Formulation and Evaluation of Tablet in Tablet containing Inner Tablet Lansoprazole as sustained release and Outer Tablet Naproxen as immediate release.

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Abstract:

In order to accomplish combination therapy with enhanced therapeutic impact and patient compliance, the study concentrated on developing and assessing tablet-in-tablet dose form. Naproxen was created as an outer layer of the tablet, while lansoprazole was incorporated into the core tablet. A number of pre-compression and post-compression parameters, including as thickness, drug content, weight variation, hardness, and friability, were assessed. In order to compare release patterns, in-vitro dissolution investigations were conducted. The tablet-in-tablet system is a viable strategy for combination therapy, since the results showed a successful formulation with desired physical and chemical qualities.

Keywords:

Lansoprazole, Naproxen, sustained release, polymer.

Introduction:

Because of its cost-effectiveness, patient acceptance, convenience of administration, and precise dose, the oral route is the most popular way to administer drugs. Because of their ease of use, reduced manufacturing costs, and attractive appearance, tablets are the most used dosage form. They are intended to elicit the intended pharmacological responses and

can be produced via dry granulation, wet granulation, or direct compression, with or without excipients. Solid oral administration methods—especially tablets—are the recommended option because they are affordable and don't require special handling[1].

Tablet in Tablet:

A tablet in tablet or compression-coated tablet is made up of two components: an external coating shell and an internal drug core. The outer layer, which envelops the inner core, primarily regulates the stability, drug release, and film coating strength. In addition to providing the drug with chemical and physical protection, the coating will alter the drug's release characteristics. . Noyes first presented the compression coating method in a patent in 1896. One of the best options for creating an innovative drug delivery system is compression coating, an innovative coating technology.

- **Advantages of Tablet in Tablet dosage form:**

It is possible to separate incompatible materials in the outer shell and core. It will be used to create a product with a modified release (such as a delayed release product).

Two distinct regions of the gastrointestinal tract may be the target of a tablet containing two different drugs.

By establishing a temporal interval between the release of concurrently administered drugs, the pharmacokinetic interaction (drug–drug) between them can be prevented in tablet dosage form.

The hygroscopic or thermo-liable drug is protected by the tablet in tablet dose form. A similar medicine or a different drug combination can have an instant release and sustained release action in a single tablet in tablet dose form

- **Disadvantages of Tablet in Tablet dosage form:**

The potential for cross-contamination between the layers.

Deal with difficulties maintaining the device's chemical and physical integrity over time when it is being stored. The large size of the tablet makes swallowing difficult.

- **Manufacturing process of Tablet in Tablet dosage form:**

Using specifically made tableting equipment , granular materials are compressed around a prepared tablet core. The two components of the tablet in tablet dosage form are the outer layer and the inside core. The tooling required to prepare the inner core, which is a small; tablet, is somewhat smaller than that used to prepare the outer coat. Following the production of the internal tablet core, it is positioned in the center of another die that is somewhat filled with coating powder and larger than the core tablet. The remaining coating powder is then deposited on top of the core tablet and compressed, creating a tablet inside a tablet[2].

Sustained release drug delivery system:

Drug delivery systems that are new and innovative have been quickly replacing traditional dose forms of medications in recent years. Among these, sustained-release and controlled-release dose formulations have grown in popularity in modern medicine[3.] Drugs with a limited therapeutic range of blood concentrations or those that remove quickly can benefit from optimal therapy when administered orally using sustained release (SR) delivery systems. With the use of an initial dose portion, SR products are made to instantly raise a drug's blood level to therapeutic concentrations[4].

Immediate release drug delivery system:

Immediate release dosage forms dissolve and break down rapidly, releasing the medication. In this instance, an adequate pharmaceutically acceptable diluent or carrier that does not significantly slow down the rate of drug release and/or absorption may be made available for quick release."Immediate release" is a term in general terms, a pharmaceutical formulation is one in which galenic changes do not significantly or intentionally slow down the rate of drug release or absorption from the formulation. Doses that dissolve and break down rapidly to release the medication are known as immediate release dose forms[5]. The fundamental procedure used in tablet development involves superdisintegrants like carboxymethylcellulose (Croscarmellose), sodium starch glycolate (Primogel, Explotab), cross-linked polyvinylpyrrolidone or crospovidone (Polyplasdone), etc. When taken in the stomach, these superdisintegrants cause the tablet to dissolve instantly[6].

Gastric acidity:

Numerous physiological functions, including the digestion of proteins, the absorption of calcium and iron, and the sterilization of food, depend on gastric acid. The quest for treatments that aim to control the secretion of gastric acid was guided by the pivotal roles that hydrochloric acid (HCl) plays in the etiology of GERD and peptic ulcer disease (i.e., gastric and duodenal ulcers). HCl is secreted into the stomach lumen by parietal cells, which are located in the glands of the oxyntic mucosa. H+ ions are transported through the parietal cell canaliculus in exchange for K+ by the stomach proton pump H+/K+-ATPase, which is found in the apical membrane of parietal cells[7].

Materials:

Lansoprazole and Naproxen wad purchased from Chempure Pvt Ltd, Mumbai.

Pre-Formulation Study:

Colour, Appearance and odour.

The sample was observed visually.

Determination of melting point:

The glass capillary method was used to determine the drug's melting point.

