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Formulation And Evaluation Of The Bilayer Tablets Of Amlodipine & Rosuvastatin By Using Natural Polymer

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ABSTRACT:

The present study was undertaken with an aim formulation and evaluation of Bilayer Tablets containing Amlodipine and Rosuvastatin by Direct compression technology was to formulate a stable, safe and convenience dosage form for the better management of most common blood pressure and the cholestrol. The formulations of bilayer tablets showed good results in case of Amlodipine immediate release layer physicochemical parameters and prepared using concentration of superdisintegrant sodium starch glycolate for the fast release layer and sustained release layer of Rosuvastatin containing Tamarind seed mucilage powder for the delay the drug release up to 10-12 hrs. The evaluation parameters are Higuchi, korsemayer peppas model as performed for the drug release mechanism.

Key words : Bilayer tablet, sodium starch glycolate, Tamarind seed mucilage, Higuchi ,korsemayer peppas.

INTRODUCTION :

Oral drug delivery system is the mostly employed for the route of drug administration. There are different routes of drug administration among these the oral route gain the more popularity regarding the drug administration because of the patient acceptance, easy to administer, which is cost effective, ease of manufacturing[1,2,3].

In the bilayer tablet there are two fractions which contain the loading dose and extended dose (or) maintanace dose, bilayer tablet can also be given as immediate release and sustain release layer. This dosage form which offers a advantage of separating the two incompatible drugs by thr inert layer placed between the two layers[4,5].

Amlodipine is a drug which is used to treat the high blood pressure and related coronary heart disease .Which consist of the chemical structure is a dihydropyridine calcium channel blocker. Consisting of the dihydropyridine ring with the methyl substituent and a diethylamino ethyl group at another carbon.

Rosuvastatin is a lipid lowering drug which is used to treat high cholesterol level and prevent the related cardiovascular disease it is a synthetic statin derivative its chemical structure consists of dihydroxypropyl side chain and that attached to bicyclic ring with the substituent flouro group.

Mechanism of Action

It is a calcium channel blocker its primary mechanism of action which involves inhibiting the influx of calcium ions into vascular smooth muscle cells and the cardiac muscle cells, which results in the vasodilation and decreased peripheral vascular resistance. This leads to reduced blood pressure and improved blood flow to the heart muscle.

Rosuvastatin is a statin class of drug which is used to lower the cholesterol levels and reduce the risk of cardiovascular disease. Its main mechanism of action involves inhibiting the enzyme HMG-CoA reductase.

HMG-CoA reductase plays a key role in cholesterol synthesis in the liver. By blocking this enzyme, reduces the production of cholesterol, leading to decreased levels of LDL (bad cholesterol) in the bloodstream. Functionally it may increase the levels of HDL (good cholesterol). The drug rosuvastatin helps to improve lipid profiles and reduce the risk of cardiovascular events.

Materials

Amlodipine and rosuvastatin was obtained from the Aurobindo Pharma Ltd, Tamarind seed mucilage powder was prepared in the Malla Reddy Pharmacy college, Sodium starch glycolate, microcrystalline cellulose ,Magnesium stearate, Talc obtained from the S D. Fine Chemicals.

Method of preparation

- Raw seeds of tamarind were cleaned with distilled water to remove any extra pulp.
- Then 250gm of cleaned seeds were broken into small pieces and grounded into fine powder.

- Powder were taken into a 1000ml beaker containing 500 ml water and boiled on water bath at 80-100oC with a constant stirring till a viscous solution was obtained.
- The solution was filtered using muslin cloth to throw away the undissolved fraction, and the supernatant was dried at 40ºC for overnight.
- Then the dried material was called as tamarind kernel powder. TSP was prepared from this tamarind kernel powder by following method.
- 20 gm of tamarind kernel powder was taken and added in 200ml of distilled water, and slurry was prepared. The slurry was boiled for 20 minutes with continuous stirring at a water bath.
- The resulting solution was kept overnight to settle most of the protein and fibers.
- This solution was then centrifuged for 20 minutes at 5000 rpm. The supernatant was separated and twice volume of ethanol poured into it with continuous stirring.
- The precipitate was dried at 40ºC. The dried film obtained was crushed to fine powder, passed through sieve no. 12.

DIRECT COMPRESSION:

Weigh all the excipients and drugs accurately and pass them through sieve #100. After that, mix all the components thoroughly in a pestle and mortar. Finally, we will compress them into tablets directly, allowing us to assess the formulation's suitability and quality through tablet production.

