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Research Article

Formulation and *In Vitro* Evaluation of Bilayer Tablets of Lansoprazole and Amoxicillin Trihydrate for the Treatment of Peptic Ulcer

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Abstract

The present work involves the formulation development, optimization and *In-vitro* evaluation of bilayer tablet containing Lansoprazole in the immediate release layer and Amoxicillin in the sustained release layer, using sodium starch glycolate as a super disintegrant for the immediate release layer and the hydrophilic matrix HPMC K100M, hydrophobic matrix Ethyl cellulose are used in the sustained release layer. Bilayer tablet showed as initial burst effect to provide dose of immediate release layer Lansoprazole to control the acid secretion level and the sustained release of Amoxicillin for 24 hours. Immediate and sustained release tablets were formulated by wet granulation method because of the poor flow property of the blends. The prepared bilayer tablet was evaluated for their precompression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content, swelling index, *In-vitro* floating studies and *In-vitro* drug release. The release of the lansoprazole from the immediate release layer was found to be $97.46 \pm 0.15\%$ in 15 minutes. The release of Amoxicillin Trihydrate for the sustained release floating layer was found to be $98.25 \pm 0.14\%$ in 12 hours. Lansoprazole potentiate the effect of Amoxicillin. Hence the bilayer tablets of Lansoprazole and Amoxicillin were used to improve patient compliance towards the effective management of ulcer.

Keywords: bilayer tablet, Lansoprazole, and Amoxicillin, sustained release

INTRODUCTION

Lansoprazole is a proton pump inhibitor (PPI) which inactivates the final step in the gastric acid secretion pathway in gastric parietal cells in a dose-dependent manner. Bioavailability is 85% after the first dose – the highest among PPIs and acid inhibition is swift, resulting in rapid relief of symptoms. Lansoprazole also exhibits antibacterial activity against *Helicobacter pylori in vitro*^{1, 2}. Lansoprazole is also effective in combination with different regimens for *H. pylori* eradication and is included in the first-line PPI-based options for this purpose³.

Amoxicillin is a semi-synthetic aminopenicillin, with a broad-spectrum bactericidal activity⁴⁻⁶, used as trihydrate in oral products³. Amoxicillin trihydrate is likely a white or almost white crystalline powder⁷, and it is well absorbed when given orally, with a bioavailability (95 Oral%) that appears to be much higher than expected based on its physicochemical and biopharmaceutical properties, and the pH partition theory⁸. Because of its poor solubility, amoxicillin trihydrate can be considered as a drug-candidate which may give rise to dissolution-related bioavailability problem⁹.

Bi-layer tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of

single or multiple active ingredients, another layer is sustained or controlled release part of single or multiple active ingredients.

Nowadays various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, diabetes and cardiovascular diseases. Combination preparation plays an important role in clinical treatment because of its better and wider curative synergism and weaker side effects. Combination therapy may be achieved by giving separate drugs or where available by giving combination drugs (monolithic or bilayer dosage form) which are dosage forms that contain more than one active ingredient.

To provide effective, safe and stable pharmaceutical oral formulation containing anti-ulcer drug Lansoprazole as immediate release layer and oral antibiotic drug Amoxicillin as sustained release layer for effective treatment of peptic ulcer¹⁰.

Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration¹¹. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled-release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of

drug plasma concentration followed by continuation of drug release from the sustained release layer¹².

MATERIALS AND METHODS

Lansoprazole and Amoxicillin were received as gift by Sri Pharmicare Powai, Mumbai, India. HPMC K100M, Ethyl cellulose, Sodium starch glycolate, Polyvinyl pyrrolidone K 30, Magnesium stearate, Talc, Microcrystalline cellulose, Isopropyl alcohol, obtained from S.D. fine chemicals, Mumbai. Sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). All other chemical was purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Formulation Development

Formulation of Immediate release granules of Lansoprazole

To improve the onset of action the immediate granules of lansoprazole were prepared by wet granulation technique. Sodium starch glycolate (SSG) was used as a super disintegrant in 4%, 6% and 8% concentrations to improve the dissolution of the drug. The granules were compressed by 10 station compression machines. Composition of tablets is mentioned in Table 1. The immediate release tablet of lansoprazole was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Table 1 Composition of Immediate Release Granules

