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FORMULATION AND IN-VITRO EVALUATION OF LANSOPRAZOLE COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Colon targeting is of value for the treatment of diseases of colon such as Gastro esophageal reflux diseases(GERD) and Zollinger- Ellison syndrome, ulcers of the stomach and duodenum. The present work is a Time dependent formulation named 'Modified Pulsincap' that would target release of Lansoprazole in the colon thereby affording relief of GERD and being devoid of unwanted systemic side effects. Bodies of hard gelatin capsules were treated with Formaldehyde keeping the cap portion as such. Lansoprazole loaded pellets were prepared by Extrusion-Spheronization technique. Pellets equivalent to 15mg of drug were filled into treated capsule shells and plugged with polymers Guar gum, HPMC 10K, Sodium CMC, Sodium Alginate and Hydroxy Propylcellulose at concentrations (20mg, 30mg and 40mg). The filled capsules were completely coated with 5% Cellulose Acetate Phthalate to prevent variable gastric emptying. The whole system, thus produced is Modified Pulsincap. All Formulations were assayed to determine drug content. The ability of Pulsincap to provide colon specific drug delivery was assessed by *In vitro* drug release studies in Buffer pH 1.2 for 2 hrs, pH 7.4 (Simulated Intestinal fluid) for 3 hrs & pH 6.8 (Stimulated Colonic fluid) for 7 hours. The results indicated that with formulations containing 30mg of Guar gum, Sodium CMC, Sodium alginate and 40 mg of Sodium alginate, negligible drug release took place in the small intestinal fluid, but the major portion of the drug was released in the colon. It was therefore concluded that Lansoprazole could be successfully colon targeted by the use of 'Modified

Pulsincap'.

KEYWORDS: Colon targeting; Extrusion; Spheronization; Pulsincap, Hydrogel polymer; Gelatin capsules.

INTRODUCTION

During the last decade there has been interest in developing site-specific formulations for targeting drug delivery to the colon. The colon is a site where both local and systemic drug delivery can take place .A local means of drug delivery could allow topical treatment of amoebiasis, Inflammatory bowel diseases, e.g. ulcerative colitis or Crohn's disease.

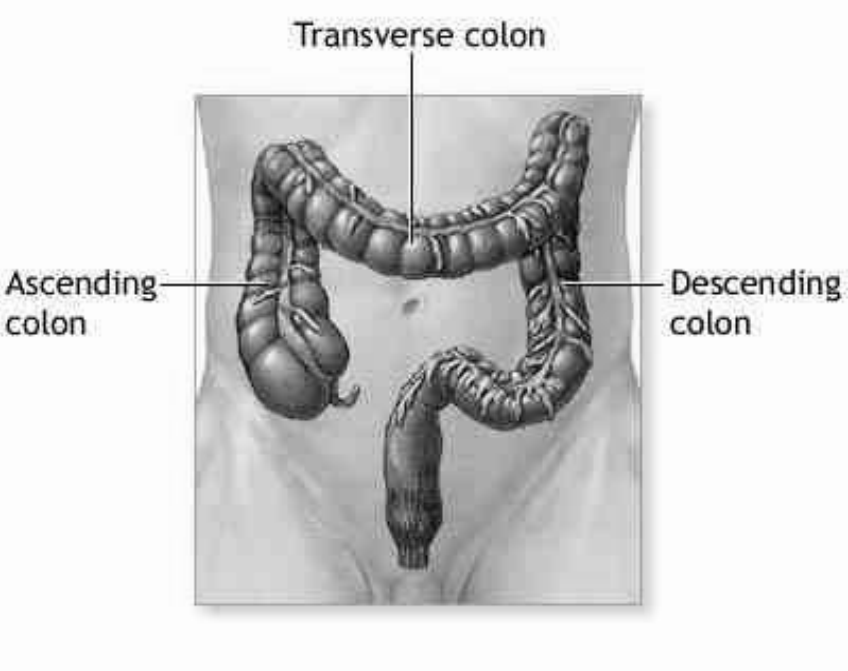

Figure No.1 Anatomy of the Colon

Approaches for Colon Specific Drug Delivery

1.Drug release based on variation of pH

The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers .The pH in the transverse colon is 6.6, in the descending colon 7.0. Use of pH-dependent polymers is based on these differences in pH levels. The polymers described as pH-dependent in colon specific drug delivery are insoluble at low pH levels but become

increasingly In the stomach the pH ranges between 1 and 2 during fasting but increases in postprandial soluble as pH rises.