Steps for compression cycle of bilayer tablet

- ✓ Filling of first layer.
- ✓ Compression of first layer.
- ✓ Ejection of upper punch.
- ✓ Filling of second layer.
- ✓ Compression of both the layers together.
- ✓ Ejection of bilayer tablets**.**

Fomulation of Bilayer Tablet(sustain release layer).

Preparation of Rosuvastatin sustain release layer.

- ❖ All the Bilayer tablets, each containing 40 mg of rosuvastatin, were prepared by direct compression method and also to study the effect of various ratios of tamarind seed mucilage powder on the drug release.
- ❖ MCC followed by rosuvastatin were passed through # 80 mesh and blended properly in a double lined poly bag for 5 min.
- ❖ The remaining excipients (details were given in table) were passed through # 80 mesh and added to the double lined poly bag for thorough mixing by blending one after another. The tablet powder was compressed into tablets on a Rotary press machine.
- ❖ punching machine to a hardness of 5- 6 kg/cm2 using 8mm round punches.

The sustain release layer tablet containing 40mg Rosuvastatin were prepared with total tablet weight of 200mg.

Table :1 Formulation of Sustain release layer

Formulation	F1	F2	F3
Rosuvastatin	40mg	40mg	40mg
Tamarind seed mucilage powder	75mg	50mg	25mg
Microcrystalline cellulose	75mg	100mg	125mg
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg
Total weight	200mg	200mg	200mg

Fomulation of Bilayer Tablet (Immediate release layer).

Preparation of Amlodipine immediate release layer.

- ❖ The immediate release layer, containing 10 mg of Amlodipine, were prepared by direct compression method and also to study the effect of various ratios sodium starch glycolate on the drug release.
- ❖ MCC followed by Amlodipine were passed through # 80 mesh and blended properly in a double lined poly bag for 5 min.
- ❖ The remaining excipients (details were given in table) were passed through # 80 mesh and added to the double lined poly bag for thorough mixing by blending one after another. The tablet powder was compressed into tablets on a Rotary press machine.
- ❖ punching machine to a hardness of 5- 6 kg/cm2 using 8mm round punches.

Table:2 Formulation of immediate release layer

Formulation	F1	F2	F3
Amlodipine	10mg	10mg	10mg
Sodium starch glycolate	45mg	30mg	15mg
Microcrystalline cellulose	40mg	55mg	70mg
Magnesium stearate	2.5mg	2.5mg	2.5mg
Talc	2.5mg	2.5mg	2.5mg
Total weight	100mg	100mg	100mg

Formulation of Optimized Bilayer tablets

Table :3 Evaluation Parameters of Optimized Formulation

Rosuvastatin sustain release layer (F1)	
Ingredients	**Quantity.(mg)**
Rosuvastatin	40mg
Tamarind seed mucilage powder	75mg
Microcrystalline cellulose	75mg
Magnesium stearate	5mg
Talc	5mg
Total weight	200mg
Amlodipine immediate release layer (F1)	
Amlodipine	**10mg**
Sodium starch glycolate	45mg
Microcrystalline cellulose	40mg
Magnesium stearate	2.5mg
Talc	2.5mg
Total weight	100mg
Total tablet weight =300mg	

IN VITRO DISSOLUTION STUDY

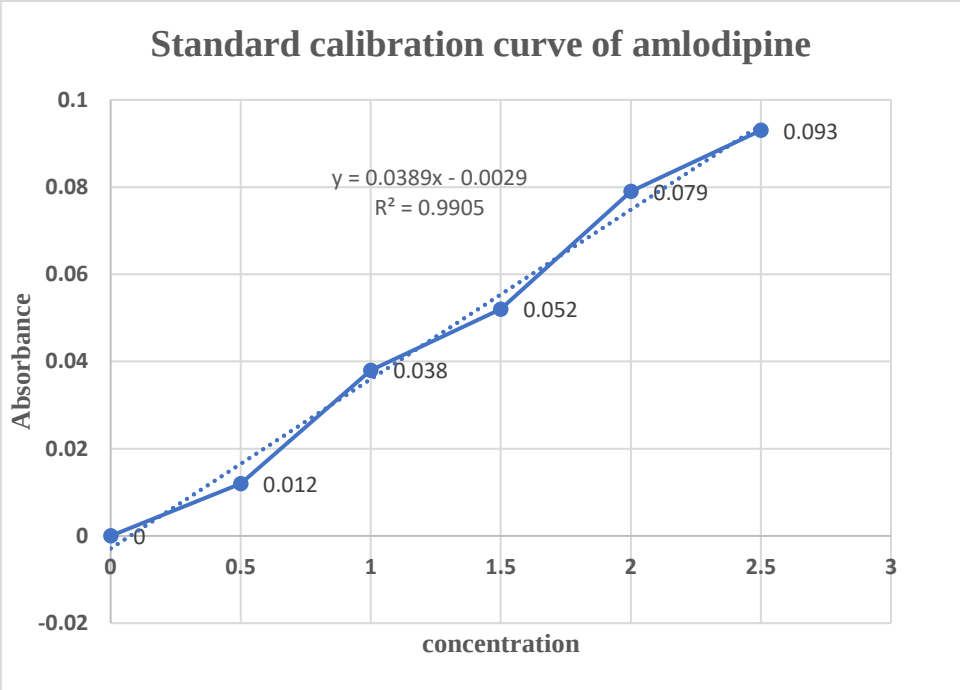
Standard calibration curve of Amlodipine

