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Preparation and Stability Studies of Sitagliptin Phosphate and Simvastatin Bilayered Tablets

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A B S T R A C T

The aim of the present work was to develop a novel and elegant pharmaceutica; combinational dosage form for simultaneous treatment of many patients with Type 2 diabetes with at high risk for coronary artery disease and associated co- morbidities. In general the work deals with the combine formulation and evaluation of bilayered tablets of DDP-4 inhibitor i.e., sitagliptin phosphate and HMG-CoA reductase i.e. simvastatin. Ten formulations of sitagliptin phosphate and simvastatin bilayered tablets were prepared by varying the ratios of polymers in the sitagliptin phosphate layer and simvastatin layer F1 to F10 by direct compression method. FTIR studies revealed there is no interaction between the drugs i.e. sitagliptin phosphate and simvastatin and the polymers such as pregelatinised starch, potato starch and sodium starch glycolate. All the powdered blends of formulations were evaluated for pre- compression parameters for flow properties such as angle of repose, tapped density, compressibility index and post compression parameters such as thickness, weight variation, friability, hardness, drug content, *In-vitro* disintegration time and dissolution studies. The physical appearance was good and elegant. The weight variation, friability and hardness of tablets were found to be within USP limits. *In-vitro* drug release for sitagliptin phosphate and simvastatin of all formulations of F1 to F10 was carried out in phosphate buffer pH 6.8 dissolution media. Among all the formulations F7 was optimised as best formulation. F7 formulation showed (97.23%) for sitaglipti phosphate and simvastatin (98.32%) maximum drug release drug release at the end of 45 minutes.

Keywords: Stability Studies, Sitagliptin Phosphate, Simvastatin, Bilayered

A R T I C L E I N F O

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1. Introduction

The objective of the present work is to formulate and evaluate a sitagliptin phosphate and simvastatin bilayered tablets. Currently sitagliptin phosphate is available as a separate tablet for the treatment of type 2 diabetes. Simvastatin is also currently available as a separate tablet for the treatment of hypercholesterolemia. This work provides a pharmaceutical composition comprising sitagliptin and simvastatin in a single bilayer tablet for superior efficacy, stability, patient convenience and compliance for the treatment of type 2 diabetes and hypercholesterolemia [1]. Hence a unique method of attempt has made to design and evaluate the bilayered tablets of sitagliptin phosphate and simvastatin by using the different polymers with respected ratios and super disintegrants to pretend the advantages such as convenient dosage, Fast disintegration, Rapid release, Improved patient compliance, Optimum versatility with low manufacturing cost.

The formulations were prepared by direct compression method. Bilayer tablets [2] contain two layers i.e. immediate release layer of sitagliptin phosphate and release layer of simvastatin (64.2/20mg) the compositions were typically done by using sodium starch glycolate in sitagliptin layer and various polymers like PVP, pregelatinised starch, potato starch, and acacia in simvastatin layer[3]. The compatibility parameters, compression parameters and *In-vivo* parameters were performed with in pharmaceutical expectable appropriate limits.

2. Materials and Methods

Sitagliptin Phosphate obtained from MSN Formulations Division, Pashamylaram, Simvastatin obtained from Mylan Pharmaceuticals, Hyderabad, Potato Starch obtained from LOBA Chemie, Thane, Pregelatinised Starch obtained from Aurbindo Pharmaceuticals Ltd, Hyderabad.

Methodology

Calibration curve of sitagliptin phosphate in pH 6.8 phosphate buffer

A spectrophotometric method based on the measurement of absorbance at 210 nm in PH 6.8 phosphate buffer was used in the present study for the estimation of sitagliptin phosphate.

Preparation of phosphate buffer pH 6.8

Dissolve 6.8045 g of potassium dihydrogen phosphate and 112 g of sodium hydroxide in volumetric flask and add sufficient water to produce 1000mL.