In ulcerative colitis pH values between 2.3 and 4.7 have been measured in the proximal parts of the colon. Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve even in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems.

Dissolution studies showed that drug release profiles from enteric-coated single-unit tablets could be altered *in vitro* by changing the ratios of the polymers, in the pH range 5.5 to 7.0.

2.Drug release based on gastrointestinal transit time

The time of transit through the small intestine is independent of formulation. It has been found that both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine.

3.Drug release based on the presence of colonic micro flora

Both anaerobic and aerobic microorganisms inhabit the human gastrointestinal tract. In the small intestine the micro flora is mainly aerobic, but in the large intestine it is anaerobic. About 400 bacterial species and some fungi have been found in the colon. Most bacteria inhabit in the proximal areas of the large intestine, where energy sources are greatest.

4. Pressure-controlled drug delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Pressure controlled colon delivery capsules have been prepared using ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon.

MATERIALS AND METHODS

Lansoprazole, Avicel PH 102, Sodium CMC, HPMC 10K

Mode: Spectrum **Starting WL**: 200.0nm **Ending WL**: 400.0nm **Number of peaks detected**:

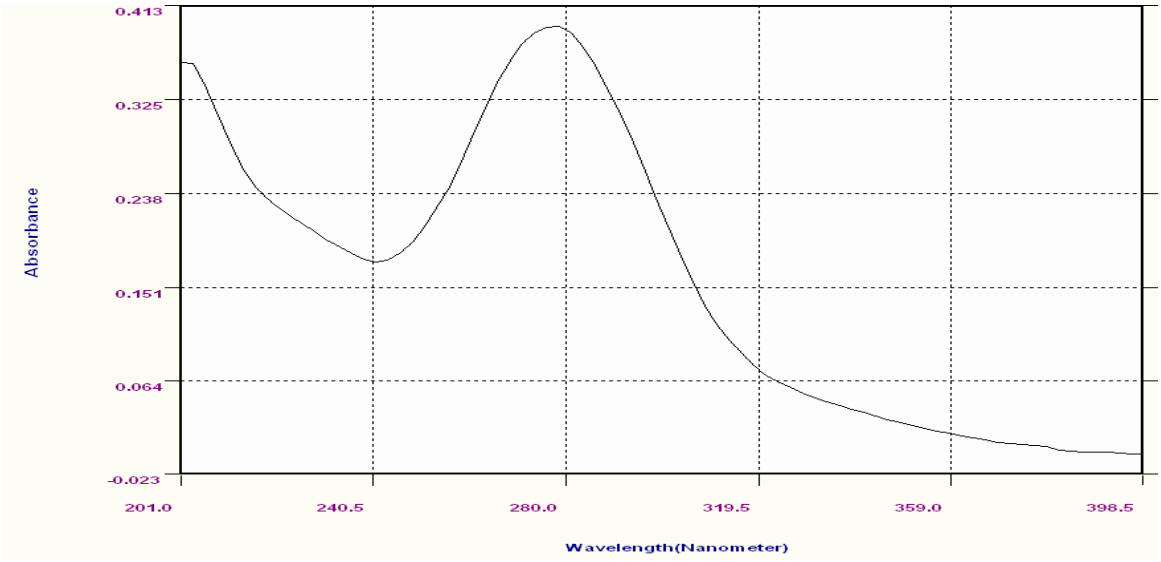

Figure No.2. UV spectrum of Lansoprazole in simulated gastric fluid(1.2pH)

Sample : Lansoprazole in simulated gastric fluid

Reference : Simulated gastric fluid (pH1.2 buffer)

Concentration : 10mcg/ml

Wavelength : 277.0 nm

Absorbance :0.394

Mode: Spectrum **Starting WL**: 200.0nm **Ending WL**: 400.0nm **Number of peaks detected**: 1

Figure No.3. UV spectrum of Lansoprazole in Phosphate buffer pH 7.4

Samp : Lansoprazole Phosphate buffer pH 7.4

Reference : Phosphate buffer pH 7.4

Concentration :8mcg/ml

Wavelength : 320.0nm

Absorbance : 0.440

Mode: Spectrum **Starting WL**: 200.0nm **Ending WL**: 400.0nm **Number ofpeaksdetected**:1

