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FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER TABLETS OF PITABASTATIN

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Abstract

The objective of the present study was to develop bi-layer tablets of Pitabastatin, a highly potent antihyperlipidemic drug with short half-life, that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products. Each of the proposed bi-layer tablets is composed of an immediate-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine. Immediate release layer prepared by using dry granulation method for immediate release of drug, roll compaction of drug with sodium citrate which act as buffering agent and create basic micro-environmental pH inside the tablets favorable to drug release in acidic conditions. Sustained release layer formulated by using HPMC as release retardant, two grades of HPMC that are HPMC K4M and HPMC K100M used to get sustained release profile for 24 hr. various trial batches are taken to get desired release profile. All the prepared bilayer tablets showed acceptable physical properties before and after storage.

Keyword: Bilayer tablets ,Antihyperlipidemic drug, Pitabastatin

Introduction

1.1 Bilayer Tablet

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. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. 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 initial dose and second layer is maintenance dose.

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. 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.

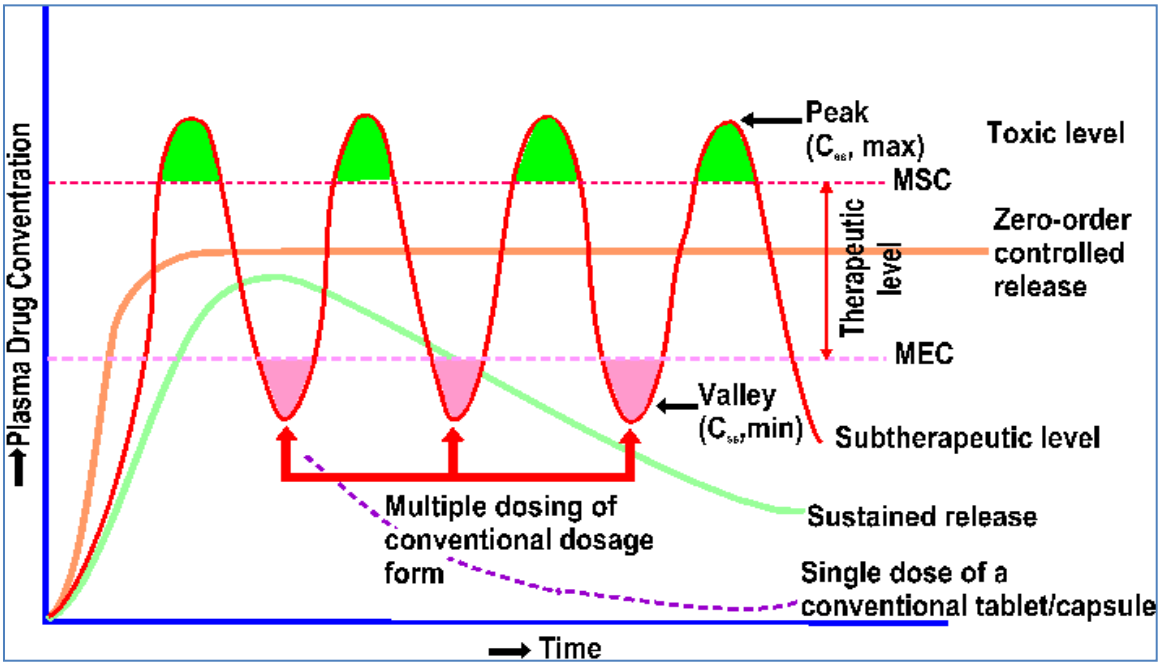

Figure 1.1: Hypothetical Plasma Concentration Vs Time ProfileAdvantages of sustained release dosage forms

1.2 Ideal characteristics of bilayer tablet

• A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.

• It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.

• It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

• It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

1.3 Objectives behind designing bilayer tablet:

1. To control the delivery rate of either single or two different active pharmaceutical ingredient.

2. To separate incompatible active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

3. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for modified release

4. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device buccal/ mucoadhesive

delivery systems and floating tablets for gastro-retentive drug delivery.