S.NO	Ingredients	N-1(mg)	N-2(mg)	N-3(mg)
1	Lansoprazole	15	15	15
2	Sodium starch glycolate	8	12	16
3	Polyvinyl pyrrolidone K-30	8	8	8
4	Magnesium stearate	4	4	4
5	Talc	2	2	2
6	Microcrystalline cellulose	162	158	154
7	Lake ponceau 4R	1	1	1
8	Isopropyl alcohol	q.s	q.s	q.s
Total weight		200	200	200

Formulation of amoxicillin sustained release tablets

The sustained release granules were prepared by wet granulation technique. Different polymers such as HPMC K 100 M and Ethyl cellulose were used in different ratios. The tablets were compressed by 10 station compression machine using mm punches. The optimized batch of sustained release

tablets of amoxicillin was then compressed with the optimized batch of immediate release Lansoprazole tablets to get bilayer tablets. Composition of tablets is mentioned in Table 2. The sustained release tablet of amoxicillin was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Table 2 Composition of Sustained Release Granules

S.NO	Ingredients	NA-1(mg)	NA-2(mg)	NA-3(mg)	NA-4(mg)	NA-5(mg)
1	Amoxicillin	500	500	500	500	500
2	HPMC K100 M	-	50	25	50	75
3	Ethyl cellulose	50	-	25	25	25
4	Polyvinyl pyrrolidone	12.5	12.5	12.5	12.5	12.5
5	Magnesium stearate	10	10	10	10	10
6	Talc	2.5	2.5	2.5	2.5	2.5
7	Microcrystalline cellulose	165	165	165	140	115
8	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
Total weight		740	740	740	740	740

Formulation of bilayer tablet

Optimized formulation N-3 of Instant release layer (Lansoprazole) and optimized formulation of NA-5 (Amoxicillin) for control release used for formulation of Bi-

layer tablet. Optimized immediate layer of Lansoprazole was prepared by wet granulation method. Optimized sustained release layer of Amoxicillin was prepared by wet granulation method.

Evaluation of Precompression Parameter¹³

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

$\theta = \tan^{-1}(h/r)$ Where, h and r are the height and radius of the powder cone respectively.

Bulk density/tapped density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula⁷⁻⁹.

Hausner's ratio = Tapped density/Bulk density.

Evaluation of Post Compression Parameter

Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester and measured in terms of kg/cm².

Weight variation

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

$$\% \text{Friability} = (\text{Loss in weight} / \text{Initial weight}) \times 100$$

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm².

Drug Content Study

1. For IR Tablets Containing Lansoprazole

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 10mg of Lansoprazole was transferred to a 100ml volumetric flask and dissolved. The volume was made upto the mark with 0.1M HCl. From this solution 10ml was taken and further diluted with 0.1M HCl in a 100ml volumetric flask. The absorbance of the resulting solution was measured at 281 nm taking 0.1M HCl as blank using UV-Visible spectrophotometer. The concentration was obtained from the calibration graph.

2. For SR Tablets Containing Amoxycillin

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 50mg of Amoxycillin was transferred to a 100ml volumetric flask and dissolved in 5ml of 0.1N NaOH and the volume was made upto the mark with pH 6.8 phosphate buffer. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in a 100ml volumetric flask. From this solution 5ml was taken and diluted with pH 6.8 phosphate buffer in 50ml volumetric flask. The absorbance of the resulting solution was measured at 228 nm taking pH 6.8 phosphate buffer as blank using UV-Visible spectrophotometer. The concentration was obtained from the calibration graph.

3. Bilayer Tablets of Lansoprazole and Amoxycillin (Simultaneous Equation Method)¹⁴

Simultaneous estimation of Lansoprazole and Amoxycillin was carried out using UV-Visible

The following equations were used to determine the contents.

$$C_x = \frac{A_{2y1} - A_{1y2}}{a_{x2} a_{y1} - a_{x1} a_{y2}}$$

$$C_y = \frac{A_{1x1} - A_{2x2}}{a_{x2} a_{y1} - a_{x1} a_{y2}}$$

where, a_{x1} and a_{x2} = The absorptivity of drug X at λ_1 and λ_2 respectively. a_{y1} and a_{y2} = The absorptivity of drug Y at λ_1 and λ_2 respectively.

