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FORMULATION, EVALUATION AND CHARACTERIZATION OF TOPICAL DRUG DELIVERY OF ISOTRETINOIN GEL

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ABSTRACT

In order to achieve the development of combination of immediate and extended release dosage form currently the bilayer technology with multiple layers having a rapid and extended has been investigated. This formulation can be used for treatment for bacterial infections. For the study, amoxicillin trihydrate and lansorazole is used as model drug for treatment of gastric ulcer which is formulated by using direct compression method. In the present work, bilayer tablets containing HPMC K4M and HPMC K15M in a ratio of 1:1 along with PVP K30 gave better controlled drug release and floating properties in comparison to the other formulations. Amoxicillin have gastric acid inhibitory properties and suggests its usage in peptic ulcer treatment.

Keywords: Isotretinoin, Gel, Topical Drug Delivery System, Formulation.

INTRODUCTION

Bilayer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles.

The manufacture of bi-layer tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as loading dose and second layer is maintenance dose. In case of bilayered tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity

The immediate release layer of bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time.

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This article explains why development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bilayer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be the best approach in producing a quality bilayer tablet under GMP-conditions, especially when high production output is required.

Amoxicillin is a broad-spectrum semisynthetic antibiotic similar to ampicillin except that its resistance to gastric acid permits higher serum levels with oral administration. Amoxicillin is commonly prescribed with clauvanic acid (a beta lactamase inhibitor) as it is susceptible to beta-lacatamase degradation. Lansoprazole is a proton pump inhibitor which prevents the stomach from producing acid. It is manufactured by TAP Pharmaceutical Products. Lansoprazole has been marketed for many years and is one of several PPI's available. Each of the proposed bi-layer tablets is composed of an immediate-release layer and a sustained-release layer, rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted effect. The present Investigation aimed to develop bilayer tablets of Amoxicillin and Lansoprazole.

MATERIALS AND METHODS

Drugs and Chemicals

The following materials that were procured from different sources some of which were analytical grade and best possible Laboratory Reagent were used as supplied by the manufacturer without further purification or investigation.

Characterization of Drug:

Physiochemical Properties of Amoxicillin Trihydrate and Lansoprazole

A) Organoleptic evaluation

It refers to the evaluation by sensory characters-taste, appearance, odor etc.

B) Solubility (at room temp :)

Solubility is determined in different solvents example water methanol, 0.1 N HCl, Ethyl Alcohol, and 0.1 N NaoH64.

C) Identification Test using FTIR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red region. Approx 5 mg of Amoxicillin Trihydrate and Lansoprazole was mixed with KBr and prepared their pallet. Pallet was analyse using FT-IR spectrophotometer (Bruker alpha, Germany) 65-66.

D) Loss on drying:

Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

E) Melting point:

It is one of the parameters for the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

F) Bulk properties

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all preformulation lots is necessary to avoid misleading predictions.

G) Compressibility Index

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20 to 30% is defind as the free flowing material.

It can be calculated as per given formula:

$C.I. = \frac{100\ (V0-Vf)}{}$ OR

$C.I = \frac{\text{Tapped density- Bulk density}}{\text{V0 Tapped density}}$

H) Hausner Ratio:

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density.

I) Flow properties

Flow properties determination of powder or granules is the unique tools to avoid the weight variation of tablet. Angle of repose, Carrs index, Hausner ratio are some examples of technique by which we can estimate the flow properties of powder.

J) Determination of λ_{max}

The absorption maxima of Amoxicillin Trihydrate and Lansoprazole were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

FORMULATION DEVELOPMENT OF BILAYER TABLETS

Preparation of Instant Layer of Lansoprazole (Phase-1)

Fast dissolving tablets of Lansoprazole were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of response, Bulk density, Tap density, Carr's index and Hausner's ratio.

Method for Preparation of Amoxicillin Trihydrate Floating Gastroretentive tablet55 Direct compression was followed to manufacture the gas generating floating tablets of Amoxicillin Trihydrate. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and

polymers were weighed as per given in Table No. 5 and all the formulation were used for further evaluations parameters.