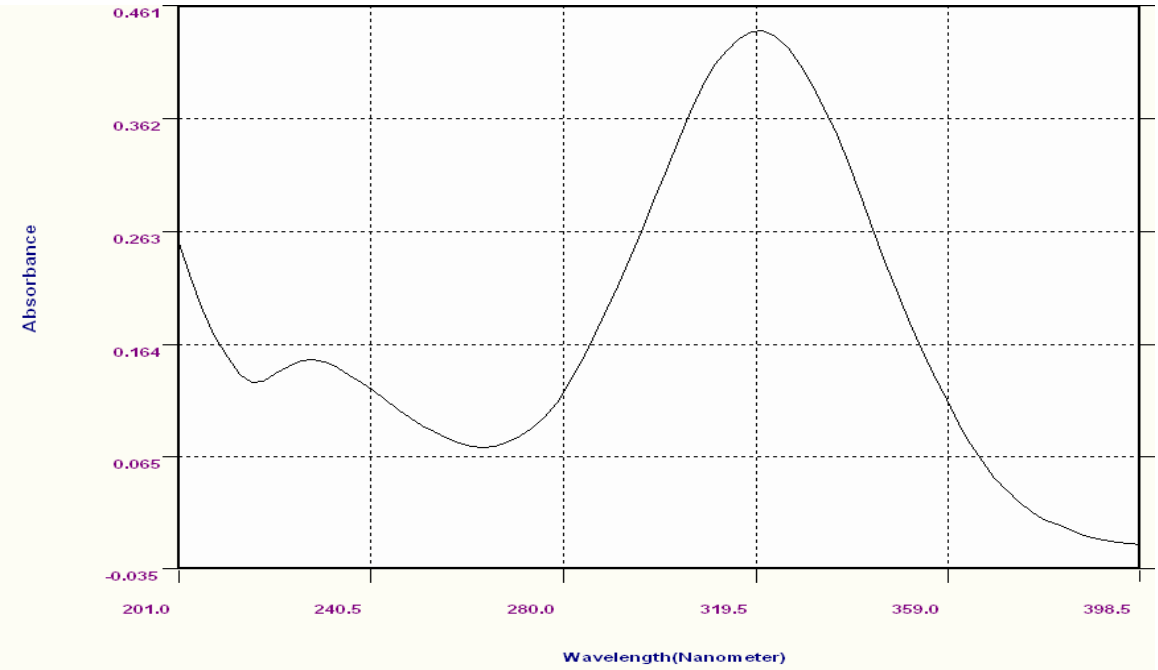

Figure No.4 UV spectrum of Lansoprazole in Phosphate buffer pH 6.8

Sample : Lansoprazole in Phosphate buffer pH 6.8

Reference : Phosphate buffer pH 6.8

Standard Calibration Curve for Lansoprazole

Stock solution

Weighed quantity of Lansoprazole (100mg) was dissolved in pH 1.2 buffer and the volume was made up to 100ml with the same medium.

⇒ 1000 mcg/ml (SS I)

10ml of SS I was then made up to 100ml with the same medium.

⇒ 100 mcg/ml (SS II**)**

Aliquots of 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml of SS II was pipetted into 50ml volumetric flasks and the volume was made upto 50ml with pH1.2 buffer. The absorbance was measured at 277 nm against reagent blank (pH 1.2 buffer).

Table No.1 Calibration curve of Lansoprazole in 0.1N Hydrochloric acid (pH 1.2 buffer)

Vol. of SSII (ml)	Absorbance at 277nm	SEM
0	0.000	0.0000
2	0.166	0.0008
3	0.248	0.0008
4	0.315	0.0008
5	0.399	0.0008
6	0.482	0.0005
7	0.557	0.0008
8	0.642	0.0014
9	0.719	0.0008
10	0.783	0.0005