A_1 and A_2 = The absorbance of sample at λ_1 and λ_2 respectively.

$$(A_1/A_2) / (a_{x1}/a_{x2}) \text{ and } (a_{y1}/a_{y2}) / (A_1/A_2)$$

The ratios should lie outside the range of 0.1 – 2.0 for the precise determination of X and Y drugs. This criteria is satisfied only when the λ_{max} of the two components is reasonably dissimilar and the components should not interact chemically.

1. Preparation of standard stock solution of Lansoprazole⁹

Lansoprazole equivalent to 100mg was accurately weighed and dissolved. The volume was made upto mark with pH 6.8 phosphate buffer in 100ml standard flask. From this solution 10ml was taken and diluted with pH 6.8 phosphate buffer in 100ml volumetric flask. From this solution 10ml

was taken and further diluted with pH 6.8 phosphate buffer in 100ml standard flask.

2. Preparation of standard stock solution of Amoxicillin⁴⁷

Amoxicillin equivalent to 100mg was accurately weighed and dissolved. The volume was made up to mark with pH 6.8 phosphate buffer in 100ml standard flask. From this solution 10ml was taken and diluted with pH 6.8 phosphate buffer in 100ml volumetric flask. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in 100ml standard flask.

3. Preparation of sample solution

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 100mg of Amoxicillin was transferred to a 100ml volumetric flask and dissolved in 5ml of 0.1N NaOH and the volume was made up to the mark with pH 6.8 phosphate buffer. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in a 100ml volumetric flask. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in a 100ml volumetric flask. The absorbance of resulting solution was measured at 281 nm and 228nm respectively. The amounts of both the drugs were determined.

In Vitro Disintegration Studies for IR Tablets

The disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in 0.1M HCl maintained at a temperature of $37\text{ C} \pm 2\text{ C}$ and the apparatus was switched on. The time taken to disintegrate the tablets completely was noted.

In Vitro Dissolution Studies¹⁵

1. For IR tablets

The release of Lansoprazole was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of 0.1M HCl was used as dissolution medium at a temperature of $37\text{ C} \pm 0.5\text{ C}$. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for 30mins. The absorbance of the solution was measured at 281 nm taking 0.1M HCl as blank using UV-Visible spectrophotometer.

2. For SR tablets

The release of Amoxicillin was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of pH 6.8 phosphate buffer was used as dissolution medium at a temperature of $37\text{ C} \pm 0.5\text{ C}$. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for 24hours. The absorbance of the solution was measured at 228 nm taking pH 6.8 phosphate buffer as blank using UV-Visible spectrophotometer.

3. For bilayer tablets

The release of bilayer tablet was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of 0.1M HCl was used as dissolution medium for first two hours followed by pH 6.8 phosphate buffer solution for next eight hours maintained at a temperature of $37\text{ C} \pm 0.5\text{ C}$. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for ten hours. The absorbance of the solution was measured at 281 nm and 228 nm taking respective buffer solutions as blank using UV-Visible

spectrophotometer and the calculations were done by simultaneous equation method.

RESULTS AND DISCUSSION

The present work was aimed to formulate bilayer tablets of immediate release Lansoprazole and sustained release Amoxicillin. The therapy with these drugs offers a good quality of life for patients who are suffering from gastric ulcer.

Preformulation Studies Drug Characterization Lansoprazole

Lansoprazole and amoxicillin were tested Description, Loss on drying, Solubility, Melting point as per in house specification and found satisfactory for formulation. The drug source is identified and found complying with the specifications.

Physical compatibility study

The compatibility studies were carried out to study the possible interactions between active ingredients (Lansoprazole & Amoxicillin) and inactive ingredients. Physical mixtures of both API and excipients were prepared separately as per the ratios mentioned in table below and kept for stability at 40 C and 75% RH for one month. Samples were taken out after every 10 days and were subjected to physical and chemical compatibility tests. The physical compatibility study was performed visually. The study implies that the drug and the excipients were physically compatible with each other as there was no change of physical parameters. The excipients which are compatible with the drug were selected for the formulation.

