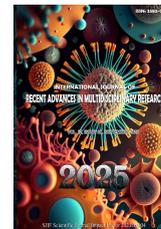




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RESEARCH ARTICLE

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FORMULATION AND EVALUATION OF SOLUBILITY-ENHANCED, FORMALIN-CROSSLINKED SUSTAINED RELEASE LANSOPRAZOLE CAPSULE

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ABSTRACT

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The present study aimed to develop and evaluate sustained release formulations of Lansoprazole capsules using solid dispersion and formalin-treated gelatin capsules to enhance solubility and achieve controlled drug delivery. Preformulation studies, including organoleptic characterization, solubility testing, and FTIR analysis, confirmed the drug's poor aqueous solubility, stability, and compatibility with selected excipients. Solid dispersions were prepared by solvent evaporation employing hydrophilic polymers (PVP K30, PEG 6000, and Poloxamer 407) in varying ratios, which significantly improved dissolution behavior. Formalin-treated gelatin capsules were designed to modulate capsule solubility and delay initial drug release. Final sustained release formulations incorporated hydroxypropyl methylcellulose (HPMC, grades 4K and 100K) and sodium CMC as release modifiers. Physicochemical evaluation showed uniform weight, acceptable assay values, and intact capsule structure. In-vitro dissolution studies revealed extended drug release with polymer- and treatment-dependent variations. Formulations containing high-viscosity HPMC exhibited superior release control, fitting well to zero-order, Higuchi, and Korsmeyer–Peppas kinetic models, indicating a predominantly diffusion-controlled mechanism. FTIR confirmed the absence of drug–excipient interactions, ensuring formulation stability. Overall, the study demonstrates that combining solid dispersion with formalin-treated gelatin capsules is a promising approach for improving solubility and sustaining the release of Lansoprazole, thereby potentially enhancing therapeutic efficacy, reducing dosing frequency, and improving patient compliance in acid-related disorders.

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INTRODUCTION

**Proton pump inhibitors:** Proton pump inhibitors are prodrugs that require activation in an acid environment. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalyzed formation of a tetracyclic sulfenamide. The activated form then binds covalently with sulfhydryl groups of cysteines in the H<sup>+</sup>,K<sup>+</sup>-ATPase, irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24- to 48-hour) suppression of acid secretion, despite the much shorter plasma half-lives (0.5 to 2 hours) of the parent compounds. Because they block the final step in acid production, the proton pump inhibitors are effective in acid suppression regardless of other stimulating factors.

**Lansoprazole:** Lansoprazole, a well-known proton pump inhibitor (PPI), is commonly prescribed for managing various

acid-related gastrointestinal issues such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. It works by permanently blocking the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme located in the stomach's parietal cells, thereby reducing the production of gastric acid. However, the drug's clinical use is limited by its short biological half-life (around 1.5 hours) and its instability in acidic environments, highlighting the need for advanced drug delivery methods to maximize its therapeutic benefits. Sustained release (SR) drug delivery systems offer a promising solution to these limitations. By allowing a gradual release of the drug over time, SR formulations help to maintain steady drug concentrations in the bloodstream, improve oral bioavailability, decrease the frequency of dosing, and boost patient adherence. In addition, these systems can reduce the variation in plasma levels, potentially enhancing therapeutic outcomes and minimizing adverse effects. Formulating a sustained release version of Lansoprazole is complex, largely due to its sensitivity to acidic pH and its absorption site being primarily in the small intestine. Therefore, the formulation

must be designed to protect the drug from degradation in the stomach and ensure its release at the appropriate site. This can be achieved through the use of enteric coatings, pH-responsive polymers, or specially designed matrix systems. This project aims to design and assess a sustained release formulation of Lansoprazole that overcomes its stability and absorption challenges, ultimately improving its clinical utility through modern pharmaceutical technologies.<sup>2-6</sup>

### Disease profile

**Gastro intestinal ulcer:** Gastrointestinal (GI) ulcers, also known as peptic ulcers, are open sores that develop on the inner lining of the stomach, small intestine, or esophagus. The most common types are gastric ulcers (stomach ulcers) and duodenal ulcers (small intestine ulcers). These ulcers form when there's an imbalance between the digestive acids in the stomach and the protective lining that normally shields the digestive tract.