Preparation of stock solution of sitagliptin phosphate

Weighed accurately 10 mg of Sitagliptin phosphate and added into a 10ml volumetric flask and dissolved in 10 mL of methanol to get 1000µg/mL

Determination of λ max of sitagliptin phosphate in pH 6.8 phosphate buffer

From the stock 1 mL was taken and diluted to 100 mL with pH 6.8 phosphate buffer. Spectrum of this solution was seen from 200-400 nm range on UV-Visible spectrophotometer for determination of λ max. And the λ max was found to be 210 nm[4].

Procedure for construction of calibration curve

1. From the above mentioned stock solution subsequent dilutions were made with pH 6.8 phosphate buffer to obtain the series of dilutions containing 2, 4, 6, 8, 10, 12, 14, 15 and 16 µg/mL of solution.
2. The absorbance of the above dilutions was measured at 210 nm by using the UV-Spectrophotometer using pH 6.8 phosphate buffer as the blank.
3. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

Calibration curve of simvastatin in pH 6.8 phosphate buffer: A spectrophotometric method based on the measurement of absorbance at 238.5 nm in PH 6.8 phosphate buffer was used in the present study for the estimation of simvastatin.

Preparation of phosphate buffer pH 6.8

Dissolve 6.8045 g of potassium dihydrogen phosphate and 112 g of sodium hydroxide in volumetric flask and add sufficient water to produce 1000mL [5].

Preparation of stock solution of simvastatin

Weighed accurately 10 mg of simvastatin and added into a 10ml volumetric flask and dissolved in 10 mL of methanol to get 1000µg/mL

Determination of λ max of in simvastatin pH 6.8 phosphate buffer: From the stock 1 mL was taken and diluted to 100 mL with pH 6.8 phosphate buffer. Spectrum of this solution was seen from 200-400 nm range on UV-Visible spectrophotometer for determination of λ max. And the λ max was found to be 238.5 nm.

Procedure for construction of calibration curve

1. From the above mentioned stock solution subsequent dilutions were made with pH 6.8 phosphate buffer to obtain the series of dilutions containing 2, 4, 6, 8, 10, 12, 14 and 15 µg/mL of solution.
2. The absorbance of the above dilutions was measured at 238.5 nm by using the UV-Spectrophotometer using pH 6.8 phosphate buffer as the blank.
3. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

Evaluation of Powdered Blends[6 to 9]

Loose Bulk Density

The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Density = Mass/Volume

Tapped Density

Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (200) then the tapped density was determined by the following formula

Density = Mass/Tapped Volume

Percentage Compressibility (or) Carr's index (%)

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

Hausner's Ratio

It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner's ratio = Tapped density/Bulk density

Angle of Repose

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose [15] was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Tan θ = h/r

$\theta = \tan^{-1}(h/r)$

Where, h = height; r = radius

Formulation

Bilayered tablets of sitagliptin phosphate and simvastatin mixtures were prepared distinctly with there respected excipients in an appropriate ratios which are mentioned in the Table1. The tablets were compressed by direct compression technique by tablet compression machine.

Evaluation of Bilayer Tablets

Physical Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

Thickness

Thickness of the tablets was calculated by the use of Vernier callipers. The tablets exhibited uniform thickness among the different formulations.

Weight variation test

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean) [10 to 13]. The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method: Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than 5% for 324 mg tablets. No tablet must differ by more than double the relevant percentage.

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method

A number of 10 tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test [12,13,14] is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test, W_2 = Weight of tablets after test

Hardness

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Determination of Drug content:

Twenty tablets were taken and powdered. The quantity of powder equivalent to 400 mg of sitagliptin phosphate and simvastatin was dissolved in 100 mL of volumetric flask containing 3 mL of methanol and was shaken for 5 min in mechanical shaker. After shaking volume was adjusted to 100mL with pH 6.8 phosphate buffer and sonicated for 5 min. This sonicated solution was filtered through 0.45µm membrane filter.1mL of the above solution was diluted to 100 mL with pH 6.8 phosphate buffer and sonicated for 5 min. The absorbance was measured at 210 nm and at 238.5 nm using UV-Visible spectrophotometer.