1.4 Advantages of the bilayer tablet:

• It is the dosage form and offers the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
• Cost is lower compared to all other oral dosage form.
• Lighter and compact.
• Easiest and cheapest to pack and strip.
• Easy to swallow with least tendency for hangup.
• Objectionable odour and bitter taste can be masked by coating technique.
• Suitable for large scale production.
• Greatest chemical and microbial stability over all oral dosage form.
• Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
• Bilayer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
• Patient convenience is improved because fewer daily doses are required compared to traditional delivery systems.
• Patient compliance is enhanced leading to improved drug regimen efficacy.

1.5 Disadvantages of bilayer tablet:

Difficult to swallow in case of children and unconscious patients.
• Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
• Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
• Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

1.6 Mechanism of drug release from matrix

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than thediffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release.

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;

c) The bathing solution provides sink conditions at all times. The release behavior for the system can be mathematically described by the following equation:

$DM/Dh = C_O . Dh\text{-}C_S$/Where,

DM = change in the amount of drug released per unit area

Dh = change in the thickness of the zone of matrix that has been depleted of drugC_O = total amount of drug in a unit volume of matrix

C_S = saturated concentration of the drug within the matrix.

2. Preparation and characterization

2.1 Formulation Development

2.2.1 Preparation of Instant Layer of Pitavastatin (Phase-1)

Fast dissolving tablets of Pitavastatin 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 repose, Bulk density, Tap density, Carr's index and Hausner's ratio. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine formulations of **Pitavastatin** granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 100mg, were obtained. Composition of tablets is mentioned in Table 2.1.

Table 2.1: Composition of Pitavastatin Fast Dissolving Tablets Pitavastatin

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Pitavastatin	50	50	50	50	50	50	50	50	50
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	25	20	15	25	20	15	25	20	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100	100

2.2.2 Evaluation of Precompression Parameter

Table 2.2: Results of pre-compressional parameters of Tablets Pitavastatin

Formulation code	Parameters			
	Loose Bulk density (gm/ml)	Tapped bulk density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.421	0.531	20.674	1.259
F2	0.426	0.537	20.559	1.257
F3	0.434	0.538	19.401	1.243
F4	0.424	0.533	20.415	1.258
F5	0.432	0.539	19.890	1.249
F6	0.438	0.535	18.659	1.231
F7	0.433	0.531	18.799	1.233
F8	0.437	0.533	18.042	1.221
F9	0.431	0.535	19.401	1.243

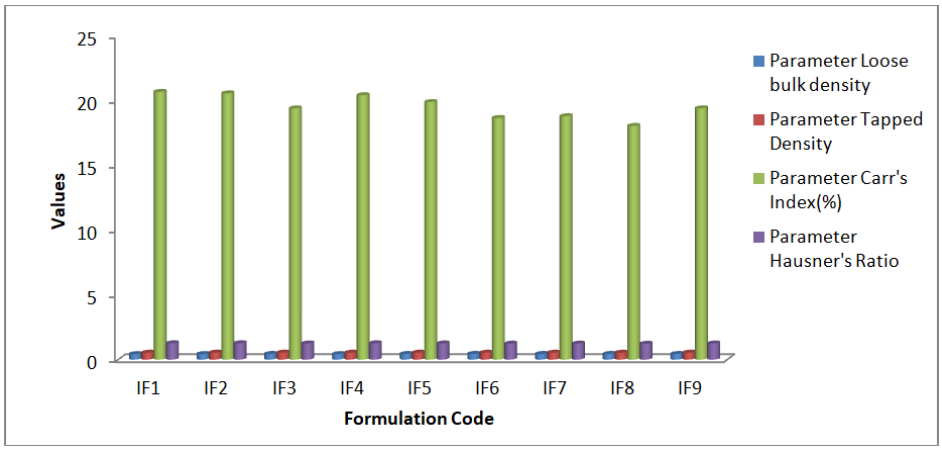

Figure 2.1: Graphical representation of Results of pre-compressional parameters of Pitavastatin