### Causes of Gastrointestinal Ulcers

- **Helicobacter pylori infection:** A bacteria that can damage the mucosal lining of the stomach or small intestine, leading to ulcer formation.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs):** Frequent use of pain relievers like aspirin or ibuprofen can irritate or inflame the stomach lining.
- **Excessive alcohol consumption:** Alcohol can irritate and erode the mucous lining of the stomach, leading to ulcers.
- **Smoking:** Smoking decreases the production of bicarbonate, which helps protect the stomach lining from acid.
- **Stress:** Though stress itself doesn't cause ulcers, it can exacerbate existing ulcers or contribute to behaviors (e.g., smoking, alcohol consumption) that increase ulcer risk.
- **Other conditions:** Certain diseases such as Crohn's disease, Zollinger-Ellison syndrome, and cancer can also increase ulcer risk.

**Symptoms of Gastrointestinal Ulcers:** Burning stomach pain, often between meals or at night, Bloating and feeling full, Heartburn or indigestion, Nausea or vomiting, Loss of appetite, Dark or black stool. Treatment include Antibiotics if caused by *H. pylori* infection, antibiotics can eliminate the bacteria. Proton pump inhibitors to reduce stomach acid production, helping ulcers heal. H<sub>2</sub>-receptor antagonists, reduce acid production in the stomach, antacids or medications to protect the stomach lining. Prevention is possible with Limited use of NSAIDs and alcohol, good hygiene to reduce the risk of *H. pylori* infection, avoiding smoking, Managing stress through relaxation techniques and lifestyle changes.<sup>7-8</sup>

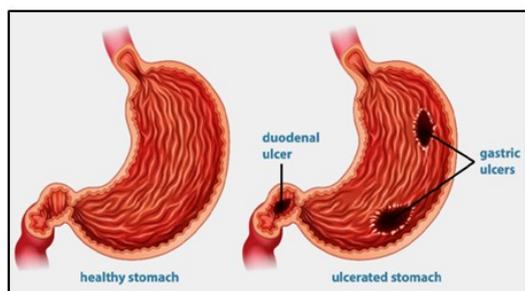


Fig. 1. Stomach and duodenal ulcer

**Formalin treated hard gelatin capsule:** Hard gelatin capsules are extensively used in the pharmaceutical field as a common oral drug delivery system. Made predominantly from gelatin sourced from animal collagen, these capsules are favored for their ease of swallowing, ability to mask unpleasant tastes, and versatility in containing a range of substances like powders, granules, and semi-solid formulations. A key challenge with standard hard gelatin capsules is their rapid breakdown and dissolution once ingested, which may not be ideal for certain drug therapies requiring slower release, such as sustained-release or enteric formulations. To overcome this, researchers have explored chemical modifications to the capsule shell. One such modification is treating the capsules with formalin, an aqueous formaldehyde solution. This treatment induces cross-linking within the gelatin matrix, resulting in capsules that are stiffer, less soluble, and dissolve more slowly. This method is useful in research settings to control drug release and study how capsule properties affect drug absorption.

### Advantages of Formalin-Treated Hard Gelatin Capsules

**Extended Shelf Life:** Treating gelatin capsules with formalin helps maintain their structure by preventing them from becoming brittle or too soft. This process ensures that the capsules stay intact for a longer period, even in fluctuating environmental conditions such as temperature and humidity.

**Enhanced Durability:** Capsules that undergo formalin treatment are less prone to breaking or warping during handling, transportation, or storage. This is particularly important in the pharmaceutical industry where the integrity of the capsules is vital to ensure the effectiveness of the product.

