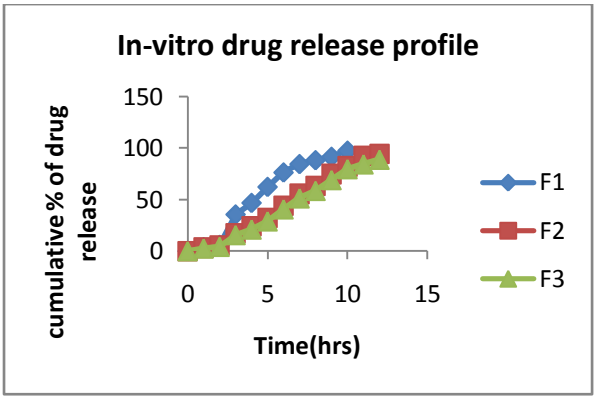


Figure 4 : *In vitro* drug release studies of formulations F1, F2, and F3.

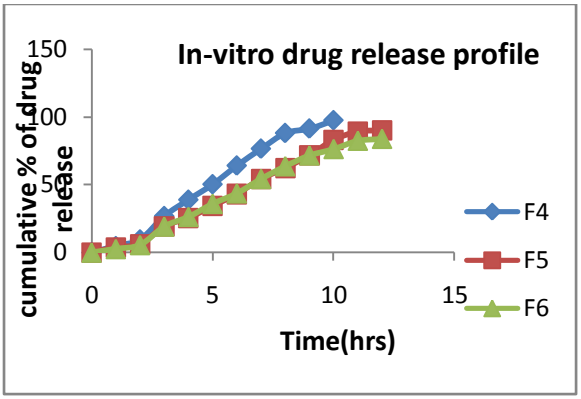


Figure 5 : *In vitro* drug release studies of formulations F4, F5, and F6.

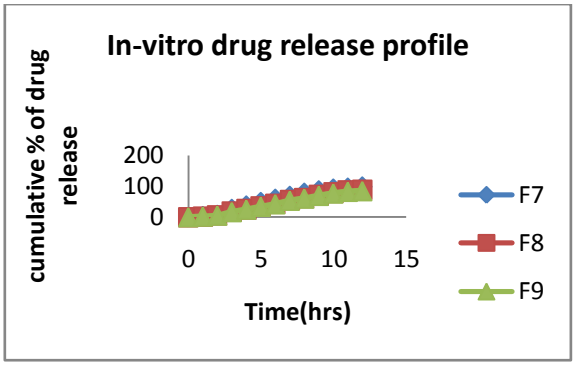


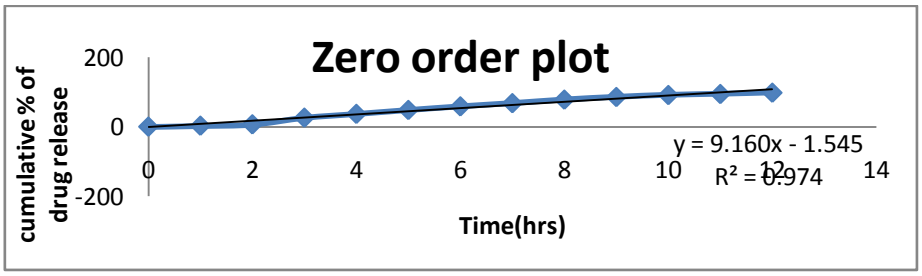
Figure 6 *: In vitro* drug release studies of formulations F7, F8, and F9

***In vitro* drug release study**

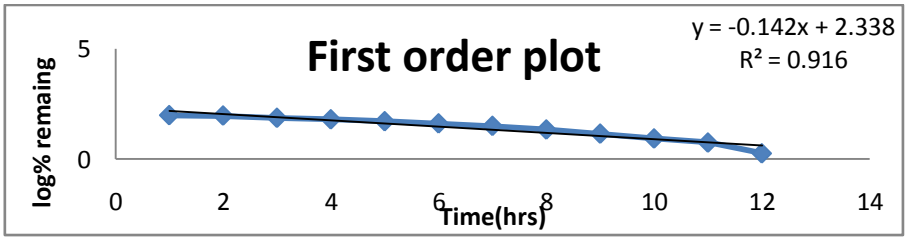
The formulation of F1 to F9 showed wide range of drug release as shown in table 4, 5 and 6. In case of Eudragit S100 batch showed drug release from F1, F2 and F3 as 97.77 ± 0.480 % in 10 h, 94.36 ± 0.145 % in 12 h, and 89.10 ± 0.629 % in 12 h respectively. In case of Eudragit L100 batch showed drug release from F4, F5 and F6 as 97.57 ± 0.721 % in 10 h, 90.03 ± 0.465 % in 11 h and 83.87 ± 0.508 % in 12 h respectively. In case of F7, F8 and F9 that the combination of Eudragit S100 and Eudragit L100 N the drug release will be 98.15 ± 0.974 %, 88.70 ± 0.712 % and 84.50 ± 1.038 % in 12 h respectively. Thus from the drug release profile F7 give excellent release in 12 h and the drug release pattern will be delayed as the concentration of polymer increases.