2.2.3 Evaluation of post compression Parameter

Table 2.3: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.1	0.490	153	2.31	99.49
IF2	3.2	0.497	151	2.43	98.82
IF3	3.1	0.760	152	2.37	99.42
IF4	3.5	0.661	148	2.32	98.92
IF5	3.5	0.696	147	2.36	99.81
IF6	3.7	0.460	153	2.33	98.93
IF7	3.3	0.563	144	2.23	99.96
IF8	3.2	0.475	140	2.26	99.71
IF9	3.5	0.659	150	2.30	99.63

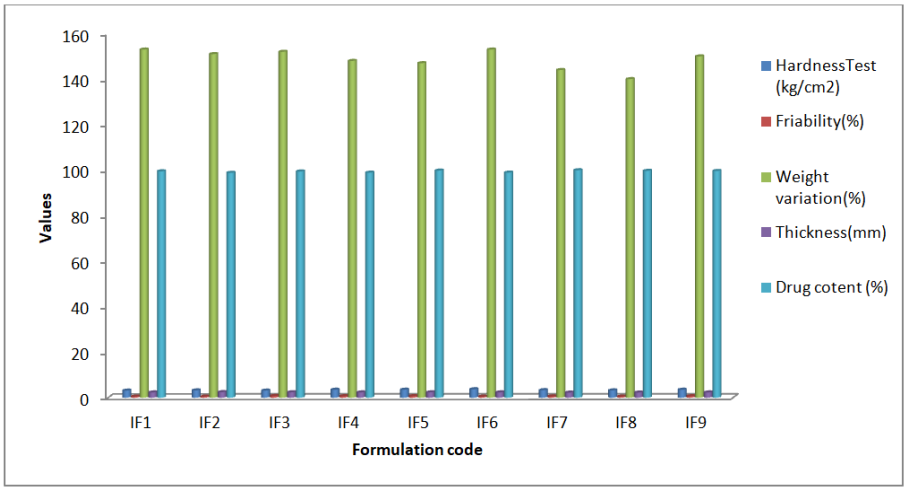

Figure 2.2: Graphical Representation of Post-Compression parameters of all formulations

Table 2.4: Results of post-compressional parameters of all formulations

Formulation code	Disintegration Time (sec.) (n=3) Mean ± SD
IF1	108±3
IF2	98±4
IF3	85±5
IF4	113±6
IF5	102±5
IF6	96±6
IF7	101±4
IF8	78±3
IF9	97±2

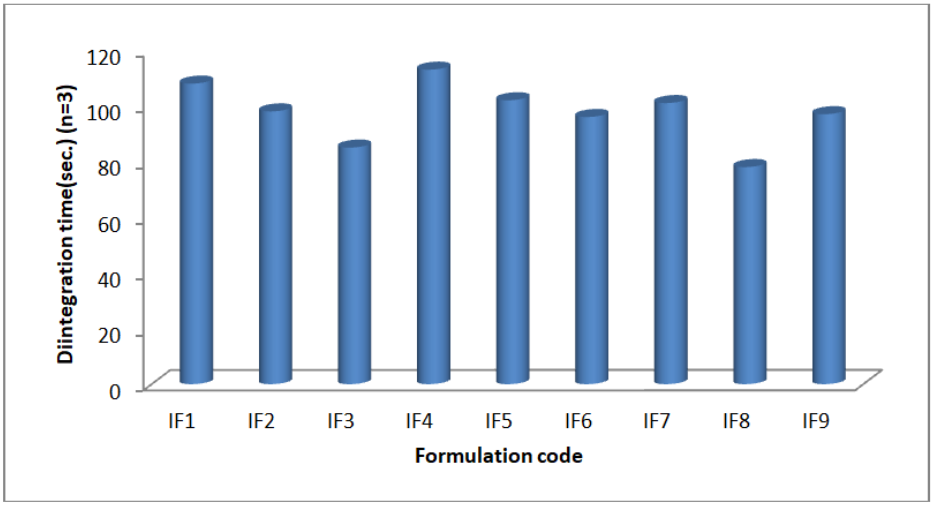

Figure 2.3: Graphical Representation of Disintegration Time

2.3 Method for Preparation of Pitavastatin tablets

Direct compression was followed to manufacture the floating tablets of Pitavastatin. Eight 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. 2.5 and all the formulation were used for further evaluations parameters.