The standard calibration curve of the Amlodipine was obtained by the plotting the graph Absorbance vs concentration. Absorbance of different concentrations were listed in the below table. The standard calibration curve of the Amlodipine was developed at λ_{max}338nm. The calibration curve was linear between 0-2.5µg/ml concentration range. R^2 Value was obtained 0.990, it indicates the linearity of the curve**.**

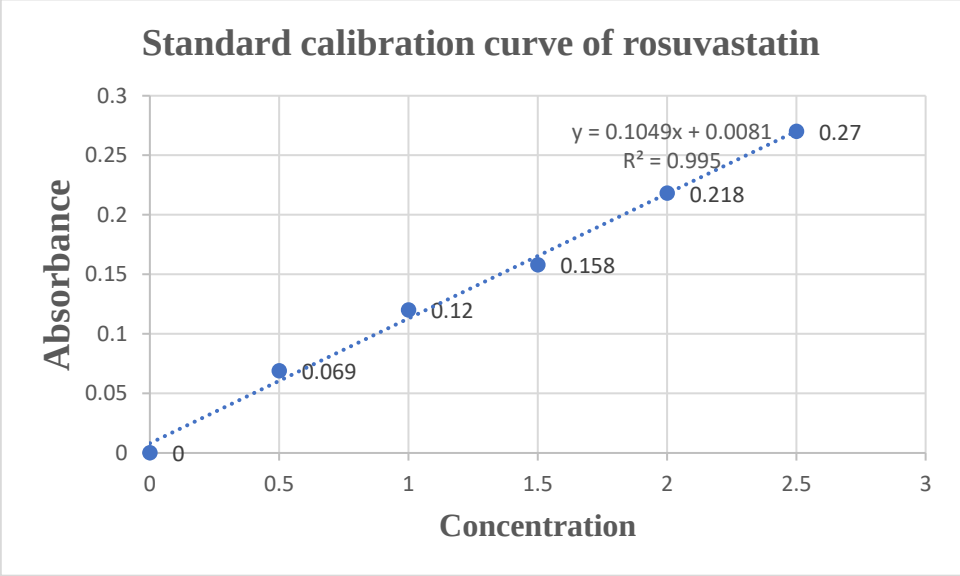
Table :4 Concentration & Absorbance of Amlodipine

S.No	CONCENTRATION	ABSORBANCE
1	**0**	**0**
2	**0.5**	**0.012**

3	**1**	**0.038**
4	**1.5**	**0.052**
5	**2**	**0.079**
6	**2.5**	**0.093**



Graph :1 Standard calibration curve of amlodipine



Graph :2 Standard calibration curve of rosuvastatin

Standard calibration curve of Rosuvastatin

The standard calibration curve of the Rosuvastatin was obtained by the plotting the graph Absorbance vs concentration. Absorbance of different concentrations were listed in the below table. The standard calibration curve of the Rosuvastatin was developed at λmax255nm. The calibration curve was linear between 0-2.5µg/ml concentration range. R2 Value was obtained 0.995, it indicates the linearity of the curve.