Spectral analysis

Spectral analysis of Lansoprazole:

Determination of UV Spectrum in Methanol:

Lansoprazole (100 µg/ml) was dissolved in methanol to prepare the stock solution. A 10 µg/ml dilution was maintained in a cuvette with a 10 mm route length. A double beam UV-VIS spectrophotometer was used to record the UV spectra in the 200–400 nm wavelength range, using methanol as a blank[8].

Spectral analysis of Naproxen:

Determination of UV Spectrum in Methanol:

Naproxen (100 µg/ml) was dissolved in methanol to prepare the stock solution. A 10 µg/ml dilution was maintained in a cuvette with a 10 mm route length. A double beam UV-VIS spectrophotometer was used to record the UV spectra in the 200–400 nm wavelength range, using methanol as a blank[9].

Differential Scanning Calorimetry:

Differential Scanning Calorimetry (DSC) was performed to evaluate the compatability of drug (API) with formulation excipient.

Pre-compression parameters:

Angle of repose(θ):

The flow characteristics of solids have been described using the angle of repose. This is the greatest angle that can exist between the granule or powder pile's surface and the horizontal plane. At a height of about 2 cm above the platform, a funnel was mounted. The loose powder was gradually moved along the funnel's wall until a powder cone formed. Measure the height of the powder cone and the radius of the powder heap to find the angle of repose[10]

$\tan \theta = h/r$

where, θ= angle of repose, h= height, r = radius

Bulk density:

It is the ratio of the powder's bulk volume to its total mass.

It is expressed in g/ml. Based on this, the bulk density is calculated using the formula given below[11]

Bulk density (g/ml) = Mass/ Volume occupied by sample in ml.

Tapped density (g/ml) = Mass/Tapped volume.

Compressibility Index and Hausner's Ratio:

Carr's index, or % compressibility, was computed as 100 times the ratio of the tapped density to the difference between the bulk and tapped densities[12].

Hausner's ratio is the ratio of tapped density to bulk density[13].

Compressibility index = tapped density – bulk density/ tapped density X 100.

Hausner's ratio = tapped density/ bulk density.

Preparation of granules of Lansoprazole tablet (by wet granulation):

- Drug and all the polymers were passed through stainless steel sieve (mesh no. 60)
- HPMC K-4M and HPMC K-100M polymer and drug required quantity were accurately weighed and blended thoroughly using glass mortar and pestle manually with starch and sodium benzoate.
- PVPK-30 was dissolved in distilled water and added to the above blend by trichurating it and passing it through sieve (mesh no.8).
- The granules were dried at 50-60^0 C and passed through sieve (mesh no.16).
- Talc and magnesium stearate were passed through sieve (mesh100) and added in to granules.

Preparation of Naproxen(IR) tablet (by wet granulation):

- The formula included variable amounts of superdisintegrant and other excipients.
- Naproxen drug per tablet were taken and then mixed with directly compressible diluents, superdisintegrant and preservative in a plastic container.
- Aerosil and talc were passed through sieve no. 100, mixed and blended with the initial mixture in the plastic container followed by compression of the blend.

Preparation of granules of Lansoprazole tablet (by wet granulation):

Formulation composition of inner tablet of Lansoprazole:

Ingredients	**SR1**	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**	**SR7**	**SR8**	**SR9**
API	30%	30%	30%	30%	30%	30%	30%	30%	30%
HPMC K-4M	10%	15%	20%	-	-	-	5%	7.5%	10%
HPMC K-100M	-	-	-	10%	15%	20%	5%	7.5%	10%

PVPK-30	10%	10%	10%	10%	10%	10%	10%	10%	10%
Starch	46.99 %	41.99 %	36.99 %	46.99 %	41.99 %	36.99 %	46.99 %	41.99 %	36.99%
Tartrazine	0.01%	0.01 %	0.01 %	0.01 %	0.01 %	0.01%	0.01 %	0.01 %	0.01 %
sodium benzoate	1%	1%	1%	1%	1%	1%	1%	1%	1%
Magnesium stearate	2%	2%	2%	2%	2%	2%	2%	2%	2%

Table No.1: Formulation composition of inner tablet of Lansoprazole(SR) tablet.

Formulation composition of outer tablet Naproxen(IR):

Ingredients	**IR1**	**IR2**	**IR3**	**IR4**	**IR5**	**IR6**	**IR7**	**IR8**	**IR9**
API	30%	30%	30%	30%	30%	30%	30%	30%	30%
Sodium starch glycolate	10%	15%	20%	-	-	-	5%	7.5%	10%
Cross carmellose sodium	-	-	-	10%	15%	20%	5%	7.5%	10%
Lactose	46.725 %	41.725 %	36.725 %	46.725 %	41.725 %	36.725 %	46.725 %	41.725 %	36.725 %
Gelatin	10%	10%	10%	10%	10%	10%	10%	10%	10%
Methyl paraben	0.025 %	0.025 %	0.025 %	0.025 %	0.025 %	0.025 %	0.025 %	0.025 %	0.025 %
Propyl paraben	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
Aerosil	1%	1%	1%	1%	1%	1%	1%	1%	1%
Talc	2%	2%	2%	2%	2%	2%	2%	2%	2%

Table No.2: Formulation composition of outer tablet of Naproxen(IR) tablet.

Post compression parameters:

I.Shape and colour of tablet

Tablets were examined under a lens for the for the shape of the tablet, and colour is observed by keeping the tablets in light.

II.Uniformity of thickness:

The tablets were picked randomly and the thickness was measured individually. Thickness of tablet was measured by vernier caliper[8].