In vitro dissolution studies of bilayer tablets

Dissolution parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	pH 6.8 phosphate buffer
RPM	--	100
Sampling intervals (min)	--	5, 10, 15, 20, 30, 4
Temperature	--	37 + 0.5°C

Dissolution Study procedure

900 mL 0f pH 6.8 phosphate buffer was placed in the vessel of USP type - II dissolution apparatus. The medium was allowed to equilibrate to temp of 37 $\pm$ 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 45 minutes at 100 rpm. At definite time intervals, 5 mL of the fluid was withdrawn; filtered and again 5 mL of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 210 nm for sitagliptin phosphate and 238.5 nm for simvastatin. The cumulative percentage of drug release of all the bilayered formulations were determined by simultaneous equation method as follows

Simultaneous equation method or Vierodt's method

If a sample contains two absorbing drugs (X and Y) each of which absorbs at the λmax different from the other, it may be possible to determine both drugs by the technique of simultaneous equations (Vierodt's method), provided certain criterias apply. The information required is (a) The aborptivities of X at and λ1 and λ2 are ax1 and ax2 respectively (b) The aborptivities of Y at and λ1 and λ2 are ay1 and ay2 respectively. (c) The absorbances of the diluted sample at λ1 and λ2 are A1 and A2 respectively. Let Cx and Cy be the concentrations of X and Y respectively in the diluted sample.

Two equations are constructed based upon the fact that at λ1 and λ2, the absorbance of the mixture is the sum of the individual absorbance of X and Y.

At λ1

$A_1 = a_{X1}\, b\, Cx + a_{Y1} bCy$---------- (1)

At λ2

$A_2 = a_{X2}\, b\, Cx + a_{Y2} bCy$---------- (2)

For measurements in 1 cm cells b=1

Rearrange eq. (2)

$Cy = A_2 - a_{X2}\, b\, Cx / a_{Y2}$

Cx = A2 aY1 - A1 aY2/ a X2 aY1 - a X1 aY2 ----------(3)

Cy = A1 a X2 – A2 a X1/ a X2 aY1 - a X1aY2----------(4)

As an exercise one needs to drive modified equation containing a symbol b for path length for application in situations where A1and A2 are measured in cells other than 1 cm path length. Criteria for obtaining maximum precision based upon absorbance ratios have been suggested that place limits on the relative concentration of the components of the mixture4. The criteria are that the ratios should lie outside the range 0.1-2.0 for the precise determination of X and Y respectively.

(A2/A1)/ax2/ax1

(A2/A1)/ax2/ax1

These criteria are satisfied only when the λ max of two component are reasonably dissimilar. An additional criterion is that the two components don't interact chemically thereby negating the initial assumption that the total absorbance is the sum of individual absorbance's. The additiviy of the absorbance should always be confirmed in the development of a new application of these techniques [14-15].

Release kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix two systems. As a model-dependent approach, the dissolution data was fitted to two popular release models such as zero-order, first-order equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The results are given in Table 12.

Zero order release kinetics

It defines a linear relationship between the fractions of drug released versus time.

$$Q = k_o t$$

Where,

Q is the fraction of drug released at time t and k_o is the zero order release [4,5,6] rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics [7,8,9] is:

$$\ln (1-Q) = - K_1 t$$

Where,

Q is the fraction of drug released at time t and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

3. Results and Discussion

Drug and excipient compatibility by FTIR studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug and excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

Procedure for FTIR Studies:

The FTIR spectra [10,11] of samples of sitagliptin phosphate, simvastatin and physical mixture of simvastatin and pregelatinized starch, simvastatin and potato starch, simvastatin and sitagliptin phosphate, sitagliptin phosphate and sodium starch glycolate were recorded by using FTIR. Spectra between 4000 and 400 cm-1 of the drug, the aforementioned polymers and for physical mixtures of drug & polymers were recorded using FTIR spectrophotometer (Bruker, ATR. version 1.2.4) by using KBr pellet sampling technique.