**Better Resistance to External Conditions:** Formalin-treated capsules are more resilient against moisture and other environmental factors, which helps to prevent premature dissolution and ensures that the capsules remain intact until they are consumed.

**Improved Aesthetic Appeal:** These capsules retain a smooth and uniform appearance over time, which is essential for maintaining product quality and meeting customer expectations, especially in the pharmaceutical market.

**Cost Savings:** By prolonging the shelf life and reducing the need for special storage conditions, manufacturers can lower costs related to capsule production and storage, benefiting both producers and consumers.

### Disadvantages of Formalin-Treated Hard Gelatin Capsules

**Health and Toxicity Concerns:** Formalin, a solution of formaldehyde, is a potent chemical with known toxic effects. There is concern about trace amounts of formalin potentially remaining in the capsules, which could pose health risks, leading to stricter regulations in some regions.

**Risk of Allergic Reactions:** Some individuals may experience allergic reactions to formalin, which can result in symptoms such as skin irritation or respiratory issues. This may limit the use of these capsules for sensitive populations.

**Potential Impact on Bioavailability:** The chemical treatment can alter how quickly or effectively the capsule dissolves,

potentially affecting the bioavailability of the active ingredients inside. This could impact how well the drug is absorbed by the body and its effectiveness.

**Environmental Concerns:** Formalin is considered hazardous to the environment. If not disposed of properly, it can lead to pollution, especially in water sources, raising environmental concerns for manufacturers and regulators.

**Regulatory Limitations:** Due to the potential carcinogenic properties of formaldehyde, many regulatory bodies (such as the FDA and EMA) have imposed strict restrictions on its use in consumer products, which could limit the marketability of formalin-treated capsules in certain regions.

**Consumer Awareness and Perception:** With increasing consumer awareness of chemical risks, products containing formalin-treated capsules may face resistance in the market. This can affect consumer trust and influence purchasing decisions, particularly among health-conscious buyers.<sup>14-18</sup>

## MATERIALS AND METHODS

**Materials:** Lansoprazole API was obtained as gift sample from Integrin Life Sciences Pvt. Ltd Andhra Pradesh. All excipients and chemicals used in the project were of analytical grade from C.I. BaidMetha college of Pharmacy, Chennai.

### EXPERIMENTAL FLOW

**Preformulation studies:** Preformulation testing is the first step in development of dosage form of drug molecules. It was carried out to investigate the physicochemical properties of drug substance alone and when combined with excipients. The aim of preformulation testing is to produce useful information to the formulator in developing stable and bioavailable dosage forms.

**Identification of Lansoprazole:** Identification of Lansoprazole was carried out by Infra-Red Absorption spectrophotometry.

**Solubility of Lansoprazole:** Solubility of Lansoprazole was determined in water, ether, acetonitrile, dimethylformamide and ethanol. Solubility studies were performed by taking excess amount of Lansoprazole in different beakers containing solvents. Then the resulting solution is tested for solubility.

### Preparation of standard graphs

**Preparation of standard graph for Lansoprazole using acetonitrile as solvent.**

**Determination of  $\lambda_{max}$ :** Stock solution containing 1000 mcg/ml LAN was prepared in acetonitrile and was diluted with water to give working concentration of 50 mcg/ml LAN.

**Procedure:** Add 10 mg of drug to 10 ml acetonitrile. From this take to 0.5 ml and make up to 50 ml with water in volumetric flask. This is 50 mcg/ml LAN.

**Construction of calibration curve:** Aliquots of 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0 and 7.0 ml of 50mcg/ml LAN standard

solutions were accurately transferred into a series of 10 ml calibrated flask and made up to the mark with the same solvent. The absorbance of the resulting solution was measured at 281 nm against acetonitrile blank. Calibration curve was prepared by plotting the absorbance *versus* concentration of drug. The concentration of the unknown was read from the calibration curve or computed from the regression equation derived using the Beer's law data.