III.Hardness test:

Hardness is used to describe a tablet's resistance to mechanical shocks. The device that is used to measure the hardness of tablets is the Monsanto hardness tester. The unit of measurement is kg/cm^2. A random selection of tablets should be made after three tablets from each batch have had their hardness evaluated. It is necessary to calculate the mean and standard deviation values[14].

IV.Friability test:

A Roche friabilator of the USP type was used to evaluate the friability of a sample of twenty tablets. For four minutes, pre-weighed tablets were positioned in a plastic-chambered friabilator that was connected to a motor and rotated at 25 rpm. Following dedusting, the tablets were reweighed, and the % weight loss was calculated[15].

% Friability = Initaial weight of tablet- Final weight of tablet/ Initial weight of tablet X100.

V.Weight variation:

The purpose of the weight variation test is to ensure that the manufactured tablets have a consistent weight. The average weight of twenty randomly chosen tablets was determined. Only two of the individual weights differ from the average weight by more than the pharmacopoeia's specified percentage, and none differ by more than twice that amount[16].

Drug Content:

- **Drug Content of Lansoprazole:**

Twenty tablets were taken, and the drug content of each tablet was determined. 10 mg of the drug powder was moved to a 100 ml standard flask after the tablets were crushed in a mortar. Methanol were used to dissolve the powder, and the same solution was then used to get it up to volume. After thoroughly mixing the material, it passed through a filter. The filtered solution was suitably diluted, and a UV spectrophotometer set to 284 nm as a blank was used to measure the drug concentration[17].

- **Drug Content of Naproxen:**

  Accurately weighing 10 mg of the preparations, they were then transferred to a 100 ml volumetric flask and dissolved in ethanol. Using the proper blank solution, the absorbance of the resultant solution was measured at 332 nm. The calibration curve was used to calculate the drug content[18].

  Disintegration Study:

  According to USP, the disintegration equipment is made up of six glass tubes with a 10-number mesh at the bottom . Six tubes are arranged in a one-liter vessel in a liquid that mimics the disintegration environment, which is kept at 37^{o}C ± 2^{o}C. This system was made to move up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Tablet was kept 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The time required for the distintegration of immediate release tablet of naproxen was recorded.

  Dissolution Studies:

  The USP- type II dissolution testing paddle apparatus was used in this investigation of experimental naproxen tablets in a phosphate buffer solution (900 ml, pH 6.8). The paddle was rotated at 50 rpm, and the temperature was kept at 37±0.5 °C. For 12 hours, aliquots (5ml) of the solution were taken out of the dissolving device every hour for Lansoprazole and at a interval of 5 minutes till 60 minutes for Naproxen and replaced with new dissolution media. Whatman filter paper no. 41 was used to filter the aliquots. In photometric mode for a single drug and in multicomponent mode analysis for a combination of drugs, the absorbance of these solutions was measured at 283 nm for Lansoprazole and 230 nm for Naproxen[16].

  Stability study:

  Tablet stability analysis F9 was conducted to ascertain the physical stability of the formulation under conditions of accelerated storage as well as the impact of formulation additions on drug stability. A 90-day stability assessment was conducted at 40±20°C and 75±5% relative humidity[8]

  Result:

  Organoleptic properties:

Sr.No.	Property	Lansoprazole	Naproxen
1	Colour	Brown	White
2	Odour	Odourless	Odourless
3	Taste	Bitter	Bitter
4	Melting point	178^0C	153^0C
5	Solubility	Methanol	Ethanol

Table No.3: Organoleptic properties of drug

Differential Scanning Calorimetry:

Differential Scanning Calorimetry (DSC) is a thermo analytical technique used for thermal transitions involving thermal energy with a great sensitivity. DSC of API is compared with DSC of API + excipients.

DSC of Naproxen API:

The Differential Scanning Calorimetry of Naproxen API was carried out at its melting point 153^0C.

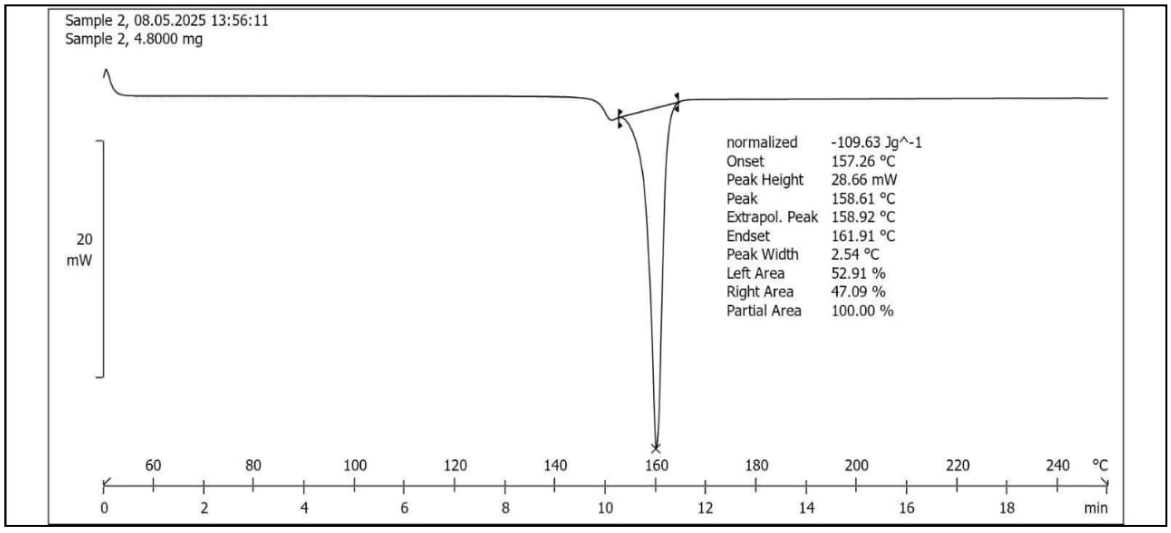

Fig.No.1: DSC of Naproxen API

DSC of Lansoprazole API:

The Differential Scanning Calorimetry of Lansoprazole API was carried out at its melting point 178^0C.