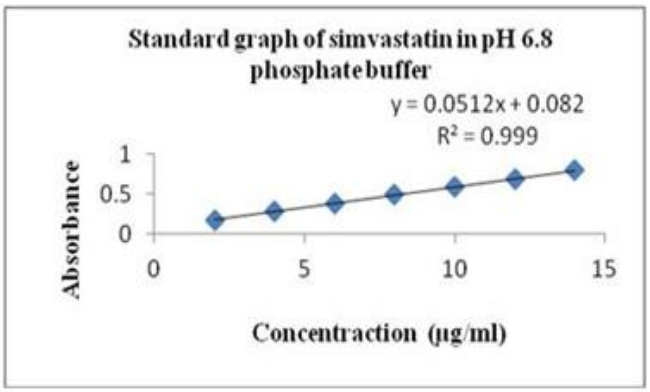

Figure 1: Standard graph of sitagliptin phosphate in pH 6.8 phosphate buffer at 210 nm.

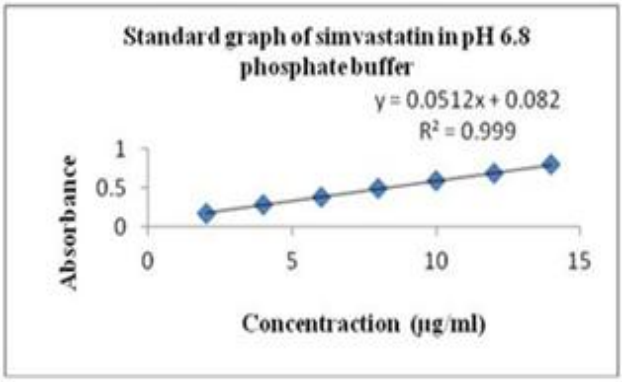

Figure 2: Standard graph of in simvastatin pH 6.8 phosphate buffer at 238.5 nm.