**Fourier Transport Infrared Spectroscopy [FTIR]:** Infrared Spectroscopy, also known as FTIR analysis, is an analytical technique used to identify organic, polymeric, and in some cases, inorganic materials. This technique uses infrared light to scan test samples and observe chemical properties.

### FORMULATION OF SUSTAINED RELEASE LANSOPRAZOLE

#### Solid dispersion of Lansoprazole

**Preparation of Solid Dispersion by Solvent Evaporation Method:** Solid dispersion was prepared using the solvent evaporation technique, in which both the drug and polymer are dissolved in a common organic solvent. The solvent is then removed at a low temperature, and the resulting solid mass is milled and passed through a suitable screen.

**Preparation of Solid Dispersion:** The solid dispersion of lansoprazole was prepared using the solvent evaporation method. Initially, lansoprazole was dissolved in methanol to form a clear solution, after which different polymers (PVP K30, PEG 6000, and Poloxamer 407) were incorporated in varying ratios (1:1, 1:2, and 1:3). The solvent was then evaporated using a water bath maintained at 60°C. The dried mass obtained was kept in a desiccator until a constant weight was achieved and subsequently passed through a #40 sieve to yield the solid dispersion.<sup>53-54</sup>

Table 1. Formulation for Lansoprazole Solid Dispersion

Sr. No.	Batch Code	Ratio	Drug	Polymer
1.	SD1	1:1	Lansoprazole	PVP K30
2.	SD2	1:2	Lansoprazole	PVP K30
3.	SD3	1:3	Lansoprazole	PVP K30
4.	SD4	1:1	Lansoprazole	PEG 6000
5.	SD5	1:2	Lansoprazole	PEG 6000
6.	SD6	1:3	Lansoprazole	PEG 6000
7.	SD7	1:1	Lansoprazole	Poloxamer 407
8.	SD8	1:2	Lansoprazole	Poloxamer 407
9.	SD9	1:3	Lansoprazole	Poloxamer 407

### Preparation of formalin treated gelatin capsule

**Preparation of Cross-Linked Gelatin Capsules:** Formalin treatment is used to alter the solubility of gelatin capsules. When exposed to formalin vapors, gelatin undergoes cross-linking between the amino groups of its molecular chains and the aldehyde groups of formaldehyde through Schiff's base condensation, leading to an unpredictable reduction in its solubility.

**Method:** A size 0 hard gelatin capsule was selected, and the caps were separated from the bodies. In a desiccator, 25 ml of 15% (v/v) formaldehyde was placed, to which a small amount of potassium permanganate was added to generate formalin vapors. The empty capsule bodies, placed on a wire mesh,

were exposed to these vapors while the caps were kept untreated to retain their water solubility. The desiccator was sealed tightly, and the exposure was maintained for 12 hours. Afterwards, the capsule bodies were removed and heated at 50°C for 30 minutes to ensure completion of the reaction between gelatin and formaldehyde vapors. They were then left to dry at room temperature to eliminate any residual formaldehyde. Finally, the treated bodies were capped with untreated caps and stored in a polythene bag.<sup>55-56</sup>

**Evaluation of formalin treated gelatin capsule:** Various physical tests include visual defect, identification attributes as, dimensions, solubility studies of treated capsules, and chemical test were carried out simultaneously for formaldehyde treated and untreated capsules. The length and diameter of the capsules were measured before and after formaldehyde treatment, using dial calliper. Variations in dimensions between formaldehyde, treated and untreated capsules were studied.

**Solubility Study of Treated Capsules:** In the solubility study of treated capsules, the capsule bodies were subjected to 15% formaldehyde solution for different time intervals, followed by drying in a hot air oven. Their solubility was then assessed in 0.1N HCl, and the time taken for the capsule body to dissolve or transform into a soft, fluffy mass was recorded.

**Qualitative Test For Free Formaldehyde:** Formaldehyde treated bodies about 25 capsules, cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hrs with a magnetic stirrer, to solubilise the free formaldehyde. The solution was then filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings.