Polymers selected for tablets are:

- Xanthan gum,
- Gaur gum,
- Karaya gum

2.5 Optimization of tablets of Pitavastatin

Table 2.5: various formulations of control release Pitavastatin tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pitavastatin	150	150	150	150	150	150	150	150	150
Xanthan gum	90	120	-	-	-	-	30	40	40
Gaur gum	-	-	90	120	-	-	30	40	40
Karaya gum	-	-	-	-	90	120	30	40	40
PVP K30	15	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Lactose	80	50	80	50	80	50	80	50	80
Total Weight	350	350	350	350	350	350	350	350	350

Table 2.6: Result of Pre-Compression Properties of control release Pitavastatin Tablets

Formulation code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.491	0.582	16.381	1.191
F2	0.487	0.586	16.929	1.202
F3	0.481	0.588	17.751	1.221
F4	0.479	0.589	18.712	1.238
F5	0.480	0.582	17.361	1.218
F6	0.483	0.581	17.334	1.218
F7	0.484	0.584	17.381	1.214
F8	0.487	0.585	16.796	1.205
F9	0.486	0.586	16.792	1.209

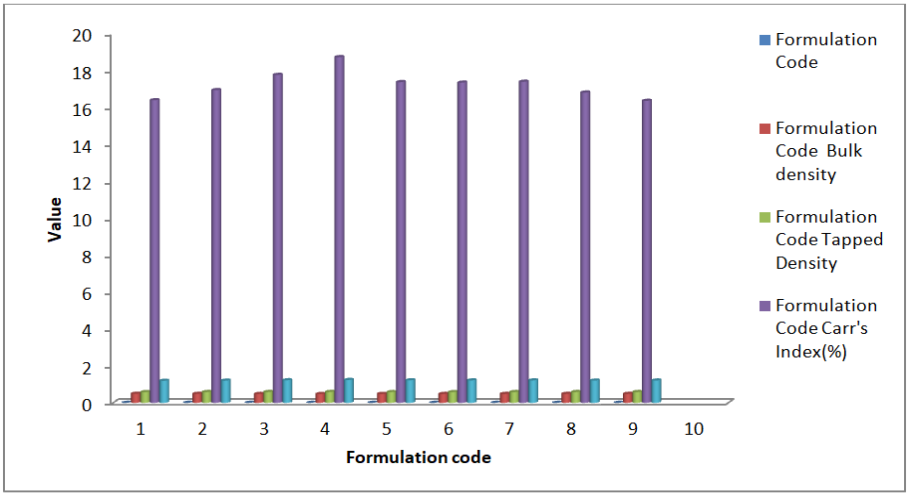

Figure 2.4: Graphical Representation of Pre-Compression Properties of Pitavastatin Tablets

2.4 Evaluation of tablets:

All the tablets were evaluated for following different parameters which includes;

Table 2.7: Results of Post Compression Properties of control release Pitavastatin Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability	Drug content (%)
F1	3.6	5.4	496	0.861	98.99
F2	3.5	5.2	492	0.662	99.88
F3	3.6	5.3	499	0.481	98.93
F4	3.8	5.6	505	0.556	99.51
F5	3.7	5.7	507	0.658	99.34
F6	3.3	5.3	506	0.857	99.59
F7	3.5	5.4	501	0.657	99.38
F8	3.4	5.5	504	0.759	99.17
F9	3.7	5.6	502	0.692	99.21

2.4.1 Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºc and rpm of 75. One Pitavastatin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 264nm using spectroscopy.