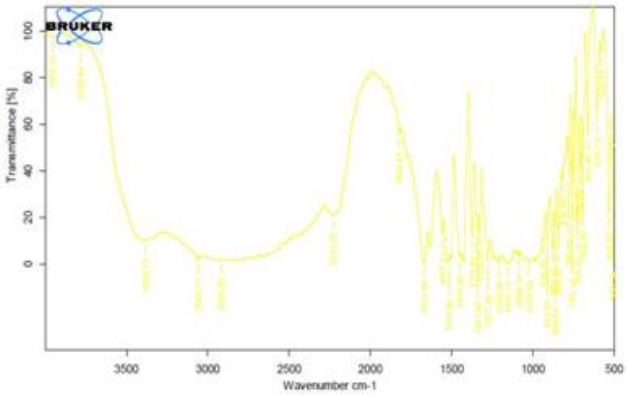

Fig.3: FTIR graph of sitagliptin phosphate

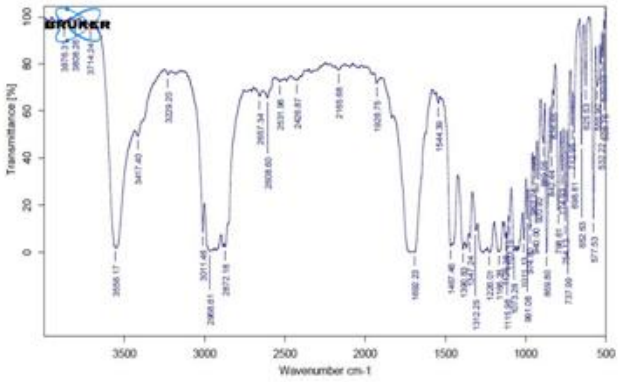

Fig.4: FTIR graph of simvastatin

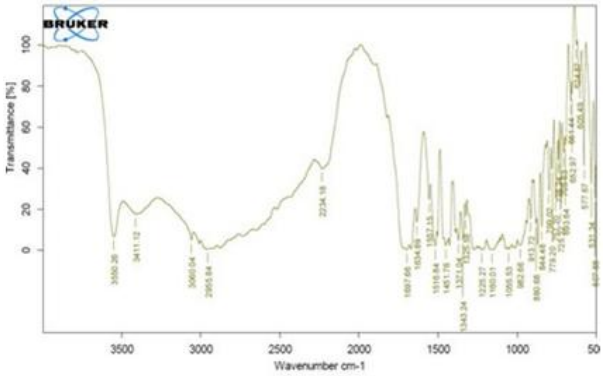

Fig.5: FTIR graph of sitagliptin phosphate and simvastatin.

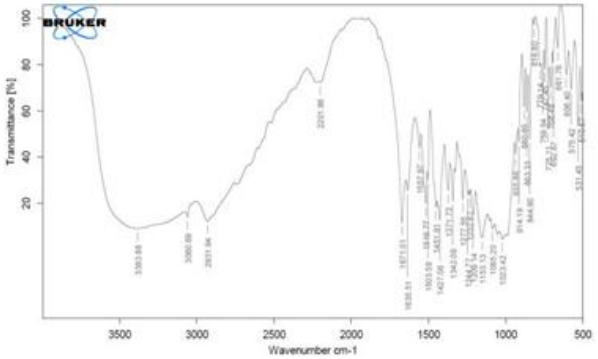

Fig.6: FTIR graph of sitagliptin phosphate and sodium starch glycolate

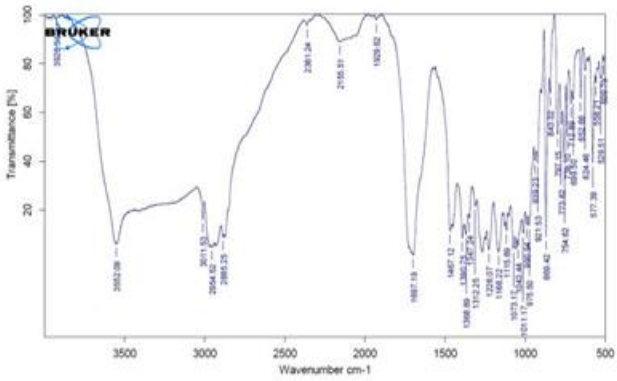

Fig.7: FTIR graph of simvastatin and pregelatinised starch

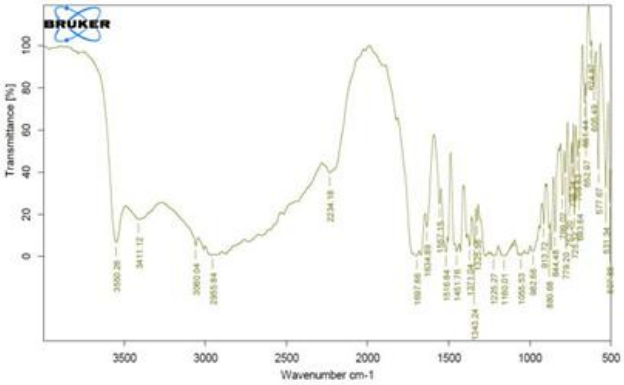

Fig.8: FTIR graph of simvastatin and starch potato.

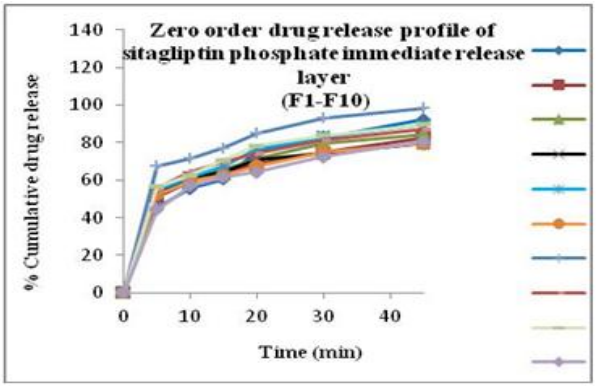

Fig. 9: Zero order drug release profile of sitagliptin phosphate immediate release layer (F1-F10).