Drug Release Kinetics for Formulation F7:

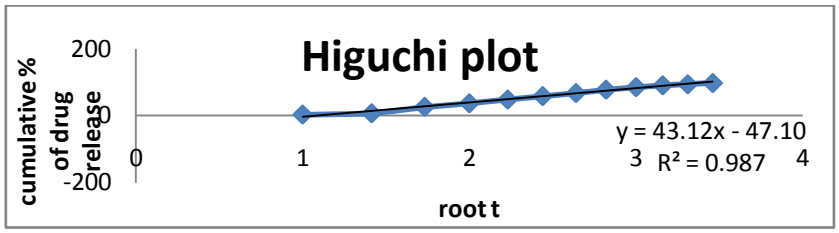
Zero order



First order plot:



Higuchi plot:



Peppas plot:

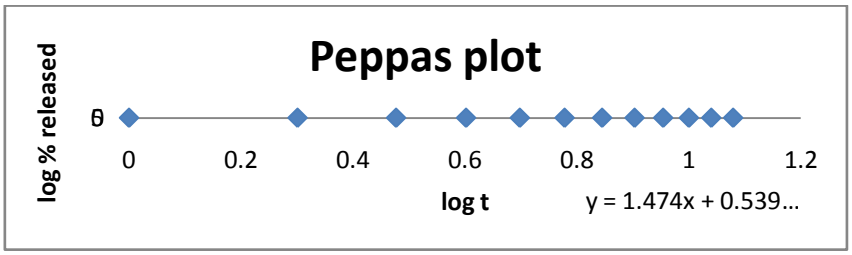


Table 7 : R^2 values of different orders:

Type of order	R^2 values
Zero order	0.974
First order	0.916
higuchi plot	0.987
Peppas plot	0.948

Kinetic Parameters

Experimental value of R^2 for zero order, higuchi and n value of Korsemeyer-peppas of F7 was near to expected values and also significant to desirable data. Formulation F7 follows zero order kinetics for erosion controlled release system.

Stability studies

The best formulation F7 stored in sealed container in aluminum foil. These were stored at room temperature for 2 months. Then the formulation was exposed to various temperature and humidity at 30 ± 2 °C (65 ± 5% RH) and 40 ± 2 °C (75 ± 5 % RH) assess their stability as per ICH guidelines. After 1 month (30 days) % DEE was found to be 94.5% for 30 ± 2 °C and 60 ± 5 % RH and 93.53 % for 40 ± 2 °C and 70 ± 5 % RH and *in vitro* drug release profile after 30 days was found to be 97.50% for 30 ± 2 °C and 60 ± 5 % RH and 96.26 % 40 ± 2 °C and 70 ± 5 % RH. After 2 month (60 days) % DEE was found to be 93.03% for 30 ± 2 °C and 60 ± 5 % RH and 91.99 % for 40 ± 2 °C and 70 ± 5 % RH and *in vitro* drug release profile after 2 month (60 days) was found to be 96.55 % for 30 ± 2 °C and 60 ± 5 % RH and 95.30 % 40 ± 2 °C and 70 ± 5 % RH.

Table 8 : Drug content of the most satisfactory formulation F7 during stability studies

Drug Content After 30 Days		Drug Content After 60 Days	
A	**B**	**C**	**D**
F7 (%)	**F7 (%)**	**F7 (%)**	**F7 (%)**
94.5	93.53	93.03	91.99

F7A, F7C = 30 ± 2 °C / 65 ± 5 % RH.
F7B, F7D = 40 ± 2 °C / 75 ± 5 % RH.