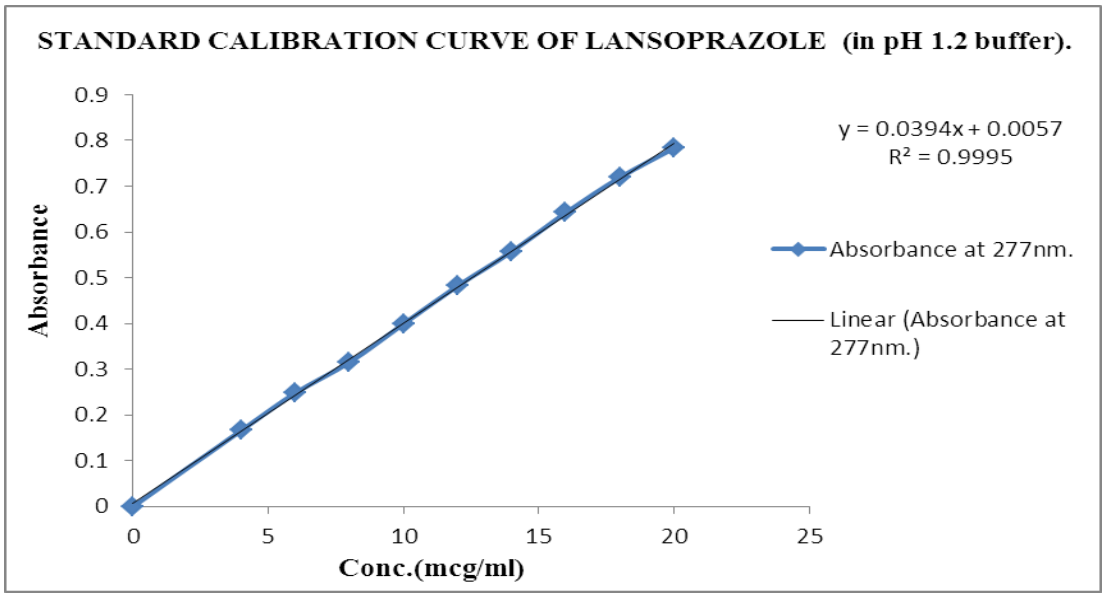

Figure No.5

Preparation of Phosphate Buffer (pH 7.4)

Table No.2. Calibration curve of Lansoprazole in 7.4 buffer

Vol. of SS II (ml)	Absorbance at 320nm.	SEM
0	0.000	0.0000
2	0.227	0.0008
3	0.343	0.0008
4	0.440	0.0008
5	0.554	0.0008
6	0.675	0.0005
7	0.785	0.0008
8	0.893	0.0014
9	1.003	0.0008

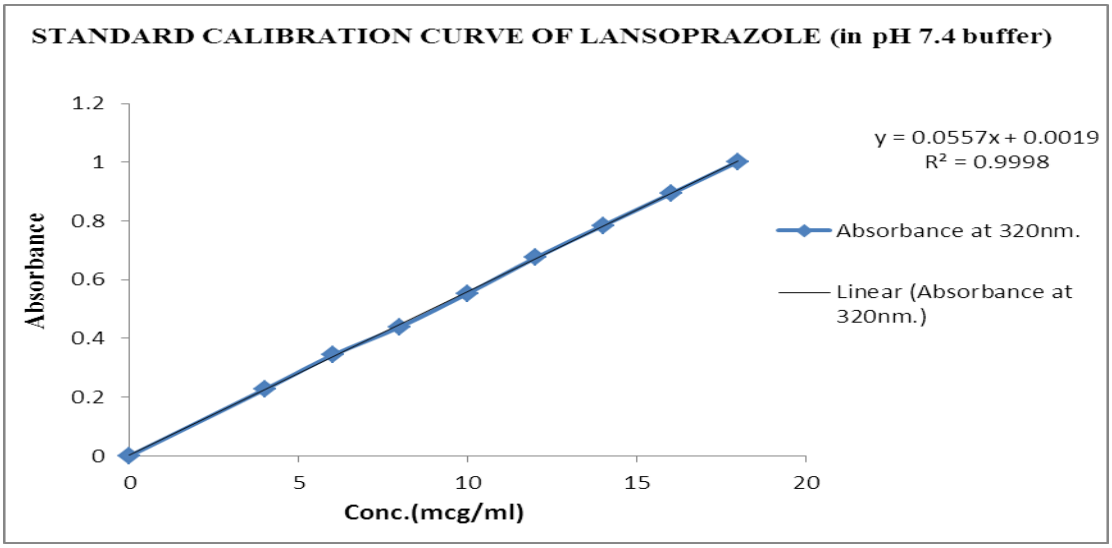

Figure No.6

Table No 3: Calibration curve of Lansoprazole in 6.8 buffer.

Vol. of SSII (ml)	Absorbance at 320nm.	SEM
0	0.000	0.0000
2	0.212	0.0008
3	0.328	0.0008
4	0.438	0.0008
5	0.540	0.0008
6	0.690	0.0005
7	0.781	0.0008
8	0.899	0.0014
9	1.019	0.0008