**Method:** 1ml of sample solution, add 9 ml of water. One millilitre of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was heated in a water bath at 40°C and allowed to stand for 40 min. The solution was less intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard solution in place of the sample solution. The comparison was made by examining tubes down their vertical axis.

### Formulation of sustained release lansoprazole capsules

Table 7. Formulation of sustained release lansoprazole capsules F1 and F2

S.no	Ingredients	F1	F2
1.	Lansoprazole	60mg	60mg
2.	HPMC 4K	120mg	—
3.	HPMC 100K	—	120mg
4.	Na CMC	60mg	60mg
5.	Aerosil	3mg	3mg
6.	Magnesium stearate	7mg	7mg
	Total weight	250mg	250mg

### EVALUATION OF FORMALIN TREATED CAPSULES OF LANSOPRAOLE:

**weight variation test:** Twenty capsules are randomly selected and weighed individually, after which the average weight is calculated. Each capsule weight is then compared with the average, and the percentage deviation is determined. According to pharmacopeial limits, capsules of 250 mg should

not deviate by more than  $\pm 7.5\%$  from the average weight. If any capsule falls outside this limit, the contents are removed and the net weight of the powder is determined to confirm compliance. The batch passes the test if not more than two capsules deviate from the specified range and none deviate by more than twice the permitted percentage.

**Assay:** For UV-Visible spectrophotometric analysis, 16 mg of solid dispersion-treated Lansoprazole was accurately weighed and dissolved in 5 ml of acetonitrile (ACN).

The solution was then transferred to a 100 ml volumetric flask and the volume was made up with distilled water. The prepared solution was scanned at 281 nm to determine the absorption maximum, and the observed absorbance value was found to be 0.477.

**Dissolution:** Dissolution studies were performed using two different media to simulate varying pH conditions:

**In 1.2 pH Hydrochloric Acid Solution:** A 1000 ml volumetric flask was prepared by dissolving 2 g of sodium chloride (NaCl) in approximately 20 ml of distilled water. Subsequently, 7 ml of concentrated hydrochloric acid (HCl) was added, and the final volume was adjusted to 1000 ml with distilled water to achieve a solution of pH 1.2.

**In 6.8 pH Phosphate Buffer Solution:** The buffer solution at pH 6.8 was prepared by dissolving appropriate quantities of potassium hydrogen phosphate and disodium hydrogen phosphate in water, followed by adjusting the solution to the desired volume in a volumetric flask.

## RESULTS

### Performulation studies

#### Organoleptic properties of Lansoprazole

Table 8. Organoleptic properties of Lansoprazole

S.No	Parameter	Description
1	Taste	Bitter
2	Odour	Odourless
3	Colour	White
4	State	amorphous

#### Solubility of Lansoprazole

Table 9. Solubility of Lansoprazole

S.No	Parameter	Description
1	Methanol Taste	Freely Soluble Bitter
2	water	Soluble
2	Ethanol Odour	Soluble Odourless
3	Liquid paraffin Colour	Not Soluble White
4	Chloroform State	Not Soluble amorphous

**Compatibility Studies (FTIR):** An FTIR study was conducted to assess the compatibility between the drug and polymer. The drug and polymer were mixed in a 1:1 ratio and the sample underwent FTIR analysis.

The results showed no significant changes in the primary functional peaks of the drug, indicating that there is no evidence of incompatibility between the excipients and the active pharmaceutical ingredient (API).