Table :5 Concentration & Absorbance of Rosuvastation

S.No	CONCENTRATION	ABSORBANCE
1	0	0
2	0.5	0.069
3	1	0.12
4	1.5	0.158
5	2	0.218
	2.5	0.27

Identification of Drugs

Identification of Rosuvastatin by FT-IR

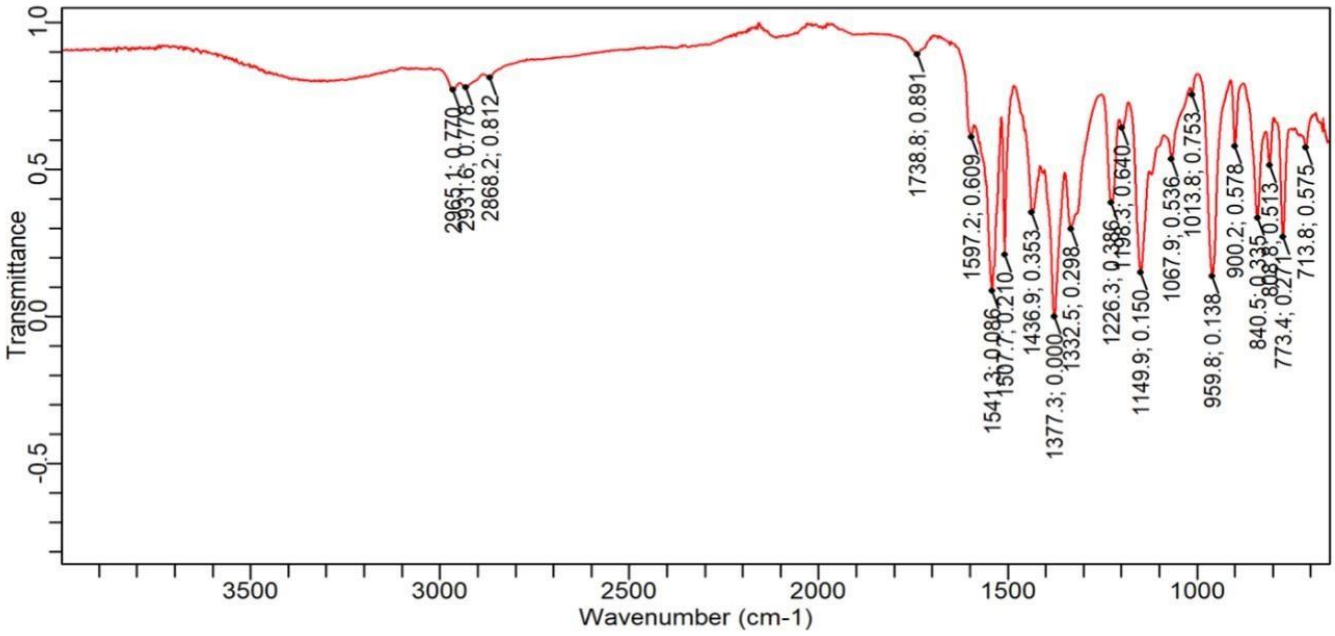


Figure 1 FT-IR of Rosuvastatin.

Table : 6Interpretation of Rosuvastatin by FT-IR Spectra

Wavenumber(cm^{-1})	Interpretation
723	N-H
2969	Carboxylic acid group
2928	O-H
1156	S=O

The FT-IR spectra of Rosuvastatin was determined by to identify the drug. Various functional groups and their respective peak values are illustrated in the table which were identical to the FT-IR spectra of drugs. The FT-IR spectra of drug also compared with the FT-IR given in the Indian pharmacopeia which leads to conclusion that there there was no significant change in the FT-IR and indicate the purity of drug.