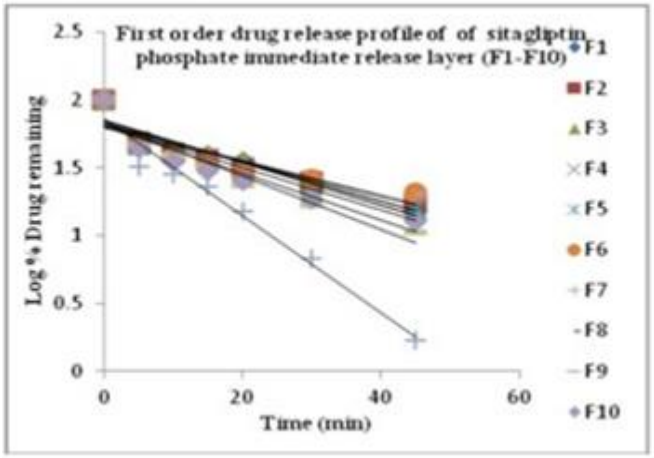

Fig.10: First order drug release profile of sitagliptin phosphate immediate release layer (F1-F10).

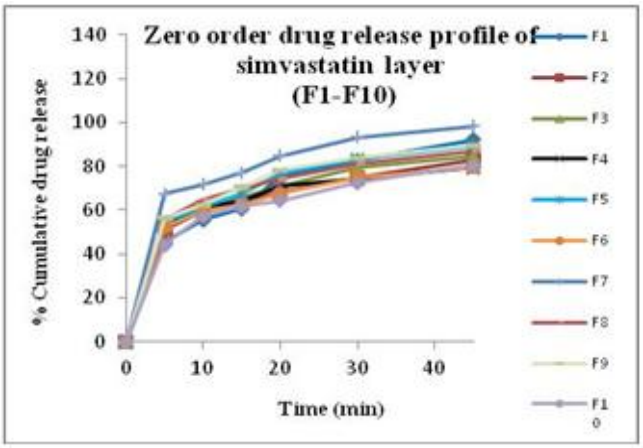

Fig. 11: Zero order drug release profile of simvastatin layer (F1-F10).

4. Conclusion

Bilayered tablets of sitagliptin phosphate and simvastatin were prepared by direct compression method by using polymers sodium starch glycolate, potato starch, pregelatinised starch, acacia, PVP for rapid drug delivery into the systemic circulation. Sodium starch glycolate is used as disintegrant for immediate release of sitagliptin phosphate and binders are used in simvastatin layer for the pyloric release. The absorption maxima of the sitagliptin phosphate in pH 6.8 phosphate buffer was found to 210 nm and for simvastatin was found to be 238.5 nm. The percentage of drug release of both drugs was estimated by simultaneous equation method by using UV spectroscopy. FTIR studies were performed for best optimized formulation F7 and percentage of drug release was found to be (97.23%) for sitagliptin phosphate and simvastatin (98.32%) maximum drug release at the end of 45 mins. Therefore it is concluded that the combination of an anti-diabetic agent and a cholesterol synthesis inhibitor into a single tablet provides a potential means of delivering combination therapy without adding to the complexity of patient's daily regimens. As the future of developing era depending upon on the multiple usage of medications upon the complexity of the pathophysiology of diseased conditions bilayered tablet formulations may gain an importance for combinational therapy of different drugs into a unit dosage form with efficacy and more of scientific research work can be contributed for the further development in the particular area of pharmaceutical drug delivery system.