Formulation Development of Bilayer Tablet

Optimized formulation IF-7 of Instant release layer and optimized formulation of F-6 for control release used for formulation of Bi-layer tablet.

Dissolution Rate Studies

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Amoxicillin Trihydrate and Lansoprazole bilayer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5 C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Labindia 3000 plus) spectrophotometer λ_{max} 238 nm and 296 nm for Amoxicillin Trihydrate and Lansoprazole respectively.

Table 1: List of Drug and Excipients Used

S. No.	Instrument	Manufacture
1.	Electronic Balance	Digital Balance Wensor
2.	FTIR	Bruker Alpha, Germany
3.	Dissolution Test Apparatus	Labindia DS 8000
4.	UV- Visible Spectrophotometer	Labindia Double Beam Spectrophotometer (3000 plus)
5.	Disintegration Test Apparatus	E.I. (Electronic India)
6.	Melting Point Apparatus	Contech Instruments Ltd., Mumbai
7.	Hardness tester	Monsanto Hardness Tester
8.	Tablet Punching Machine	10 Station punching machines

Table 2: Carr's Index Range

S. no.	% Comp. Index	Properties
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair passable
4	23-25	Poor
5	33-38	Very Poor
6	>40	Extremely poor

Table 3: Hausner ratio and flow property characteristics

S. no.	Hausner ratio	Property
1.	0.0 - 1.2	Free flowing
2.	1.2 - 1.6	Cohesive powder

Standard Value of Hausner Ratio Is 1.35.

Table 4: Composition of Lansoprazole Fast Dissolving Tablets (F1-F9) (Instant Layer).

Ingredients(mg)	Formulation Code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Lansoprazole	15	15	15	15	15	15	15	15	15
Sodium Starch Glycolate	10	20	30	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	20	30	-	-	-
Crospovidone	-	-	-	-	-	-	10	20	30
Microcrystalline Cellulose	114	104	94	114	104	94	114	104	94
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Total weight	150	150	150	150	150	150	150	150	150

Table 5: Various Formulations of Amoxicillin Trihydrate Gastro Retentive Tablets.

Excipients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Amoxicillin Trihydrate	300	300	300	300	300	300	300	300	300
HPMC K 4	50	80	110				25	40	55
HPMC K 15				50	80	110	25	40	55
PVP K30	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	10	10	10	10	10	10	10	10	10
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	65	35	5	65	35	5	65	35	5
Total Weight	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**

Table 6: Organoleptic property of Amoxicillin Trihydrate and Lansoprazole

Organoleptic property	**Amoxicillin Trihydrate**	**Lansoprazole**
Color	White crystalline powder	White to off white powder
Odor	Odorless	Odorless
Taste	Bitter	Bitter

Table 7: Solubility Studies of Amoxicillin Trihydrate and Lansoprazole in Different Solvent.

S. No.	**Solvent used**	**Amoxicillin Trihydrate**	**Lansoprazole**
1.	Water	Slightly	Soluble Sparingly
2.	0.1N HCl	Soluble	Soluble
3.	Ethanol	Slightly Soluble	Soluble
4.	Methanol	Freely	Soluble Soluble
5.	0.1N NaOH	Soluble	Slightly Soluble
6.	Chloroform	Soluble	Soluble

Figure 1: FT-IR Spectrum of Pure Drug (Amoxicillin Trihydrate)