Identification of Amlodipine by FT-IR

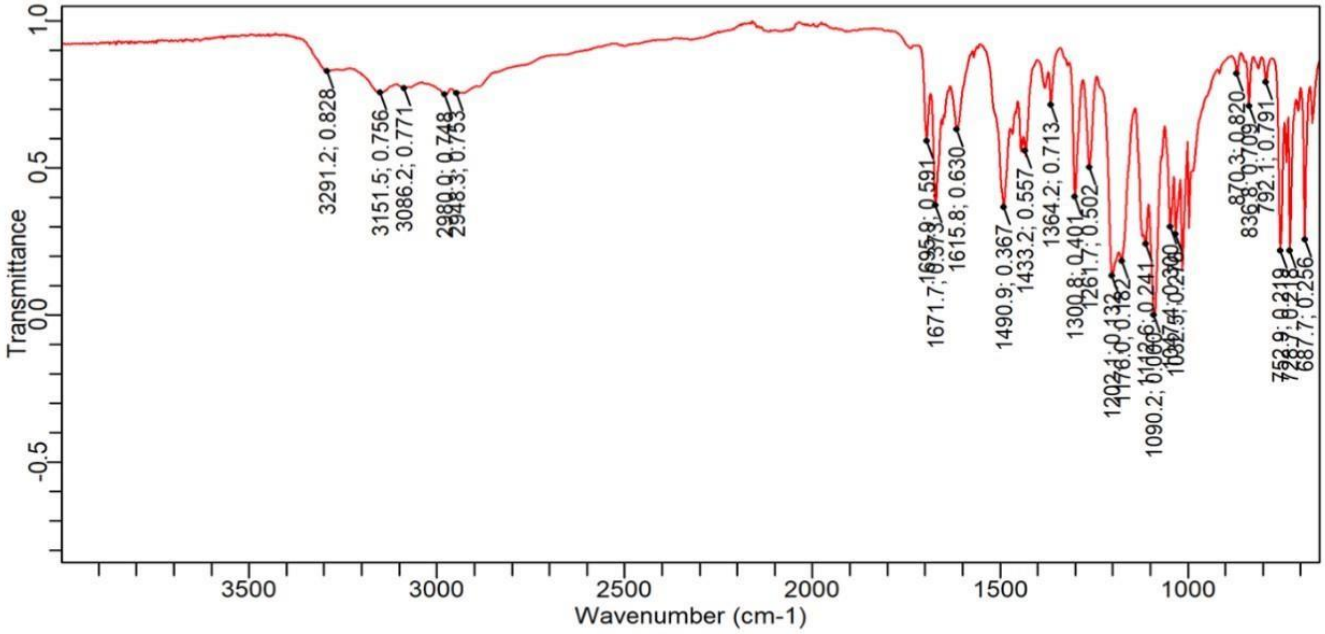


Figure 2 FT-IR of Amlodipine

Table :7 Interpretation of Amlodipine by FT-IR Spectra

Wavenumber	interpretation
3298	NH Streching of primary amino group
1685	C=O
2985	C-H
1099	NH Streching of secondary amino group
1614	C=C
3157	O-H Streching of SO_3H

The FT-IR spectra of Amlodipine was determined by to identify the drug. Various functional groups and their respective peak values are illustrated in the table which were identical to the FT-IR spectra of drugs. The FT-IR spectra of drug also compared with the FT-IR given in the Indian pharmacopeia which leads to conclusion that there there was no significant change in the FT-IR and indicate the purity of drug.