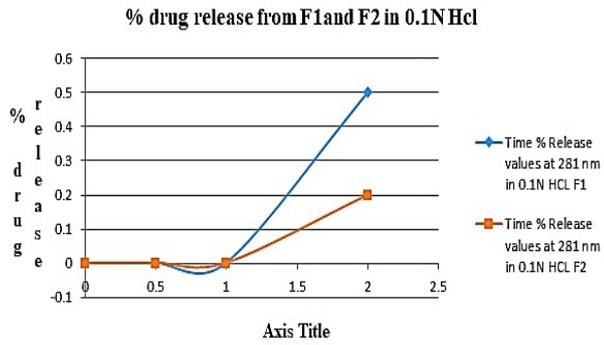


Fig 8: Percentage drug release from F1 and F2 in 0.1N HCl

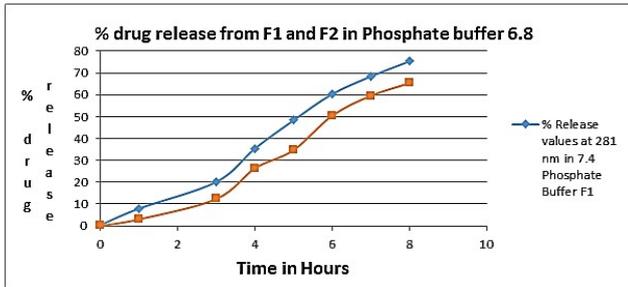


Fig 9: Percentagedrug release from F1 and F2 in Phosphate buffer 6.8

Table 15. Zero order release kinetics data of lansoprazole formalin treated capsule

S.no	Time in hrs	% Drug release F1	% Drug release F2
1.	0	0.5	0.2
2.	1	8	3.2
3.	3	20.2	12.5
4.	4	35.5	26.5
5.	5	48.4	34.8
6.	6	60.4	50.5
7.	7	68.5	59.6
8.	8	75.4	65.4

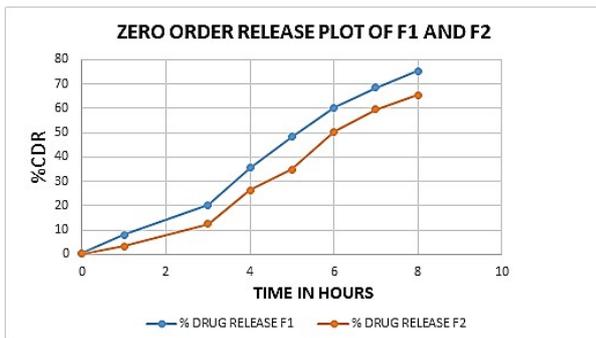


Fig 10: Zero Order Release plot

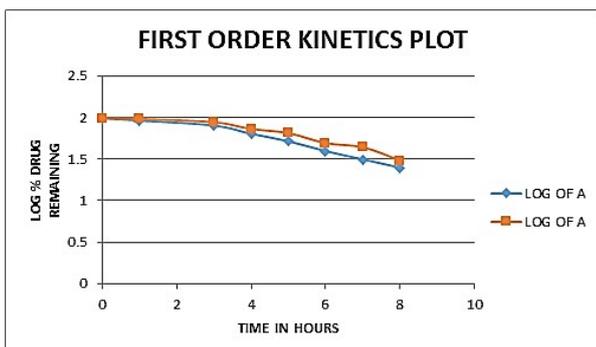


Fig 11. First order kinetics plot

Table 16. First-order release kinetics date of lansoprazole of formalin treated capsule:

S.no	Time hrs	F1		F2	
		% Drug remaining (A)	Log of A	% Drug remaining(A)	Log of A
1.	0	99.5	1.99	99.8	1.99
2.	1	92	1.96	96.8	1.98
3.	3	79.8	1.9	87.5	1.94
4.	4	73.5	1.8	73.5	1.86
5.	5	51.6	1.71	65.2	1.81
6.	6	39.6	1.59	49.5	1.69
7.	7	31.5	1.49	40.4	1.64
8.	8	24.6	1.39	34.6	1.48

Table 17: Higuchi Matrix Release Model

S.no	√ time	% drug release F1	% drug release F2
1.	0	0.5	0.2
2.	1	8	3.2
3.	1.732	20.2	12.5
4.	2	35.5	26.5
5.	2.236	48.4	34.8
6.	2.229	60.4	50.5
7.	2.646	68.5	59.6
8.	2.828	75.4	65.4