Table 1: Formulations of Sitagliptin Phosphate and Simvastatin Bilayer Tablet.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Sitagliptin phosphate	64.26	64.26	64.26	64.26	64.26	64.26	64.26	64.26	64.26	64.26
Sodium starch glycolate	4	4	4	4	4	4	4	4	4	4
Dibasic calcium phosphate	103.8	103.8	103.8	103.8	103.8	103.8	103.8	103.8	103.8	103.8
MCC	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	8	8	8	8	8	8	8	8	8	8
Simvastatin	20	20	20	20	20	20	20	20	20	20
Lactose	141.5	141.5	141.5	141.5	141.5	141.5	141.5	141.5	141.5	141.5
Micro crystalline cellulose	10	10	10	10	10	10	10	10	10	10
Butylated hydroxyanisole	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Ascorbic acid	5	5	5	5	5	5	5	5	5	5
Citric acid	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Acacia	_	_	20	_	_	10	_	_	10	10
Pregelatinised starch	_	_	_	20	10	_	10	_	10	_

Starch potato	_	20	_	_	_	_	10	10	_	10
PVP K 30	20	_	_	_	10	10	_	10	_	_
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Total (mg)	400	400	400	400	400	400	400	400	400	400

Table 2: USP limits for Tablet Weight variation test.

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

Table 3: Mechanism of drug release

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

Table 4: Flow properties of lubricated powder of simvastatin layer.

Formulation code	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
	(Mean ± s.d; n=3)				
simvastatin	0.47±0.02	0.65±0.04	27.69±0.43	1.38±0.13	46.78±0.14
F1	0.32±0.02	0.41±0.01	21.95±0.56	1.28±0.23	37.46±0.24
F2	0.36±0.07	0.43±0.04	16.27±0.24	1.19±0.17	36.98±0.29
F3	0.34±0.01	0.44±0.04	22.72±0.21	1.29±0.41	41.65±0.17
F4	0.31±0.05	0.39±0.02	20.51±0.35	1.25±0.35	36.87±0.31
F5	0.36±0.09	0.43±0.07	16.27±0.27	1.19±0.11	43.41±0.11
F6	0.37±0.06	0.46±0.04	19.56±0.37	1.24±0.06	31.70±0.15
F7	0.36±0.04	0.44±0.06	18.18±0.22	1.22±0.36	34.35±0.26
F8	0.33±0.07	0.40±0.01	17.50±0.14	1.21±0.41	43.12±0.14
F9	0.33±0.11	0.43±0.03	23.25±0.37	1.30±0.12	31.14±0.21
F10	0.36±0.09	0.43±0.07	16.27±0.27	1.19±0.11	43.41±0.11

Table 5: Post compression parameters of bilayered tablets of sitagliptin phosphate and simvastatin.

Formulation code	Average weight (mg)	Friability (%) (n=10)	Drug Content (%)	Hardness (kg/cm^2)	Thickness (mm)
	(mean ± s.d; n=10)		**(mean ± s.d; n=3)**		
F1	401±3.64	0.41±0.001	96.76±1.43	4.8±0.1	4.41±0.02
F2	408±2.46	0.42±0.011	95.98±2.32	5.6±0.2	4.40±0.02
F3	420±3.23	0.39±0.017	97.91±1.87	5.9±0.1	4.41±0.01
F4	401±2.15	0.32±0.040	98.65±1.41	5.7±0.1	4.42±0.03
F5	389±2.75	0.32±0.040	95.68±1.80	5.5±0.3	4.43±0.02
F6	423±2.22	0.39±0.017	97.59±1.68	5.9±0.2	4.46±0.01
F7	401±2.19	0.35±0.042	98.84±2.14	5.8±0.2	4.41±0.03
F8	416±3.28	0.38±0.013	96.83±2.11	6.0±0.1	4.40±0.02

F9	396±2.10	0.33±0.013	98.17±1.74	5.2±0.2	4.43±0.03
F10	389±2.75	0.32±0.040	95.68±1.80	5.5±0.3	4.43±0.02

Table 6: Zero order release profile of sitagliptin phosphate immediate release layer.