FT-IR of Rosuvastatin and Amlodipine

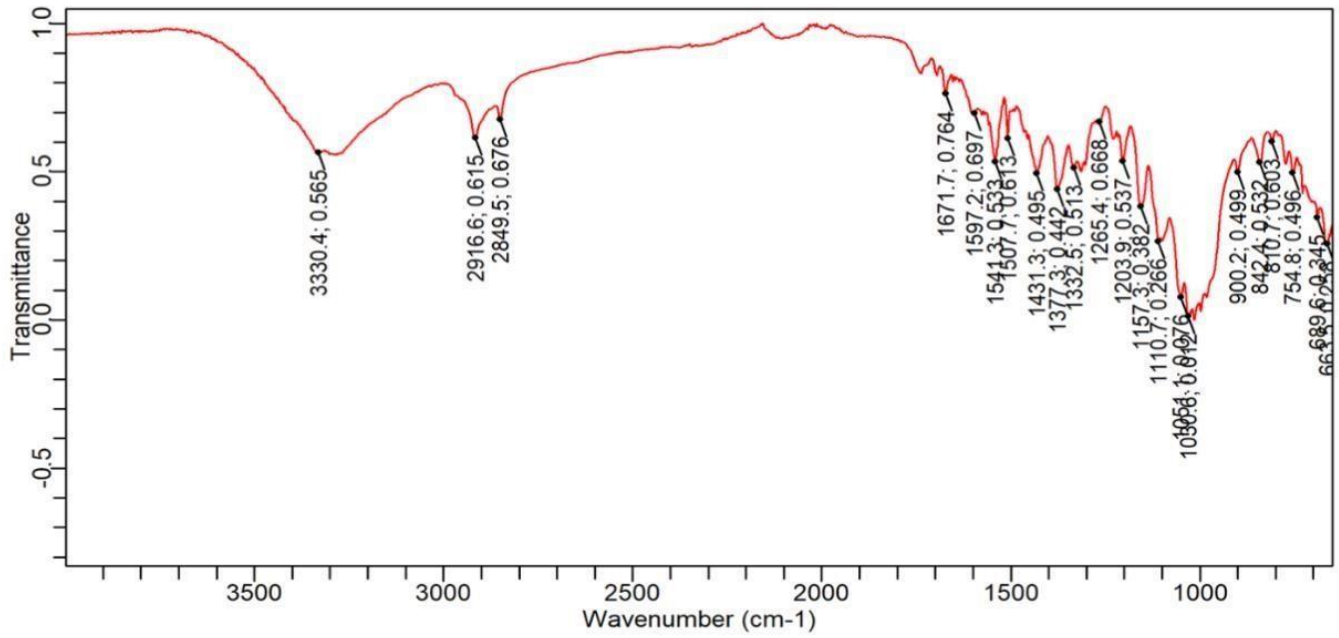


Figure 3 FT-IR of Rosuvastatin and Amodipine

FT-IR of Rosuvastatin and Tamarind seed mucilage powder.

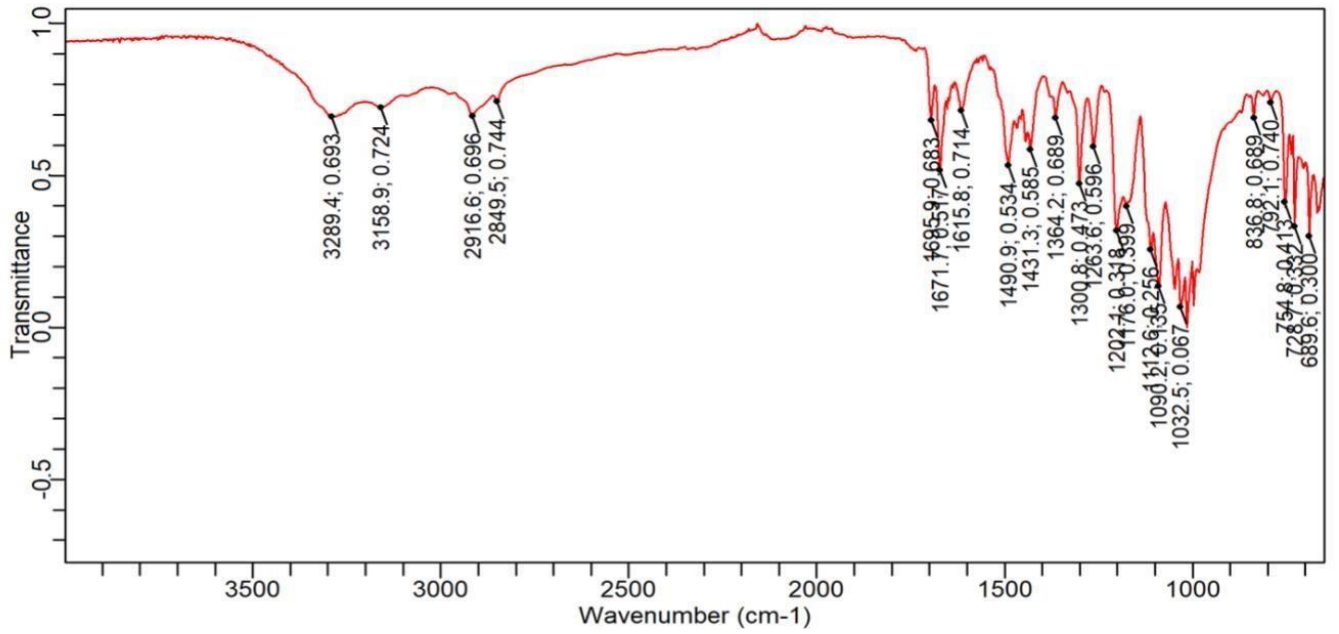


Figure 4 FT-IR of Rosuvastatin and Tamarind seed mucilage powder.

FT-IR of Amlodipine and Sodium starch glycolate.