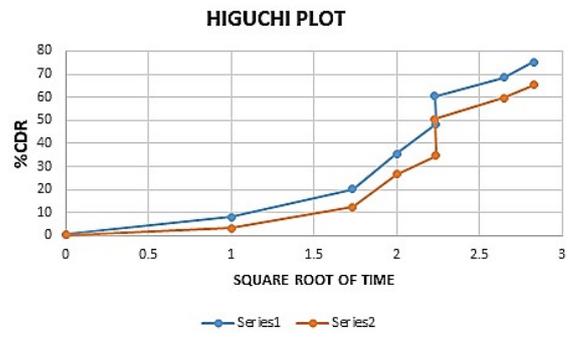


Fig 12. Higuchi plot

Table 18. KORSMEYER-PEPPAS MODEL

S.no	Log time (h)	Log %CDRF1	Log %CDR F2
1.	0	0.301	-0.698
2.	0	0.903	0.505
3.	0.477	1.305	0.505
4.	0.602	1.55	1.423
5.	0.698	1.684	1.541
6.	0.778	1.781	1.703
7.	0.845	1.835	1.775
8.	0.903	1.877	1.815
		R=0.9540	R= 0.9220
		Slope:: 0.6194	Slope: 0.3830

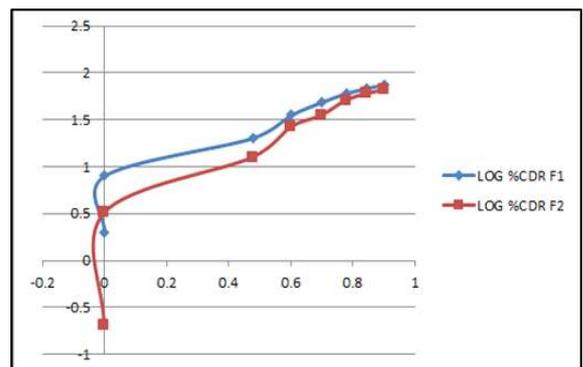


Fig 13:korsmeyer -peppas plot

## Weight variation test

**In vitro release studies for lansoprazole formalin treated capsules:** In-vitro release studies were carried out using USP-XXIII dissolution assembly. The results of in-vitro release studies were plotted into four models of data treatment as follows.

## SUMMARY

The present work focused on the formulation and evaluation of sustained release Lansoprazole capsules using solid dispersion techniques and formalin-treated gelatin capsules. Preformulation studies including organoleptic properties, solubility analysis, and FTIR compatibility confirmed that Lansoprazole is a poorly water-soluble, stable, and compatible drug for formulation development. Solid dispersions were successfully prepared using the solvent evaporation method with hydrophilic polymers (PVP K30, PEG 6000, and Poloxamer 407) at different ratios, which enhanced solubility and dissolution properties. Formalin-treated hard gelatin capsules were developed to control the initial release of the drug by reducing capsule solubility. Final sustained release formulations were prepared with different viscosity grades of HPMC (4K and 100K), along with sodium CMC as a release modifier. Evaluation of the formulations showed acceptable weight variation, assay, and capsule integrity. In-vitro dissolution studies indicated that the optimized formulations achieved controlled release of Lansoprazole over an extended period, with different release profiles depending on the polymer and capsule treatment. The release kinetics data fitted well to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, suggesting a diffusion-controlled mechanism with polymer-dependent release modulation.

## CONCLUSION

The study demonstrated that the combination of solid dispersion and formalin-treated gelatin capsules is an effective strategy for enhancing solubility and achieving sustained release of Lansoprazole. Among the tested formulations, those containing higher viscosity HPMC provided better control of drug release compared to lower viscosity grades. FTIR results confirmed no significant drug-excipient interaction, ensuring stability of the formulation. Thus, the developed sustained release Lansoprazole capsules have the potential to improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance in the treatment of acid-related disorders

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