Chemical compatibility study

All the samples were scanned at the wave number region of $4000-400\text{ cm}^{-1}$ using KBr disc method. This KBr discs were formed by taking drug and KBr in a ratio of 1: 100 respectively. Then this mixture was mixed well in mortar for three to five minutes. A very small amount of this mixture was uniformly spread and sandwiched between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1min. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region. No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drugs and also with the excipients in the final formulation.

Drug Content study

Calibration Curve of Lansoprazole

Calibration curve of Lansoprazole in 0.1M HCl is shown that the solution of Lansoprazole in 0.1M HCl show linearity ($R^2 = 0.999$) at concentrations of 5-25 ($\mu\text{g/ml}$) and obey Beer Lambert Law at λ_{max} 281 nm.

Calibration Curve for Amoxicillin

Calibration curves of Amoxicillin in pH 6.8 phosphate buffer is shown It was found that the solution of Amoxicillin in pH 6.8 phosphate buffer show linearity ($R^2 = 0.999$) at concentrations of 2-10 ($\mu\text{g/ml}$) and obey Beer and Lambert Law at λ_{max} 228 nm.

Precompression Study for IR Formulation

The API and the formulated blends were evaluated for precompression parameters and results were shown in table 3.

Table 3 Precompression Study of API and Formulated Blends

API and formulation	Bulk density g/cm ³	Tapped density g/cm ³	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (Degree)
Lansoprazole	0.217 ±0.36	0.383 ±0.02	17.69 ±0.37	1.20 ±0.24	30° 37' ±0.54
N-1	0.224 ±0.03	0.387 ±0.01	21.89 ±0.26	1.25 ±0.46	31° 04' ±0.72
N-2	0.223 ±0.06	0.379 ±0.02	21.74 ±0.83	1.28 ±0.67	30° 36' ±1.69
N-3	0.219 ±0.012	0.386 ±0.03	22.54 ±0.46	1.29 ±0.92	32° 33' ±0.91

Mean ± S.D (n=3)

The bulk density of the IR blends ranged from 0.217 ± 0.36–0.224 ± 0.03 g/cm³ and the tapped density ranged from 0.379 ± 0.02–0.387 ± 0.01 g/cm³. The compressibility index of the IR blends ranged from 17.69 ± 0.37% - 22.54 ± 0.46% and Hausner's ratio ranged from 1.20 ± 0.24–1.29 ± 0.92. The angle of repose of the IR blends ranged from 30° 37' ± 0.

54–32° 33' ± 0.91. The formulated blends showed good flow property, so wet granulation technique was used for preparing IR granules of Lansoprazole.

The IR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of repose. The results are given in Table 4.

Table 4 Precompression Study of Formulated IR Granules

Formulation	Bulk density g/cm ³	Tapped density g/cm ³	Compressibility index (%)	Hausner's ratio	Angle of Repose (Degree)
N-1	0.213 ±0.26	0.37 ±0.09	23.27 ±0.88	1.26 ±0.67	32° 61' ±0.39
N-2	0.213 ±0.32	0.38 ±0.43	24.83 ±0.78	1.32 ±0.42	31° 40' ±1.10
N-3	0.221 ±0.42	0.35 ±0.09	25.68 ±0.84	1.28 ±0.63	31° 64' ±0.13

Mean ± S.D (n=3)

The bulk density of the IR granules ranged from 0.213 ± 0.26–0.221 ± 0.42 g/cm³ and tapped density ranged from 0.35 ± 0.09–0.38 ± 0.43 g/cm³. The compressibility index of the IR granules ranged from 23.27 ± 0.88% - 25.68 ± 0.84% and Hausner's ratio ranged from 1.26 ± 0.67–1.32 ± 0.42. The angle of repose of the IR granules ranged from 31° 40' ± 1.10–32° 61' ± 0.39. The formulated IR granules showed good flow property.

Preparation of IR tablets of Lansoprazole

Wet granulation technique was employed for the formulation of IR granules of Lansoprazole. Three formulations of immediate release layer of Lansoprazole (N1, N2 and N3) were prepared using sodium starch glycolate (super disintegrant) in three different ratios. The granules were compressed using 10 station tablet compression machine using 10/32 punches. The result of Post Compression Study for Tablets was shown in table 5.