Time (min)	% cumulative drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	45.5	42.25	47.09	48.4	53.39	45.23	60.3	38.7	44.25	44.25
10	55.56	50.23	5308	55.52	60.5	50.52	69.56	48	51.65	57.18
15	60.5	62.25	66.56	65.39	68.81	57.65	75.52	57.18	60.25	61.7
20	75.56	73.32	73.30	72.21	77.92	65.25	86.63	62.52	68.56	64.4
30	82.79	85.56	85.56	82.63	82.25	72.21	89.65	75.78	75.68	72.5
45	92.25	92.21	92.21	90.61	90.6	80.42	97.23	85.56	82.56	80.56

Table 7: First order release profile of sitagliptin phosphate immediate release layer.

Time (min)	Log% Drug remaining									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	2	2	2	2	2	2	2	2	2	2
5	1.736	1.761	1.723	1.712	1.668	1.679	1.598	1.787	1.746	1.746
10	1.647	1.696	1.664	1.65	1.593	1.599	1.483	1.716	1.684	1.631
15	1.595	1.576	1.524	1.539	1.493	1.54	1.393	1.631	1.599	1.583
20	1.388	1.443	1.426	1.443	1.343	1.382	1.13	1.576	1.497	1.483
30	1.235	1.238	1.159	1.239	1.249	1.291	1.115	1.384	1.385	1.443
45	0.899	0.926	0.891	0.971	0.97	1.216	0.503	1.159	1.241	1.288

Table 8: Zero order release profile of simvastatin layer

Time (min)	% cumulative drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	45.5	51.34	54.45	53.32	54.34	52.45	67.54	55.74	56.42	44.25
10	55.56	59.47	59.56	61.65	61.54	59.56	71.75	64.75	62.53	57.18
15	60.58	63.53	65.83	64.24	67.56	62.54	77.25	69.65	70.64	61.7
20	75.56	68.36	71.23	71.15	76.63	67.46	84.93	74.35	78.24	64.42
30	82.79	74.82	79.51	74.24	83.34	75.12	93.25	81.34	83.83	72.5
45	92.25	82.85	84.45	79.45	89.47	79.64	98.32	87.14	89.76	80.56

Table 9: First order release profile of simvastatin layer

Time (min)	Log% Drug remaining									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	2	2	2	2	2	2	2	2	2	2

5	1.672	1.687	1.673	1.687	1.658	1.669	1.511	1.677	1.66	1.646
10	1.627	1.608	1.628	1.608	1.607	1.584	1.451	1.607	1.585	1.547
15	1.585	1.562	1.585	1.562	1.534	1.553	1.357	1.574	1.511	1.482
20	1.54	1.5	1.54	1.5	1.459	1.46	1.178	1.512	1.369	1.409
30	1.372	1.401	1.373	1.401	1.312	1.411	0.829	1.396	1.222	1.271
45	1.183	1.234	1.184	1.234	1.192	1.313	0.225	1.309	1.022	1.109

Table 10: Correlation coefficient (r2) values of different formulation of sitagliptin phosphate and simvastatin bilayered tablets.

Formulation code	**Zero order (R^2 value)**	**First order (R^2 value)**	**Zero order (R^2 value)**	**First order (R^2 value)**
	Sitagliptin phosphate release layer		**Simvastatin release layer**	
F1	0.755	0.977	0.652	0.899
F2	0.787	0.963	0.620	0.863
F3	0.863	0.978	0.613	0.966
F4	0.726	0.968	0.551	0.871
F5	0.653	0.932	0.643	0.920
F6	0.704	0.909	0.920	0.810
F7	0.611	0.987	0.585	0.954
F8	0.802	0.975	0.591	0.891
F9	0.710	0.918	0.617	0.904
F10	0.661	0.877	0.616	0.816

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