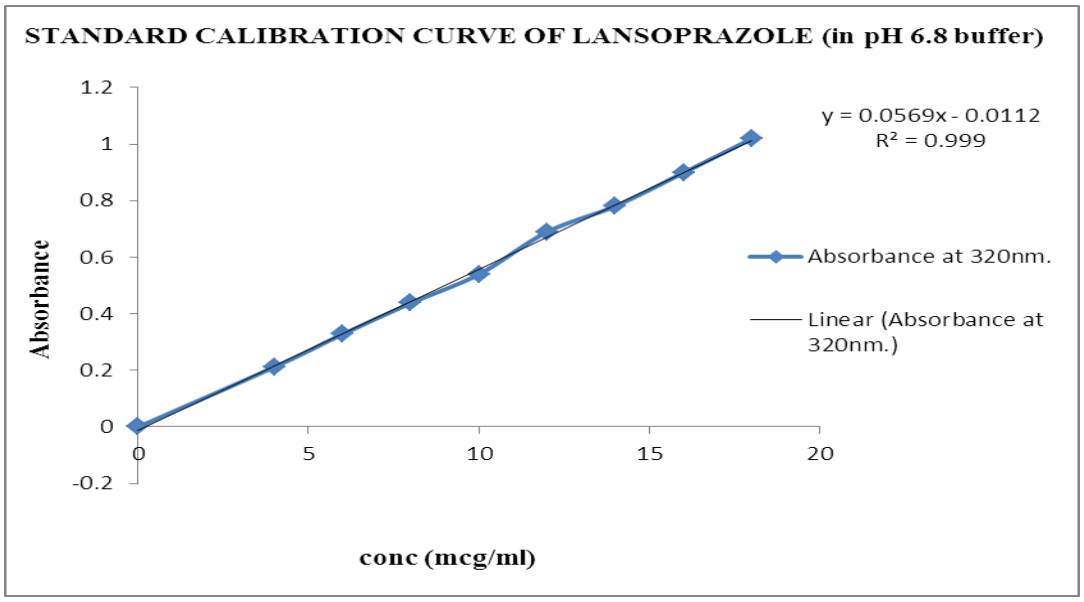

Figure No.7

Formulation Design

The steps involved in the formulation of Lansoprazole pellets are,

1. Weighing the calculated quantity of drug and excipient.
2. Sifting the material through appropriate sieves
3. Mixing of the ingredients.
4. Dissolving the binder in water
5. Granulation.
6. Extrusion through extruder
7. Spheronization using spheronizer
8. Drying the pellets using a tray drier
9. Sifting the pellets
10. Filling the pellets of required size range into capsules by hand filling.

Table No. 4. Formulation of Lasoprazole pellets

Sl.No	Ingredients	Quantity
1	Lansoprazole	100g
2	Microcrystalline Cellulose	97.5g 2.5g
3	PVP K-30	2.5g

Batch size - 200g

Evaluation Parameters for Lansoprazole pellets

- Size of the pellets
- Flow properties of pellets
- Description of pellets

1.Size of the pellets

Size and size distribution of the pellets was determined by sieve analysis. The size fraction that has passed mesh # 16 and retained on mesh # 20 was used to fill into capsules.

2.Flow properties of pellets

The flow properties of the pellets were studied by measuring the Carr's index and angle of repose of pellets.

Angle of Repose (θ)

Angle of Repose is an indication of the frictional forces existing between the pellets (θ). This is the maximum angle possible between the surface of a pile of pellets and the horizontal

plane.

$\tan\theta = h / r$

$\theta = \tan^{-1} (h / r)$

Where,θ is the angle of repose h is the height in cmr is the radius.

Table No.5. Angle of Repose values

Angle of repose (in degrees)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

3. Description of pellets: The pellets were evaluated for brittleness, shapes like rod,dumbbell and spherical by scanning Electron Microscopy.

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

Objective of the Study

The purpose of stability testing is to provide evidence on who the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light enables recommended storage conditions, re-test periods and shelf-lives to be established.

The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.
ICH specifies the length of study and storage conditions.

Long-term testing: 25^{O} C ± 2^{o} C or 60 % RH ± 5 % for 12 Months

Accelerated testing: 40^{O} C ± 2^{o} C or 75 % RH ± 5 % for 6 Months

Stability studies were carried out at 25^{o} C or 60 % RH and 40^{o} C or 75 % RH for the following formulations for 2 months.

METHODS

The selected formulations were packed in amber-colored bottles, tightly plugged with cotton and capped. They were then stored at 25^{o} C / 60 % RH and 40^{o} C / 75 % RH for two months and evaluated for their physical appearance and drug content.

Physical Appearance

The physical appearance of the samples kept for stability studies were checked each month.

Drug Content

Each capsule from the selected formulations were taken from the stored container and assayed for drug content.