Table 5 Post Compression Study of the Formulated Tablets

Formulation	Uniformity of weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm ²)	% Friability	(% w/w) Drug Content	Disintegration time (sec)
Specified limit	189.8 - 206.4	4.5 - 5.0	2.5 - 3	3.5 - 4	Not more than 1.0%	90 - 110%	
N-1	197.21 ± 0.35	4.9 ± 0.18	2.6 ± 0.49	3.88 ± 0.48	0.67 ± 0.12	96.17 ± 0.99	42.02 ± 0.79
N-2	196.14 ± 0.78	4.87 ± 0.09	2.62 ± 0.19	3.78 ± 0.94	0.72 ± 0.02	98.44 ± 0.94	29.05 ± 0.90
N-3	199.38 ± 0.91	4.82 ± 0.24	2.68 ± 0.03	3.72 ± 0.36	0.70 ± 0.12	99.09 ± 0.32	24.07 ± 0.92

Mean ± S.D (n=5)

The tablets comply with the test for uniformity of weight, uniform in thickness and diameter have sufficient mechanical strength to resist the transportation. The percentage friability of all the formulations was within the acceptable limits. i.e not more than 1%. The drug contents of all three IR formulations were found to be within the limit.

i.e the drug content was not less than 90% and not more than 110% (as per IP: 2010). The disintegration time of the IR tablets ranged from 43.02 seconds to 19.07 seconds. The disintegration time of the IR tablets containing 8% sodium starch glycolate was found to have optimum disintegration time (19.07 seconds) for IR tablets.

In Vitro Dissolution Study

The in vitro dissolution of immediate release formulations of Lansoprazole is shown in table 6 and Fig 1.

Table 6 In Vitro Dissolution Study of Immediate Release Tablets

Time(minutes)	Cumulative % Drug release		
	N-1	N-2	N-3
0	0 ± 0.00	0 ± 0.00	0 ± 0.00
10	62.6 ± 0.61	80.42 ± 0.16	87.58 ± 0.31
20	72.43 ± 0.59	87.43 ± 0.61	92.49 ± 0.18
30	80.26 ± 0.18	94.63 ± 0.41	99.74 ± 0.25
40	85.14 ± 0.42	97.87 ± 0.41	
50	92.54 ± 0.74		
60	97.66 ± 0.70		

Mean ± S.D (n=3)

The in vitro dissolution study of IR tablets showed that 8% concentration of SSG was found to be optimum for immediate release of Lansoprazole. The 4% and 6% concentration of SSG was found to be releasing the drug slowly when compared to 8% SSG. The 8% concentration of

SSG released 98.94% at the end of 30minutes. Therefore, formulation N-3 was optimized and selected for final bilayer tablets. Formulation N-3 was optimized and selected for final bilayer tablets.

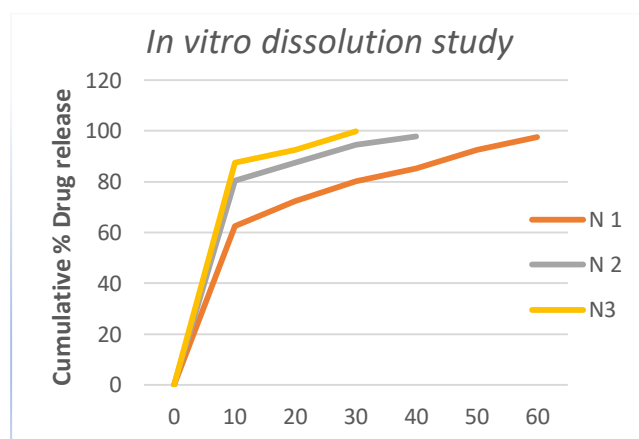


Figure 1 In vitro dissolution study of IR tablets of Lansoprazole

Precompression Study for SR Tablets

The API and the formulated blends of SR were evaluated for precompression parameters. The results are given in table 7.