Table 9 : Drug release profile of the most satisfactory formulation F7 during stability studies

TIME (h)	After 30 Days		After 60 Days	
	A	**B**	**C**	**D**
	F7 %	**F7 %**	**F7 %**	**F7 %**
1	2.53	2.08	2.35	1.81
2	6.53	6.26	6.26	5.71
3	25.56	24.81	24.81	23.75
4	36.36	35.90	35.76	34.84
5	47.67	46.91	46.91	45.54
6	59.19	58.58	58.28	57.65
7	67.32	66.55	66.70	65.47
8	78.95	77.87	77.72	76.64
9	85.68	84.60	84.60	83.66
10	92.00	91.21	90.76	90.27
11	94.44	93.81	93.20	92.10
12	97.50	96.26	96.55	95.30

CONCLUSION

From the above results and discussion it is concluded that the present investigation showed promising result of microspheres of Lansoprazole formulation F7 which is Eudragit S100 and Eudragit L100 combination (1:1:1) proved as best formulation.

REFERENCES

1. Kubo, K., Oda, K. Kaneko, T., Satoh, H. and Nohara, A.: Synthesis of 2-[[(4-‰uoroalkoxy-2- pyridyl)methyl]sulˆnyl]-1H- benzimidazoles as antiulcer agents. *Chem. Pharm. Bull*. **1990**; 38: 2853–2858.
2. Satoh, H., Inatomi, N., Nagaya, H., Inada, I., Nohara, A., Nakamura, N. and Maki, Y.: Antisecretory and antiulcer activities of a novel proton pump inhibitor AG-1749 in dogs and rats. *J. Pharmacol. Exp. Ther*. **1989**; 248: 806–815.
3. Nagaya, H., Satoh, H. and Maki, Y.: Possible mechanism for the inhibition of acid formulation by the proton pump inhibitor AG-1749 in isolated canine parieta cells. *J. Pharmacol. Exp. Ther*. **1990**; 252: 1289–1295.
4. Jain KS, Shah AK, Bariwal J, Shelke SM, Kale AP, et al,. Recent advances in proton pump inhibitors and management of acid-peptic disorders. *Bioorg Med Chem*. **2007**;15(3):1181 205.
5. Spencer, C. M. and Faults, D.: Lansoprazole: A reappraisal of its pharmacodynamic and pharmacokinetic properties, and its therapeutic e‹cacy in acid-related disorders. *Drugs*, **1994**; 48: 404–430.
6. Firth, M. and Prather, C. M.: Gastrointestinal motility problems in the elderly patient. *Gastroenterol*. **2002**; 122:1688–1700.
7. Sharma VK, Vasudeva R, Howden CW, Simplified lansoprazole suspension--a liquid formulation of lansoprazole--effectively suppresses intragastric acidity when administered through a gastrostomy. *Am J Gastroenterol*. **1999**; 94(7):1813-1817.
8. Baldi F, Malfertheiner P. Lansoprazole fast disintegrating tablet: a new formulation for an established proton pump inhibitor. *Digestion*. **2003**;67(1-2):1-5.
9. Baldi F. Lansoprazole oro-dispersible tablet : pharmacokinetics and therapeutic use in acid-related disorders. *Drugs*. **2005**;65(10):1419-26.
10. S.K.Singh, C. H. Borkhataria, Dr. N.R. Seth, Dr. R. P. Patel, S. Singh and G. R. Parmar. Formulation and in vitro evaluation of lansoprazole micropellets. *Int.J. PharmTech Res.***2009**,1(4): 1531-1540.
11. Diwakar Pachabhai, S. Bhama, R. Sambath Kumar, P. Perumal. Formulation and evaluation of lansoprazole enteric Coated pellets. *International journal of pharma world research*, **2012**; 3(2):1-19.
12. Wang S, Wu M, Li D, Jiao M, Wang L, Zhang H, Liu H, Wang D, Han B. Preparation, characterization and related in vivo release, safety and toxicity studies of long acting lanreotide microspheres. *Biol Pharm Bull*. **2012**;35(11):1898-1906
13. Jelvehgari M, Barar J, Valizadeh H, Shadrou S, Nokhodchi A. Formulation, characterization and in vitro evaluation of theophylline-loaded Eudragit RS 100 microspheres prepared by an emulsion-solvent diffusion/evaporation technique. *Pharm Dev Technol*. **2011**;16(6):637-644.