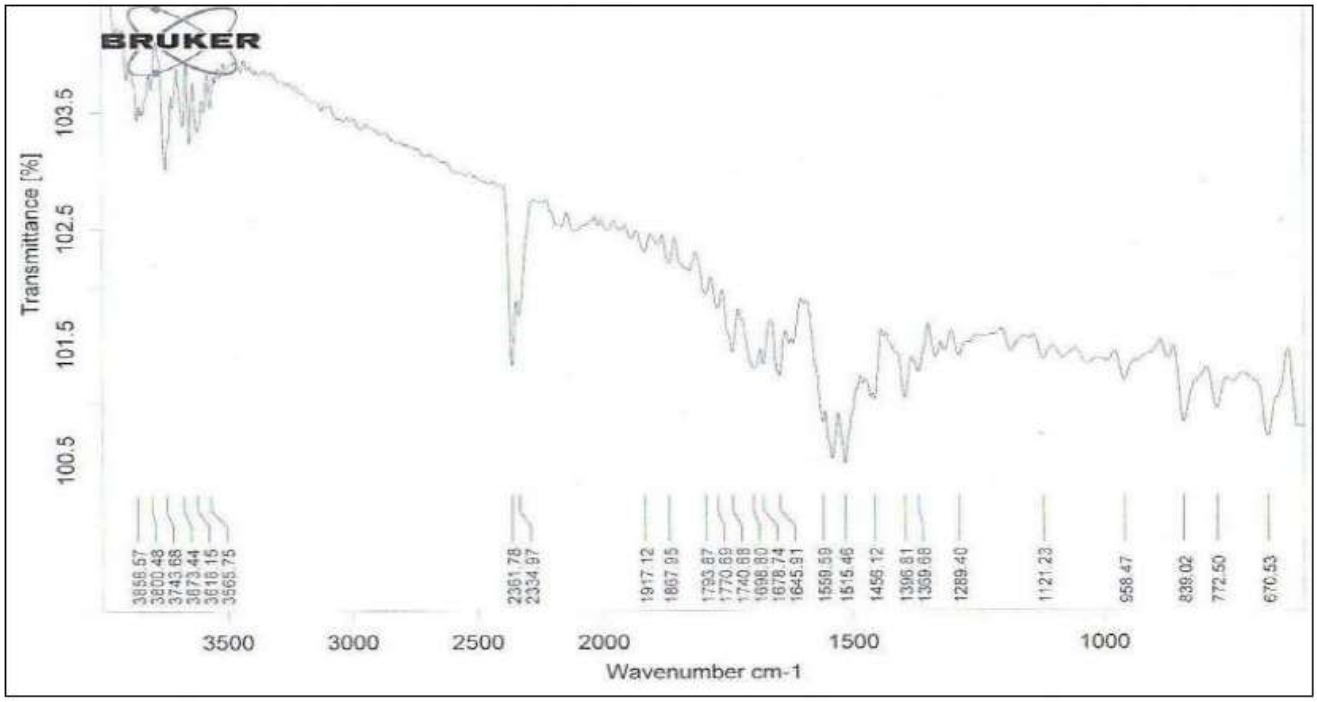


Figure 2: FT-IR Spectrum of Pure Drug (Lansoprazole).

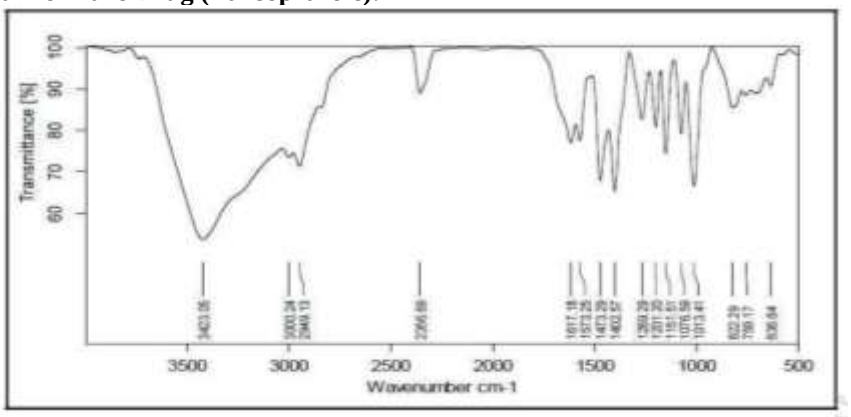


Figure 3: Determination of λmax of Amoxicillin Trihydrate in 0.1 N HCl.