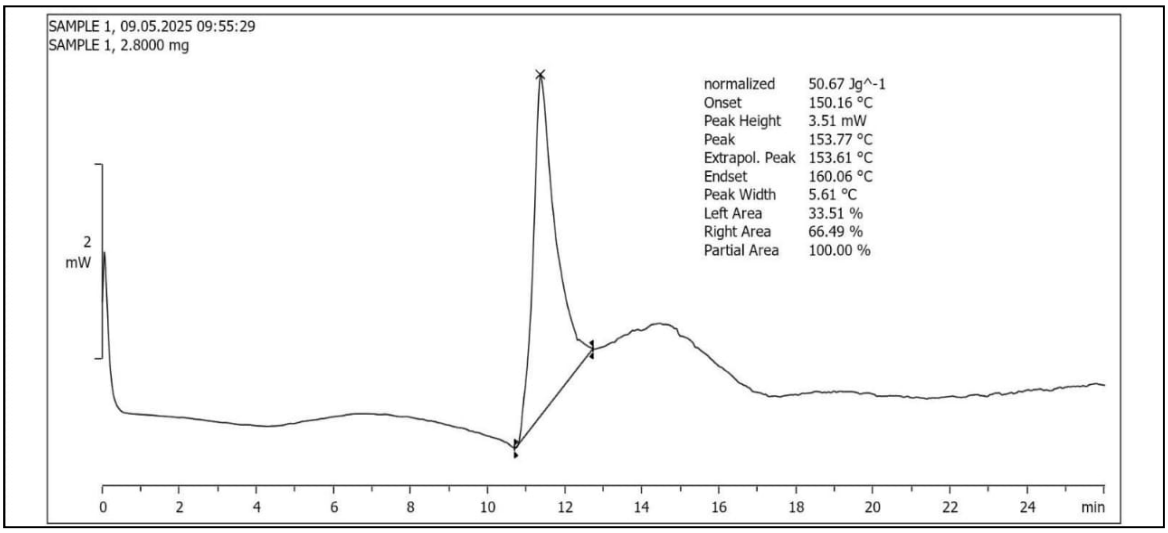

Fig.No.2: DSC of Lansoprazole API

DSC of Naproxen API+DSC of Naproxen API+ Excipients:

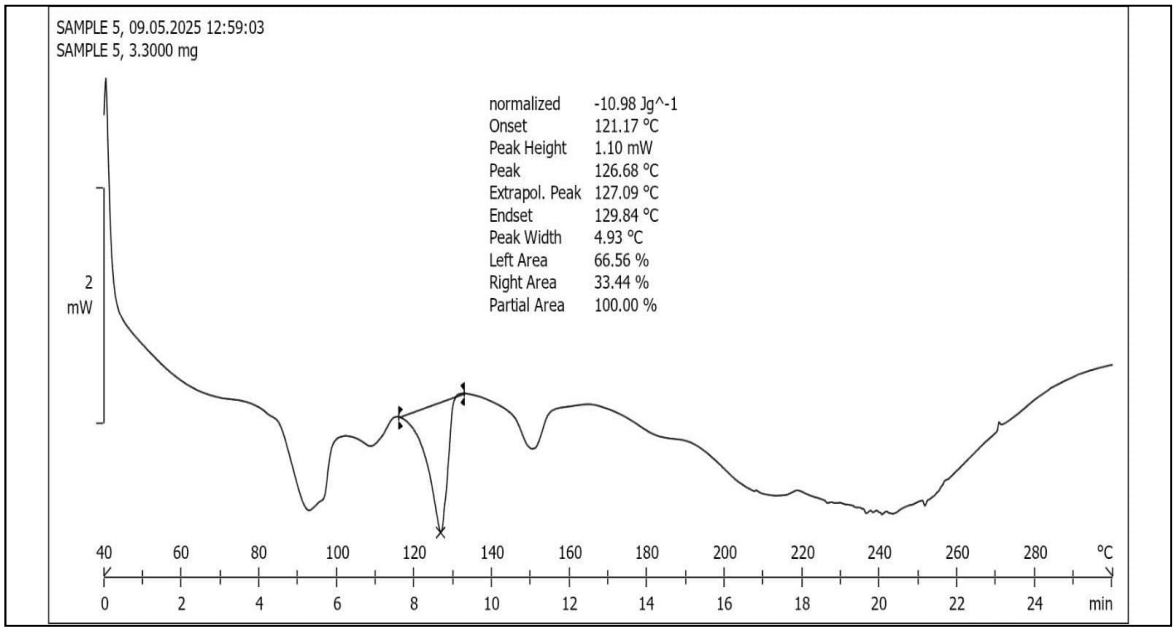

Fig.No.3: DSC of Naproxen API+DSC of Naproxen API+ Excipients

Standard calibration curve of Lansoprazole:

The drug was scanned over a range 282 nm. The peak was observed at the for Lansoprazole. The obtained results confirmed the identification of Lansoprazole.