Tablet 7 Precompression Study of API and Formulated Blends

API and formulation	Bulk density g/cm ³	Tapped Density g/cm ³	Compressibility Index (%)	Hausner's ratio	Angle of Repose (Degree)
Amoxycillin	0.26 ± 0.03	0.32 ± 0.22	26.36 ± 1.35	1.40 ± 0.58	29° 66' ± 0.03
NA-1	0.25 ± 0.02	0.33 ± 0.82	25.05 ± 1.33	1.44 ± 0.80	30° 34' ± 0.90
NA-2	0.27 ± 0.02	0.29 ± 0.42	17.02 ± 0.69	1.69 ± 0.85	31° 40' ± 1.10
NA-3	0.27 ± 0.03	0.31 ± 0.60	17.82 ± 0.01	1.81 ± 0.97	31° 58' ± 1.64
NA-4	0.27 ± 0.06	0.33 ± 0.12	18.70 ± 0.14	1.17 ± 0.08	32° 40' ± 0.66
NA-5	0.26 ± 0.03	0.29 ± 0.16	18.82 ± 0.99	1.17 ± 0.59	31° 83' ± 0.64

Mean ± S.D (n=3)

The bulk density of the SR blends ranged from 0.25 ± 0.02 – 0.27 ± 0.06 g/cm³ and the tapped density ranged from 0.29 ± 0.16 – 0.33 ± 0.82 g/cm³. The compressibility index ranged from 17.02 ± 0.69 %– 26.36 ± 1.35 % and Hausner's ratio ranged from 1.17 ± 0.08 – 1.69 ± 0.85 . The angle of repose of the SR blend ranged from $29^{\circ} 66' \pm 0.03$ – $32^{\circ} 40' \pm 0.66$. The

formulated blends showed good flow property so wet granulation technique was used for preparing SR granules of Amoxicillin. The SR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The results are given in table 8.

Table 8 Precompression Study of Sustained Release Granules

Formulation	Bulk density g/cm ³	Tapped density g/cm ³	Compressibility Index (%)	Hausner's ratio	Angle of Repose
NA-1	0.27 ± 0.06	0.35 ± 0.09	22.27 ± 1.88	1.28 ± 0.67	$31^{\circ} 24' \pm 0.90$
NA -2	0.31 ± 0.01	0.38 ± 0.43	18.79 ± 0.96	1.23 ± 0.45	$31^{\circ} 21' \pm 0.39$
NA -3	0.25 ± 0.05	0.29 ± 0.42	15.02 ± 0.61	1.17 ± 0.85	$31^{\circ} 78' \pm 0.53$
NA -4	0.26 ± 0.13	0.31 ± 0.60	15.82 ± 0.69	1.18 ± 0.07	$31^{\circ} 27' \pm 0.36$
NA -5	0.27 ± 0.26	0.33 ± 0.82	16.70 ± 0.14	1.20 ± 0.08	$31^{\circ} 23' \pm 0.86$

Mean \pm S.D (n=3)

The bulk density of the SR granules ranged from 0.25 ± 0.05 – 0.31 ± 0.01 g/cm³ and the tapped density ranged from 0.29 ± 0.42 – 0.38 ± 0.43 g/cm³. The compressibility index ranged from 15.02 ± 0.61 – 22.27 ± 1.88 % and Hausner's ratio ranged from 1.17 ± 0.85 – 1.28 ± 0.67 . The angle of repose of the SR granules ranged from $31^{\circ} 21' \pm 0.39$ – $31^{\circ} 78' \pm 0.53$. The formulated SR granules showed good flow property.

Formulation Development of SR Tablet

Wet granulation technique was employed for the formulation of SR granules of Amoxicillin. Five batches of SR granules were prepared by using hydrophilic polymer HPMC K100M and hydrophobic polymer EC in varying proportions. The formulations were compressed on a 10 station tablet compression machine and the result of post compression study shown in table 9.