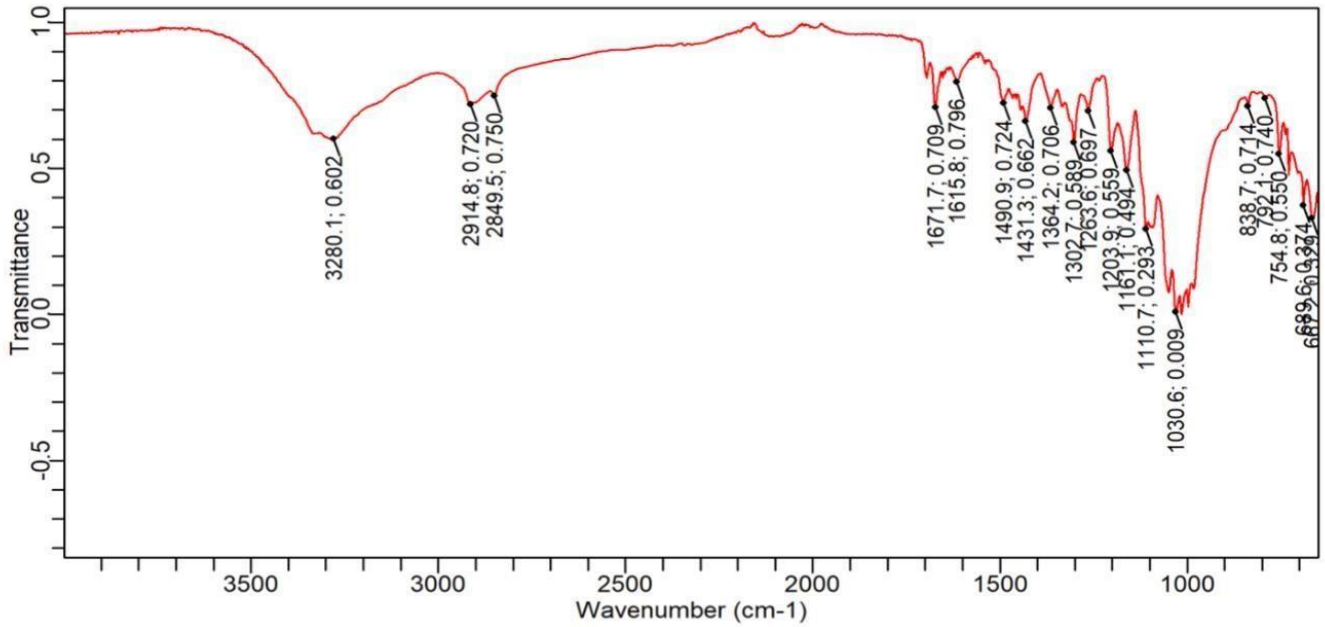


Figure 5 FT-IR of Amlodipine and Sodium starch glycolate.

Table : 8 Interpretation of FT-IR spectra of Rosuvastatin with all excipients

Drug + Excipients mixture	**Functional Group wavenumber (cm^{-1})**			
	O-H Group	Carboxylic acid Group	N-H	S=O
Rosuvastatin + Tamarind seed mucilage powder	2916	2932	751	1168
Rosuvastatin + MCC	2919	2982	772	1179
Rosuvastatin + Magnesium stearate	2924	2969	769	1165
Rosuvastatin + Talc	2913	2992	774	1171

Drug and excipients compatibility study was performed by using the FT-IR spectrophotometer. Here, the peak of pure Rosuvastatin was correlated with the peak of drug in presence of other excipients. In all the FT-IR spectra, identical peak of rosuvastatin was not varied than of its original peak. So, it would be concluded that, the drug is compatible with all the excipients used in the formulation.

Table :9 Interpretation of FT-IR spectra of Amlodipine with all excipients

Drug + Excipients mixture	**Functional group wave number(cm^{-1})**					
	O-H Streching Group	N-H Streching primary amino group	C=O Group	C-H Group	C=C	N-H Streching secondary amino group
Amlodipine + Sodium starch glycolate	3154	3297	1684	3029	1615	1098
Amlodipine + MCC	3163	3298	1685	3032	1613	1097
Amlodipine + Magnesium stearate	3159	3296	1664	2997	1621	1089
Amlodipine + Talc	3147	3289	1676	2987	1611	1099

Drug and excipients compatibility study was performed by using the FT-IR spectrophotometer. Here, the peak of pure Amlodipine was correlated with the peak of drug in presence of other excipients. In all the FT-IR spectra, identical peak of Amlodipine was not varied than of its original peak. So, it would be concluded that, the drug is compatible with all the excipients used in the formulation.