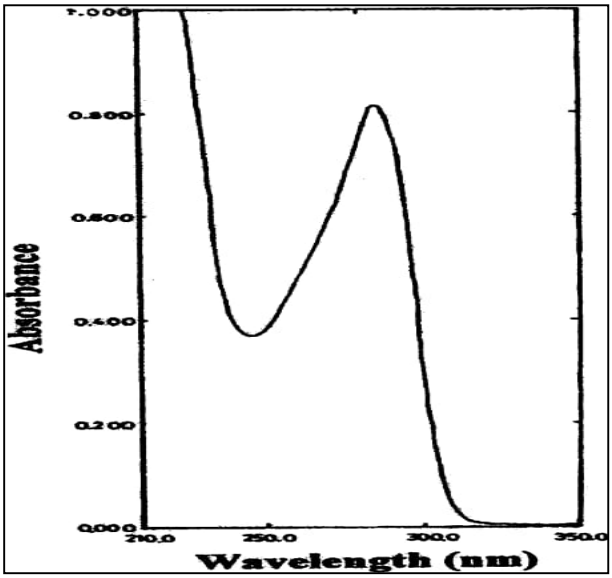

Fig.No.4: Standard calibration curve of Lansoprazole

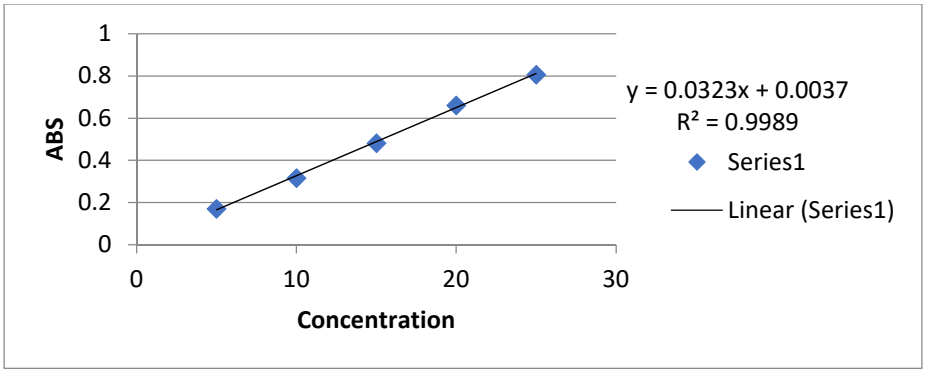

Fig.No.5: Standard calibration curve of Lansoprazole

Standard calibration curve of Naproxen:

The drug was scanned over a range 230 nm. The peak was observed at the for Naproxen. The obtained results confirms the identification of Naproxen.

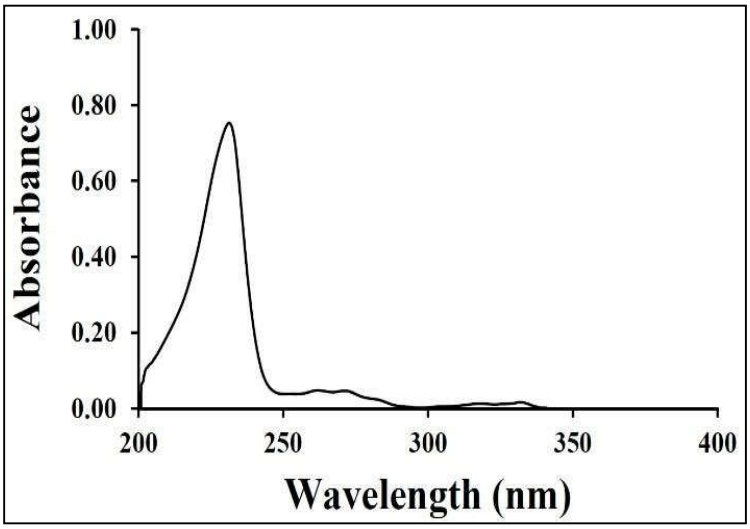

Fig.No.6: Standard calibration curve of Naproxen

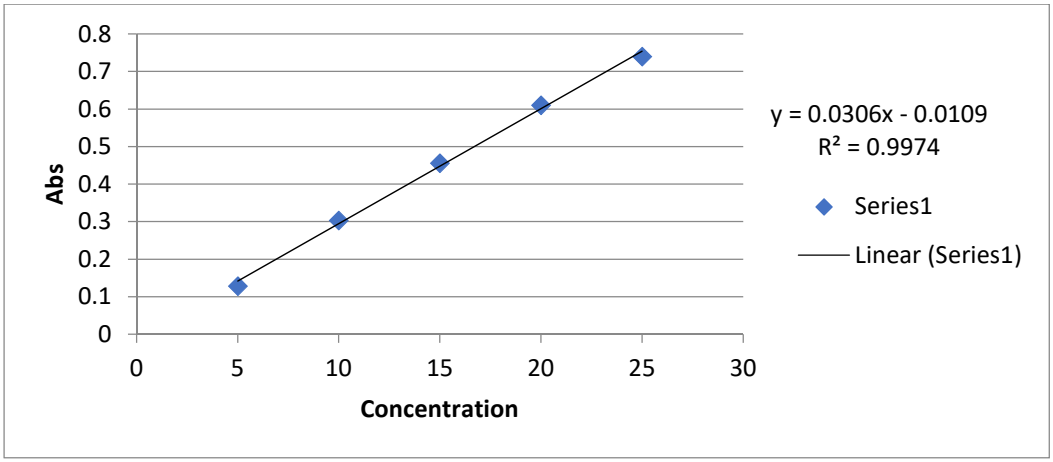

Fig.No.7: Standard calibration curve of Naproxen

Pre-compression parameters:

Precompression parameters of Lansoprazole(SR):

Formulation	Angle of Repose(Ø)	Bulk Density(gm/cm2)	Tapped Density (gm/cm3)	Hausner's Ratio	Carr's Index (%)
SR1	36±0.57	0.43±0.005	0.58±0.005	1.348±0.1	34.88±0.24
SR2	23±0.53	0.42±0.007	0.56±0.001	1.333±0.3	33.33±0.24
SR3	22±0.56	0.40±0.001	0.58±0.002	1.45±0.2	45±0.25
SR4	24±0.45	0.53±0.004	0.62±0.006	1.16±0.4	16.98±0.24
SR5	32±0.55	0.51±0.009	0.60±0.004	1.17±0.4	17.64±0.22
SR6	24±0.46	0.54±0.007	0.63±0.006	0.09±0.1	16.66±0.25
SR7	34±0.35	0.52±0.006	0.60±0.007	0.08±0.1	15.38±0.28
SR8	39±0.22	0.53±0.003	0.64±0.005	0.06±0.4	10.34±0.23
SR9	**32±0.20**	**0.58±0.002**	**0.64±0.004**	**0.08±0.2**	**14.28±0.35**

Table.No.4: Evaluation of Precompression parameters of Lansoprazole(SR)

Post-compression parameters of Lansoprazole(SR):

Formulation	Thickness(mm)	Hardness((kg/cm2)	Friability(%)	Drug content(%)	Weight variation(mg)
SR1	0.24±0.01	6±0.57	0.48±0.4	95.07±0.61	98.4±0.82
SR2	0.23±0.03	5.5±0.86	0.54±0.3	96.27±1.31	99.42±0.80
SR3	0.22±0.05	6±0.45	0.52±0.4	96.63±0.92	98.75±0.89
SR4	0.24±0.02	5±0.23	0.46±0.2	94.45±1.42	95.06±0.77
SR5	0.26±0.05	5.6±0.23	0.45±0.2	94.02±0.22	98.75±0.72
SR6	0.29±0.03	6±0.21	0.51±0.1	96.54±0.57	98.23±0.72
SR7	0.3±0.09	5.5±0.55	0.52±03	96.63±0.43	96.03±0.53
SR8	0.22±0.02	6±0.34	0.45±0.1	95.03±0.34	98.4±0.88
SR9	**0.24±0.05**	**6±0.11**	**0.55±0.5**	**97.47±0.24**	**99.45±0.12**

Table.No.5: Evaluation of Postcompression parameters of Lansoprazole(SR)

Precompression parameters of Naproxen(IR):

Formulation	Angle of repose(Ø)	Bulk density(gm/cm2)	Tapped density(gm/cm2)	Carr's index(%)	Hausner's ratio
IR1	24.20±0.25	0.53±0.03	0.62±0.01	13.65±0.95	1.16±0.48
IR2	24.02±0.12	0.52±0.03	0.61±0.02	14.27±0.73	1.18±0.47
IR3	23.25±0.45	0.52±0.02	0.61±0.04	14.27±0.42	1.18±0.56
IR4	24.28±0.56	0.54±0.01	0.63±0.09	16.66±0.45	1.16±0.72
IR5	26.02±0.89	0.62±0.03	0.71±0.03	14.51±0.26	1.14±0.66

IR6	**27.56±0.01**	**0.53±0.01**	**0.62±0.01**	**16.98±0.32**	**1.16±0.41**
IR7	30.03±0.55	0.61±0.05	0.70±0.05	14.75±0.44	1.14±0.47
IR8	24.21±0.45	0.60±0.04	0.69±0.03	15±0.21	1.15±0.23
IR9	29.72±0.25	0.54±0.05	0.63±0.03	16.66±024	1.16±0.21

Table.No.6: Evaluation of Precompression parameters of Naproxen(IR)

Post-compression parameters of Naproxen(IR):

Formulation	Thickness(mm)	Hardness(kg/cm2)	Friability(%)	Weight variation(mg)	Drug content(%)	Disintegration Time for IR(min)
F1	0.51±0.0012	2.5±0.28	0.52±0.3	696.05±2.02	95.07±0.51	2±0.57
F2	0.50±0.001	3±0.57	0.55±0.5	696.00±3	96.27±0.26	2.5±0.35
F3	0.54±0.003	3±0.43	0.58±0.4	693.09±6.007	95.63±0.22	2±0.25
F4	0.50±0.001	2.2±0.54	0.62±0.1	705.03±3.403	94.23±0.15	2±0.55
F5	0.50±0.001	2.3±0.24	0.55±0.5	690.05±2.02	92.72±0.52	2±0.45
F6	**0.50±0.001**	**2.5±0.12**	**0.52±0.3**	**690.05±2.02**	**98.37±0.62**	**2±0.32**
F7	0.51±0.0012	2.5±0.23	0.52±0.3	696.00±3	91.23±0.35	1.5±0.57
F8	0.51±0.0012	2.7±0.45	0.58±0.4	705.03±3.403	90.12±0.43	2±0.24
F9	0.50±0.001	3±o.1	0.62±0.1	693.09±6.07	94.23±0.22	1.5±0.23

Table.No.7: Evaluation parameters for post-compression parameters of Tablet in Tablet of Lansoprazole(SR) and Naproxen(IR).