Table 9 Post Compression Study

Formulation	Uniformity of weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm ²)	Friability	Drug content (%w/w)
Specified limit	703-777	2.5 - 3.5	4.5 - 5.5	4-6	Not more than 1.0%	90-110%
NA-1	751.32 ± 0.79	2.92 ± 0.87	4.8 ± 0.49	4.72 ± 0.69	0.79 ± 0.26	96.22 ± 0.88
NA -2	761.38 ± 0.53	2.85 ± 0.39	4.72 ± 0.69	5.06 ± 0.56	0.82 ± 0.00	98.47 ± 0.65
NA -3	754.38 ± 0.15	2.86 ± 0.48	4.76 ± 0.19	5.12 ± 0.15	0.70 ± 0.46	97.52 ± 0.95
NA -4	754.00 ± 0.93	3.18 ± 0.20	4.74 ± 0.16	5.24 ± 0.89	0.91 ± 0.27	98.95 ± 0.24
NA -5	754.4 ± 0.92	3.12 ± 0.66	4.72 ± 0.95	5.18 ± 0.94	0.65 ± 0.98	99.30 ± 0.23

Mean \pm S.D (n=5)

The tablet complies with the test for uniformity of weight, uniform in thickness, diameter and hardness. The percentage friability of all formulations was within the acceptable limits. i.e. not less than 1%. The drug contents of all five SR formulations were found to be within the limit. i.e.

the drug content was not less than 90% and not more than 110% (as per IP: 2010)

In Vitro Dissolution Study of SR Tablets

The in vitro dissolution study of SR tablets is given in table 10 and Fig 2.

Table 10 In Vitro Dissolution Study of SR Tablets

Time (minutes)	NA-1	NA-2	NA-3	NA-4	NA-5
0	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
30	42.38 ± 0.56	41.47 ± 0.55	36.34 ± 0.94	26.42 ± 0.70	23.97 ± 0.42
60	50.55 ± 0.48	46.57 ± 0.58	41.50 ± 0.11	32.59 ± 0.72	27.37 ± 0.69
120	58.22 ± 0.32	55.56 ± 0.15	46.28 ± 0.83	39.44 ± 0.68	33.59 ± 0.53
180	67.05 ± 0.13	65.53 ± 0.33	52.28 ± 0.18	45.36 ± 0.40	39.45 ± 0.72
240	72.56 ± 0.87	71.50 ± 0.97	59.38 ± 0.89	50.45 ± 0.32	47.84 ± 0.50
300	81.24 ± 0.75	79.31 ± 0.24	68.37 ± 0.51	56.28 ± 0.84	54.10 ± 1.40
360	92.25 ± 0.21	84.58 ± 0.30	77.45 ± 0.53	62.45 ± 0.72	59.57 ± 0.60
420	96.39 ± 0.91	90.64 ± 0.51	83.28 ± 0.87	67.25 ± 0.54	67.53 ± 1.14
480	98.42 ± 0.90	97.49 ± 0.82	88.78 ± 0.22	73.28 ± 0.93	68.40 ± 0.56
540		99.51 ± 0.46	93.35 ± 0.94	79.26 ± 0.34	77.54 ± 0.34
600			99.23 ± 0.25	87.92 ± 0.23	84.78 ± 0.59
660				99.73 ± 0.83	92.34 ± 0.85
720					99.82 ± 0.95

Mean ± S.D (n=3)

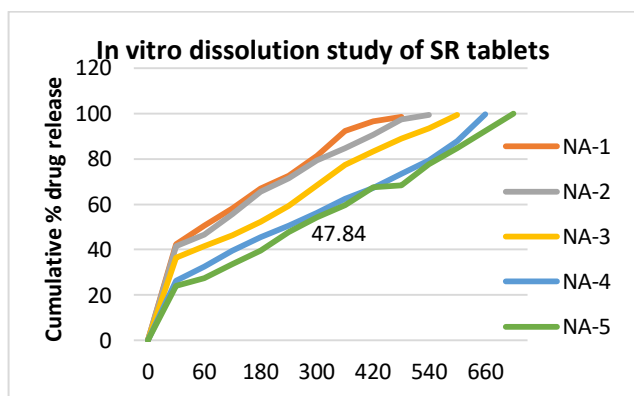


Figure 2 In vitro dissolution study of SR tablets

Based on the comparative release profile, formulation NA-5 was selected for the final bilayer tablets.

Formulation Development Preparation of Bilayer Tablets

Optimized immediate layer of Lansoprazole was prepared by wet granulation method. Optimized sustained release layer of Amoxicillin was prepared by wet granulation method. The granules were compressed on 10 station bilayer tablet compression machines and result were shown in table 11.