2.4.2 *In vitro* drug release study of Gastro retentive tablet

Table 2.8 *In-vitro* Drug Release Study of Tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	55.56	45.54	43.23	40.23	38.89	35.56	33.21	30.12	25.65
1	75.56	58.89	55.56	52.32	45.65	42.23	40.23	38.89	30.12
1.5	85.56	88.89	80.25	75.65	68.89	65.65	60.32	55.65	45.58
2	99.89	98.29	89.98	85.65	78.38	73.25	71.12	65.65	55.87
3	-	-	98.89	92.25	85.56	80.32	78.89	70.23	64.85
4	-	-	-	98.65	90.23	86.69	82.23	78.32	70.45
6	-	-	-	-	99.52	92.23	89.98	85.56	82.23
8	-	-	-	-	-	99.85	95.59	90.23	89.98
12	-	-	-	-	-	-	99.12	93.32	90.12

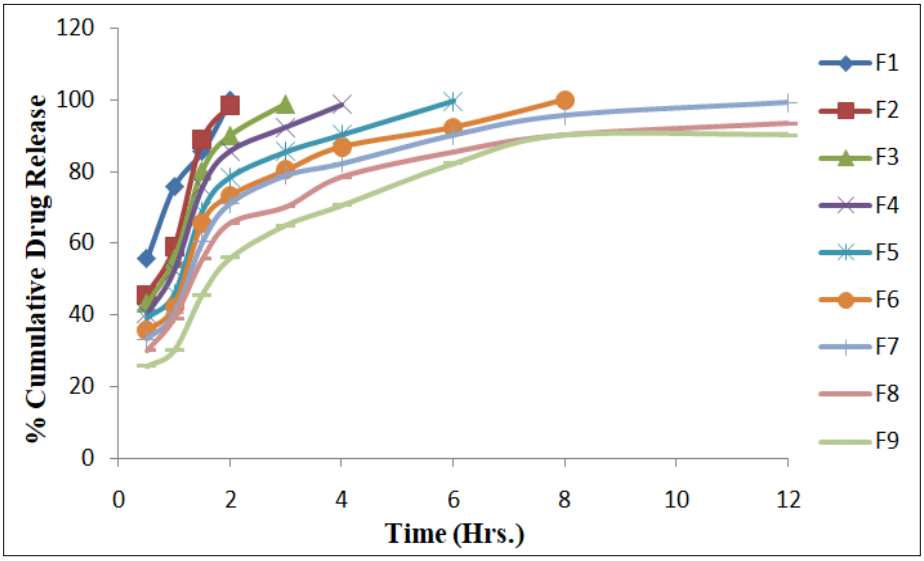

Figure 2.5: Graph of *In-vitro* Drug Release Study of control layer

2.5 Formulation development of bilayer tablet

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

2.5.1 Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

1. General Appearance Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

2. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

3. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

4. Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

5. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

6. Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 5mg of Pitavastatin was transferred to 10ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCL and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10 ml suitably 10 ppm solutions and determines the Conc. of drug at 264nm.

7. 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 Pitavastatin 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 at λmax 264nm.

2.5.2 Evaluation of bilayer tablets

Table 2.9 Post-Compressional Parameters of Optimized Formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.4±0.1	0.859	Passes	5.32

2.6. Drug content

Table 2.10 Results of Drug content analysis

Formulation	Pitavastatin (% Label Claim)
In-house Bilayer tablet	99.12

2.7. Dissolution rate studies of Instant layer

Table 2.11 Results of Dissolution rate studies of Instant layer

Time (min)	% Drug Release of Instant layer
15	98.92±1.65

2.8. Dissolution rate studies of bilayer tablets

Table 2.12 Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release
0.5	35.25±0.58
1	44.25±0.45
1.5	57.65±1.25
2	68.98±1.22
4	80.89±1.45
6	82.25±1.21
8	87.65±0.85
10	93.56±0.32
12	98.92±0.45