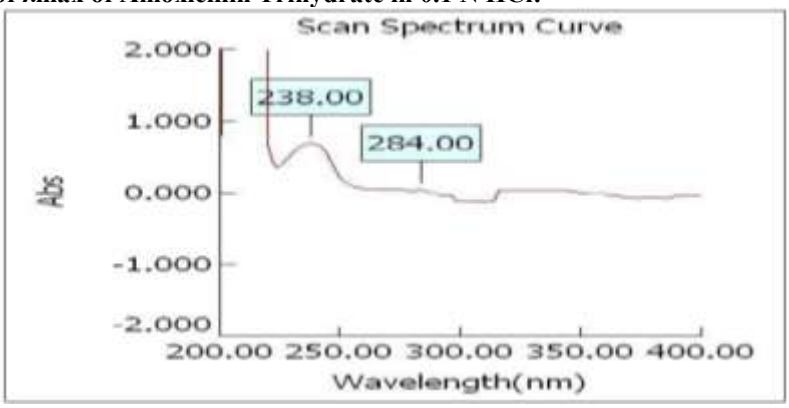


Figure 4: Determination of λmax of Lansoprazole in 0.1 N HCl

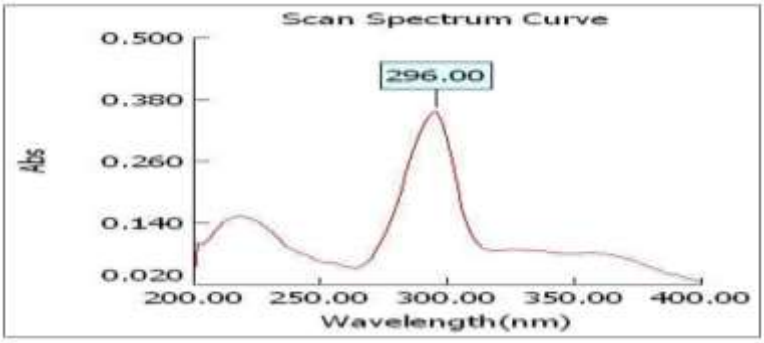
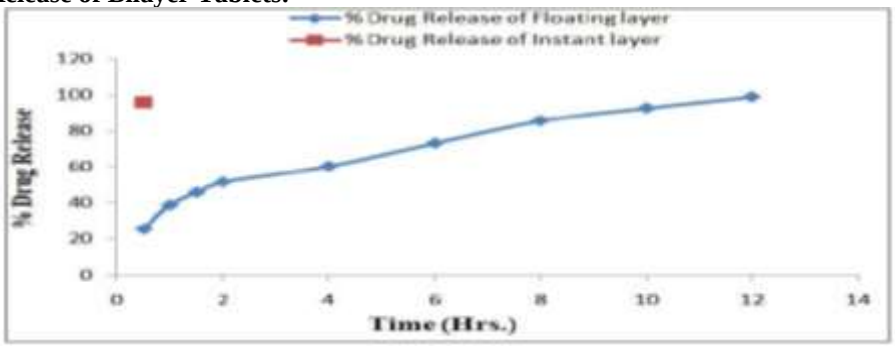


Figure 5: Graph of Release of Bilayer Tablets.



RESULTS AND DISCUSSION

Solubility

Solubility studies of Amoxicillin Trihydrate and Lansoprazole have been done in various solvent such as water, Chloroform, Ethanol, Methanol, and 0.1N HCl solution. We were found that a solubility of Amoxicillin Trihydrate and Lansoprazole is good in a Methanol solution.

Determination of λ_{max} By Uv-Visible Spectroscopy:

The λ_{max} found for Amoxicillin Trihydrate and Lansoprazole were found 238.0 nm and 296 nm.

Dissolution rate studies of Floating layer

A dissolution study shows the release of Amoxicillin Trihydrate and Lansoprazole. The Instant layer of Lansoprazole release approx 95.65±0.65percent drug within 30 minutes and control floating layer Amoxicillin Trihydrate shows release up to 12 Hours Approx. 98.96±0.12 percent of drug release in 12 hours.

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