Table 11 Post Compression Study of Bilayer Tablets

Parameters	Bilayer tablet
Uniformity of weight (mg)	824.18 ± 0.63
Thickness (mm)	5.21 ± 0.07
Diameter (mm)	4.71 ± 0.15
Hardness (kg/cm ²)	5.02 ± 0.28
Friability (%)	0.37 ± 0.13
Drug content* (simultaneous estimation method)	
1. Lansoprazole	1. 97.46 ± 0.15
2. Amoxicillin	2. 98.25 ± 0.14

Mean ± S.D (n=5)

*Mean ± S.D (n=3)

In Vitro Dissolution Study of Lansoprazole in Bilayer Tablet

The in vitro dissolution study of drugs in bilayer tablets is given in table 6.12 and Fig 3

Table 12: The in vitro dissolution study of Lansoprazole in bilayer tablet

Time (minutes)	% Drug release
0	0 ± 0.00
10	78.27 ± 0.26
20	92.24 ± 0.12
30	97.46 ± 0.15

Mean ± S.D (n=3)

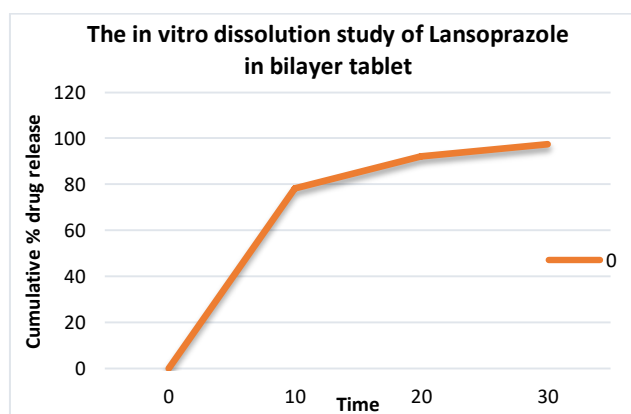
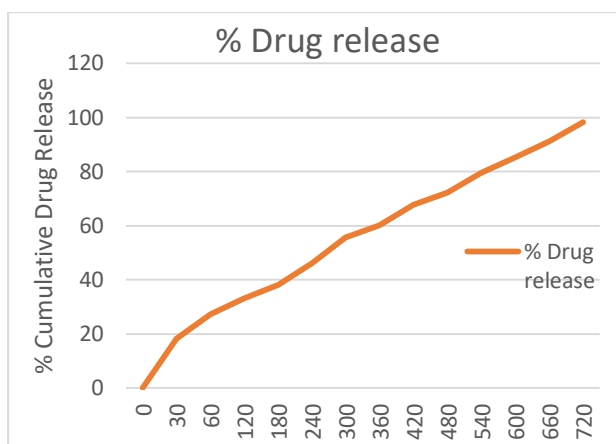


Figure 3 The in vitro dissolution study of Lansoprazole in bilayer tablet

Table 13: In Vitro Dissolution Study Of Amoxicillin In Bilayer Tablet

Time (minutes)	% Drug release
0	0 ± 0.00
30	18.32 ± 0.15
60	27.14 ± 0.91
120	33.21 ± 0.14
180	38.24 ± 0.25
240	46.27 ± 0.15
300	55.66 ± 0.48
360	60.15 ± 0.69
420	67.71 ± 0.07
480	72.16 ± 0.43
540	79.47 ± 0.31
600	85.15 ± 0.65
660	91.17 ± 0.41
720	98.25 ± 0.14

Mean ± S.D (n=3)

**Figure 4 In vitro dissolution study of Amoxicillin in bilayer tablet**

CONCLUSION

Lansoprazole potentiate the effect of Amoxicillin. Hence the bilayer tablets of Lansoprazole and Amoxicillin were used to improve patient compliance towards the effective management of ulcer. Thus, from the result, it can be concluded that the bilayer tablets containing 15 mg of Lansoprazole as immediate release component and 500 mg amoxicillin as sustained release component has successfully developed. The results of current study clearly show that bilayer tablet was developed as a stable dosage form.

Lansoprazole and amoxicillin bilayer tablet have a promising potential as an alternative to the conventional dosage form. This new dosage form has commercial marketing potency as no such delivery systems are presently available in market.

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