Graph of Release of Bilayer tablets

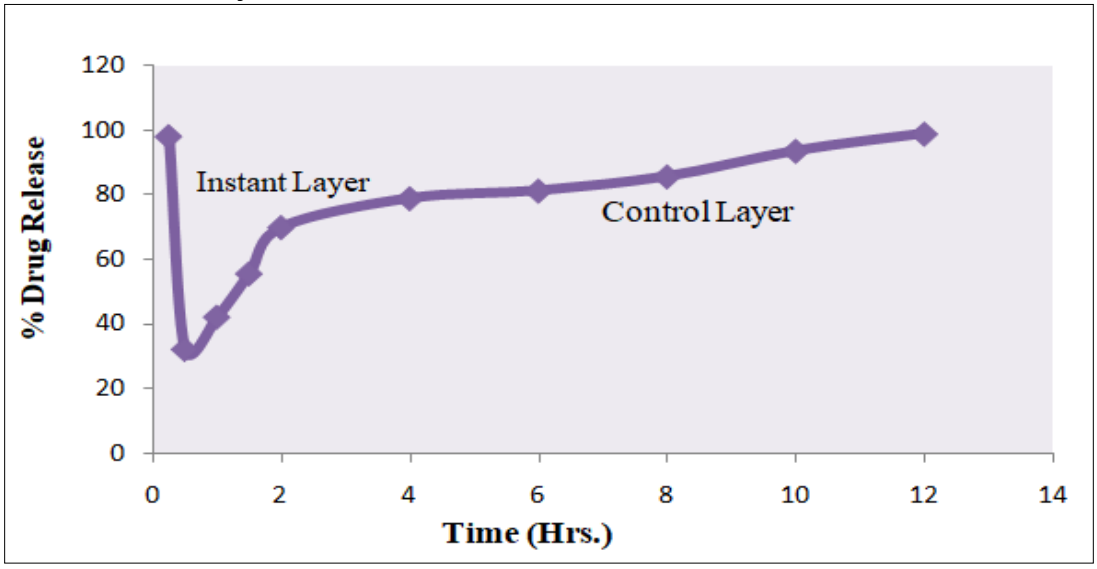

Figure 2.6: Graph of Release of Bilayer tablets

A dissolution study shows the release of Pitavastatin The Instant layer of Pitavastatin release approx 98.92±1.65 percent drug within 15 minutes and control floating layer Pitavastatin shows release up to 12 Hours Approx 98.92±0.45percent of Drug release in 12 hours.

Conclusion

The preliminary study showed that Pitavastatin is White to off white powder and Odorless powder. It is freely soluble in methanol and ethanol, soluble in 0.1 N HCl, sparingly soluble in 0.1 N NaOH, The melting point was in the range of 191^{o}C which is compliance with the standard value. Identification of Pitavastatin was performed by UV/VIS Spectroscopy. The 10 µg/ml solutions of Pitavastatin was scanned in the range of 200-400nm to determine the λ_{max} for drug. The λ_{max} of sofosbuvir was found to be 264nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25µg/ml Sofosbuvir was prepared and scanned in UV region. Their absorbances were noted at 264.0 nm and calibration curve was plotted as absorbance vs concentration and their linearity range was determined. From the FT-IR data of the physical mixture obviously functionalities of drug have stayed unaltered including forces of the peak. This proposes amid the procedure drug and excipient has not responded with the drug to offer ascent to reactant items. So there is no interaction between them which is in favor to proceed for formulation of vesicular drug delivery system. Preformulation studies reported that the formulation of floating of Pitavastatin can be prepared with appropriate methods. A study involving preparation and evaluation of bilayer tablets of Pitavastatin were made. Physicochemical parameters of bilayer tablets were performed using natural polymers. *In vitro* drug release profiles of bilayer tablets were performed. A dissolution study shows the release of Pitavastatin. The Instant layer of Pitavastatin release approx 98.92±1.65percent drug within 15 minutes and control floating layer Pitavastatin shows release up to 12 Hours Approx 98.92±0.45percent of Drug release in 12 hours.

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