In-vitro dissolution studies of Lansoprazole:

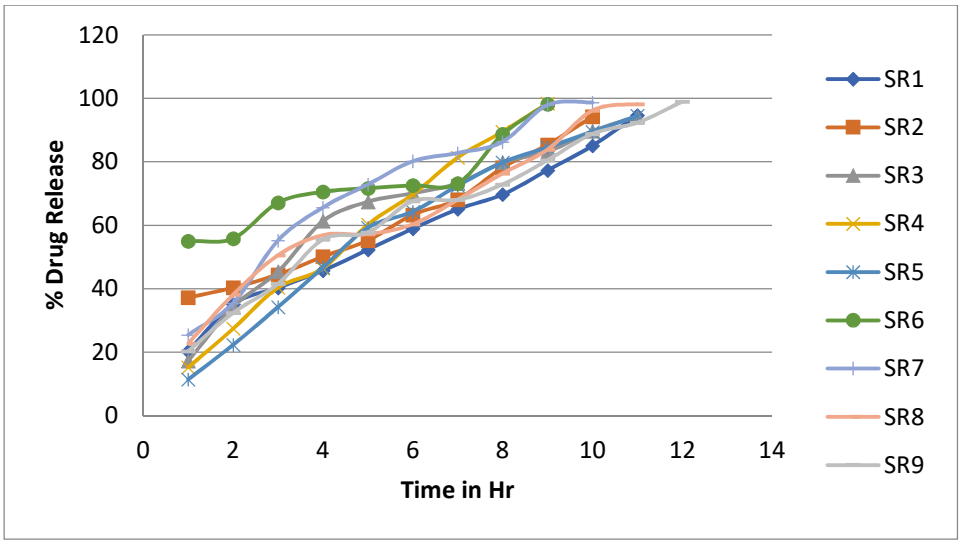

Fig.No .6: Invitro % drug release of all formulations of Lansoprazole.

Release kinetics and mechanism:

R^2 values for zero order, first order, Koyesmer-Peppas matrix, and Hixon-Crowel models were compiled in a table to determine the release mechanism and kinetics of optimal formulations of Lansoprazole.

Model Fitting :

Model name	**R**
Zero order	0.7866
1st order	0.9675
Higuchi	0.9709
Korsmeyers peppas	0.9887 (Best fit)
Hixon. Crow	0.9685

Table.No.8: Invitro Drug Release Kinetics of SR9 formulation.

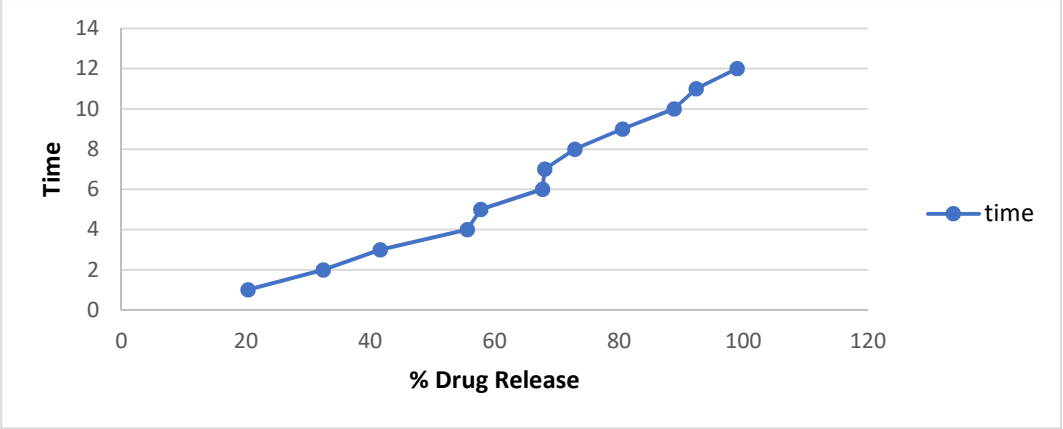

Fig.No .7 : Invitro % drug release kinetics of SR9 formulation

In-vitro dissolution studies of Naproxen:

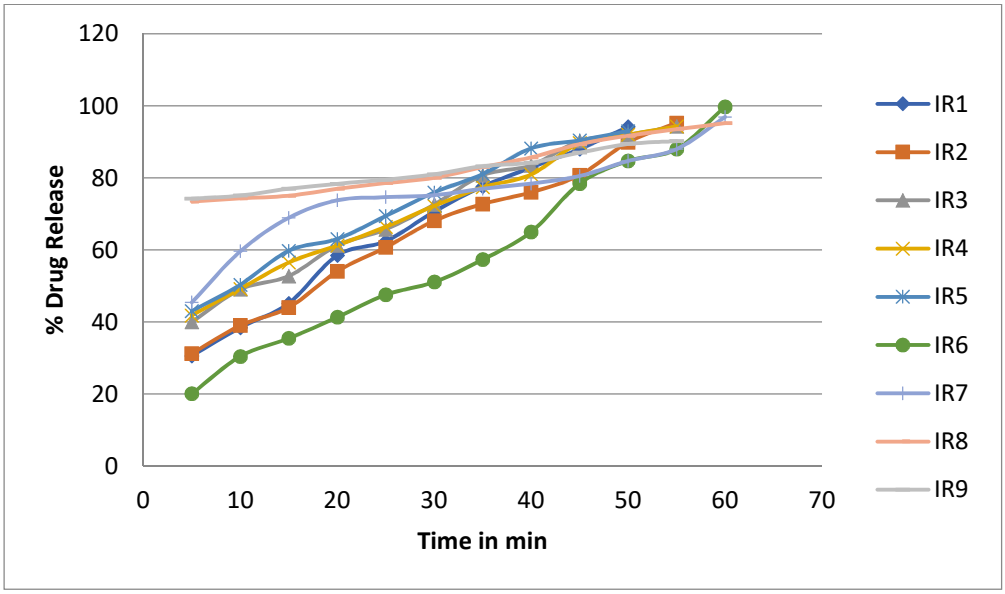

Fig.No .8: Invitro % drug release of all formulations of Naproxen

Model Fitting :

Model name	**R**
Zero order	0.9218
1st order	0.9090
Higuchi	0.9002
Korsmeyers peppas	0.9703 (Best fit)
Hixon. Crow	0.9354

Table.No.9: Invitro Drug Release Kinetics of IR6 formulation.

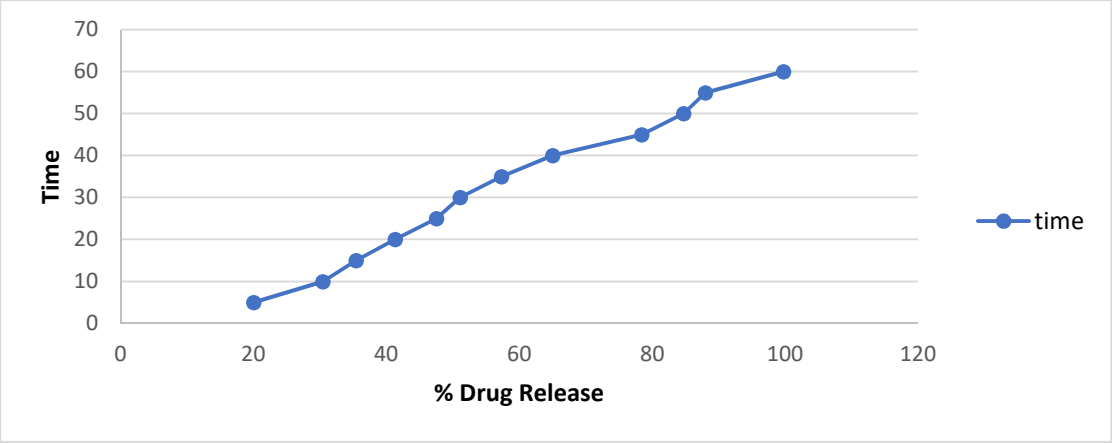

Fig.No .9: Invitro % drug release kinetics of IR6 formulation

Stability study:

Time interval	% Drug content of Lansoprazole	% Drug content of Naproxen
0 day	96.54 ±0.01%	97.45±0.02%
30th day	96.54±o.12%	96.02±0.42%
60th day	95.03±0.55%	94.22±0.22%
90th day	96.63±0.65%	95.23±0.22%

Table.No.10: Stability study data of optimized batch

Conclusion and Summary:

The goal of the current study was to formulate sustained-release tablets containing 30 mg of Lansoprazole and 180 mg of Naproxen. According to the results of combination therapy, naproxen effectively relieves pain, while lansoprazole is used to decrease the acidity caused by naproxen.

The UV and DSC analysis of the sample were done. Differential scanning calorimetric data indicated that there was no interaction between drug and excipients. Different concentrations of HPMCK-4M and HPMC K-100M polymers, ranging from 15% to 30%, were used to prepare the inner tablets. The produced granules were assessed including bulk density, tapped density, and angle of repose.

Different concentrations of superdisintegrants were used to prepare outer tablet.

The tables were evaluated for weight variation, thickness, hardness, friability, percent drug content, dissolution study, disintegration study.

It was concluded that:

Compression-coated offer significant advantages over traditional coating techniques, particularly in terms of formulation stability and manufacturing simplicity.

The physical characteristics of the tablets and the outcomes of the powder blends were satisfactory for every composition.When compared to previous batches, the optimized batch of Lansoprazole (SR9) showed the highest in-vitro drug release rate. For immediate release of Naproxen tablets, sodium starch glycolate and sodium cross-carmellose sodium were employed as superdisintegrants.

Based on in vitro dissolution studies, immediate release formulation IR6 was optimized, drug release was found to be 99.77% within 60 minutes.

Based on their pharmacological mechanisms, Naproxen a non-steroidal anti-inflammatory drug reduces pain and Lansoprazole, helps avoid the gastrointestinal adverse effects of naproxen. By combining the two drugs into a single tablet is beneficial to treat pain with less stomach distress.

Naproxen's immediate release relieves pain and inflammation quickly. Long-lasting acid suppression and protection are ensured by sustained release of lansoprazole, which keeps the stomach pH high for an extended amount of time. With this dual-release technique, adverse effects are reduced and the therapeutic benefit is maximized.

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