RESULTS AND DISCUSSIONS

In the present study, an attempt was made to develop and evaluate Modified Pulsincap formulation for Colon Specific delivery of Lansoprazole for better treatment of ulcers of the stomach and duodenum infections & Gastroesophageal reflux diseases. Colonic delivery of Lansoprazole could prevent unwanted systemic side effects.

InVitro Release Profile

Dissolution media: Simulated gastric fluid, pH 1.2 for 2 hours.

Simulated small intestinal medium pH 7.4 for 3 hours. Simulated colonic medium pH 6.8 for subsequent hours.

Volume of dissolution media: 900 ml

Volume withdrawn: 5ml every hour upto 12 hours.

Volume made upto: 50ml

Dissolution apparatus: USP type 1, basket

Revolutions per minute: 50rpm

Temperature: 37 ± 0.5^{o}C

Regression equation Y = mX + C = 0.0394 X + 0.0057 for pH 1.2

Regression equation Y = mX + C = 0.0556 X + 0.0029 for pH 7.4

Regression equation Y = mX + C = 0.057 X - 0.0109 for pH 6.8

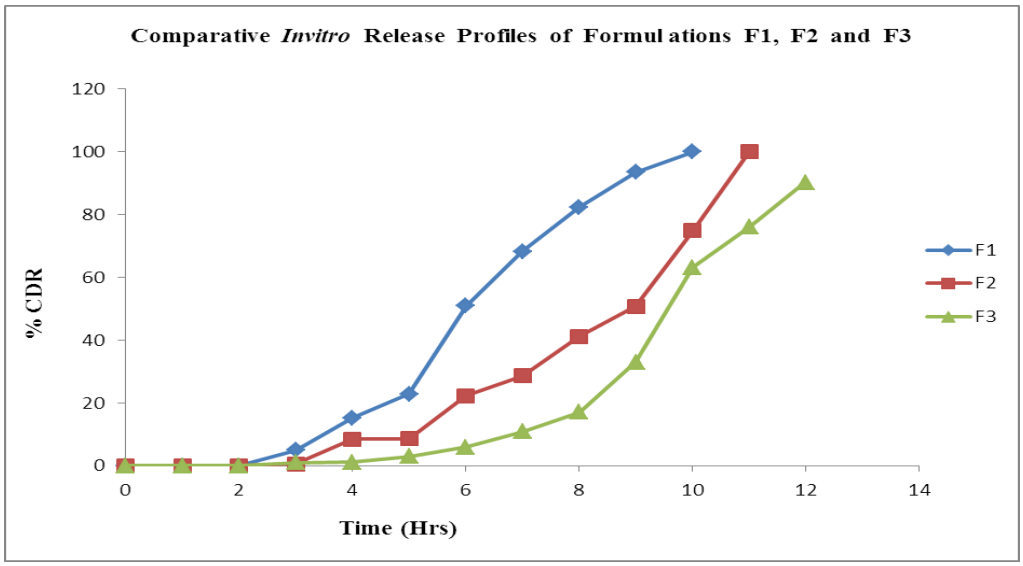

Figure No.8 : Comparative *Invitro* Release Profiles of Formulations

Stability Studies

In view of the potential utility of Modified Pulsincap for targeting of Lansoprazole to the colon, stability studies were carried out on selected formulations F2, F5, F11 and F12 at 25^0C / 60%RH and 40^0C / 75%RH for 2 months. These formulations were selected for stability studies as they were found to be suitable for colon targeting. After storage, the formulations were observed for physical change and assayed for drug content. These results indicated that all the formulations when stored at 25^0C / 60%RH showed no change in physical appearance or drug content. When the same formulations were stored at 40^0C / 75%RH for 2 months, there was a slight change in appearance but negligible change was observed in drug content.

CONCLUSION

The present investigation was carried out to develop a Time- dependent colon specific drug delivery system known as "Modified Pulsincap" for targeting Lansoprazole to the colon. From the study conducted, the following conclusions are drawn.

The release of Lansoprazole from Modified Pulsincap is proportional to the concentration of hydrogel. As the concentration of polymer increased, the drug release rate decreased.

Polymers like Guar gum, Sodium CMC, HPMC10K, Sodium alginate and HPC can be used as hydrogels to delay the drug release until the formulation reaches the colon and the drug is

released in the colon.

Therefore, the study proves that Lansoprazole can be successfully colon targeted by the use of a Time dependent formulation 'Modified Pulsincap'.

Thus Modified Pulsincap can be considered as one of the promising formulation techniques for preparing site-specific drug delivery systems.

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