Physical Characterization of Rosuvastatin and Amlodipine

Organoleptic Characteristics

Table : 10 Organoleptic Characteristic of API

Properties	**Rosuvastatin**	**Amlodipine**
Description	White crystalline powder	White crystalline powder
Color	White	White
Odor	Odorless	Odorless
Taste	Bitter	Bitter

Solubility

Table : 11 Solubility of API in Different media

Media	**Solubility of Rosuvastatin (mg/ml)**	**Solubility of Amlodipine (mg/ml)**
Water	Slightly Soluble	Slightly Soluble
0.1N HCl	Soluble	soluble
Buffer PH 6.8	Very soluble	Spraingly soluble
Alcohol	marginally soluble	soluble

Evaluation Parameters of Amlodipine

Pre-compression Evaluations of Batches F1 to F3

The Powder blend of all 3 formulations were evaluated for bulk density which ranged from 0.27 ± 0.002 to 0.29 ± 0.002 gm/cm^3, tapped density ranged from 0.31 ± 0.02 to 0.33 ± 0.002 gm/cm^3, Carr's index ranged from 11.62 ± 0.076 to 12.76 ± 0.076%, Hausner's ratio from 1.11 ± 0.0045 to 1.15 ± 0.0061 and Angle of repose ranged from 22.06 ± 0.05 to 23.54 ± 0.02. All these results indicate that, the powers blend possess excellent to good flow ability and compressibility properties.

Table :12 Pre-Compression Evaluations of Batches F1to F3

Batch Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	% Carr's index	Hausner's ratio	Angle of repose (Ɵ)
F1	0.27 ± 0.002	0.31 ± 0.002	12.73 ± 0.075	1.15 ± 0.0059	23.52 ± 0.01
F2	0.28 ± 0.003	0.32 ± 0.003	12.76 ± 0.076	1.15 ± 0.0061	23.54 ± 0.02
F3	0.28 ± 0.002	0.33 ± 0.002	12.21 ± 0.075	1.15 ± 0.0054	22.55 ± 0.05

Post Compression Evaluation of Batches F1 to F3

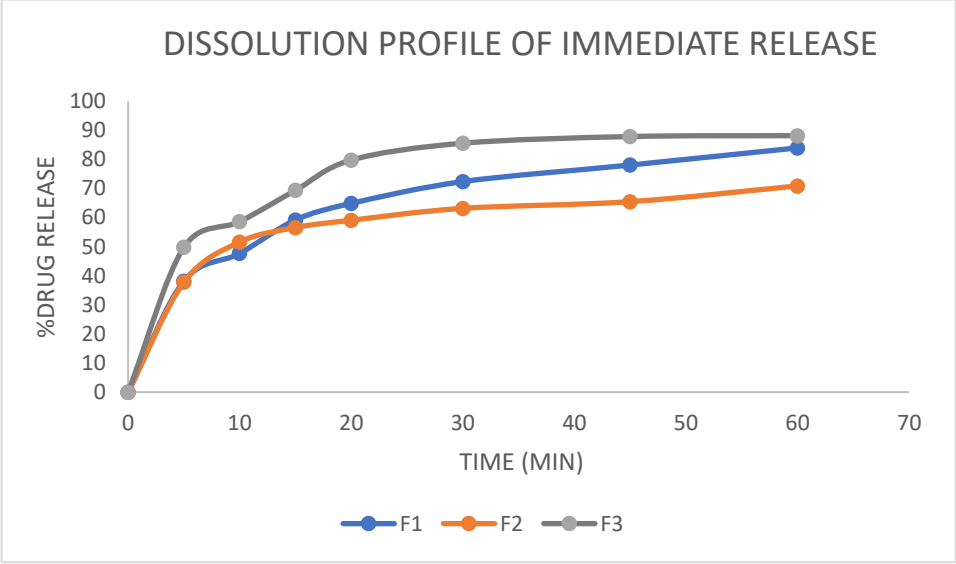
All the tablets were evaluated for various physical parameters before proceeding further. Table includes the values (mean ± SD) of weight variation, hardness, thickness, friability of batches F1 to F3 prepared using different combinations of functional excipients. Tablet weights in all the 3 batches varied between 249.82 mg to 251.19 mg. All the formulated (F1 to F3) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ± 5% of the weight. Thickness of all tablets was in the range 4.51 ± 0.054 mm to 4.67 ± 0.037 mm. Hardness of tablets was in range 3.18 ± 0.03 kg/cm^2 to 3.35 ± 0.04 kg/cm^2. Friability was in range 0.40 ± 0.02% to 0.48 ± 0.03%. Friability values were less than 1 % in all cases shows good mechanical strength at the time of handling and transports. Thus, all the physical parameters of the manually compressed tablets were quite within control.

Table : 13 Post-Compression Evaluation Parameters of Batches F1to F3

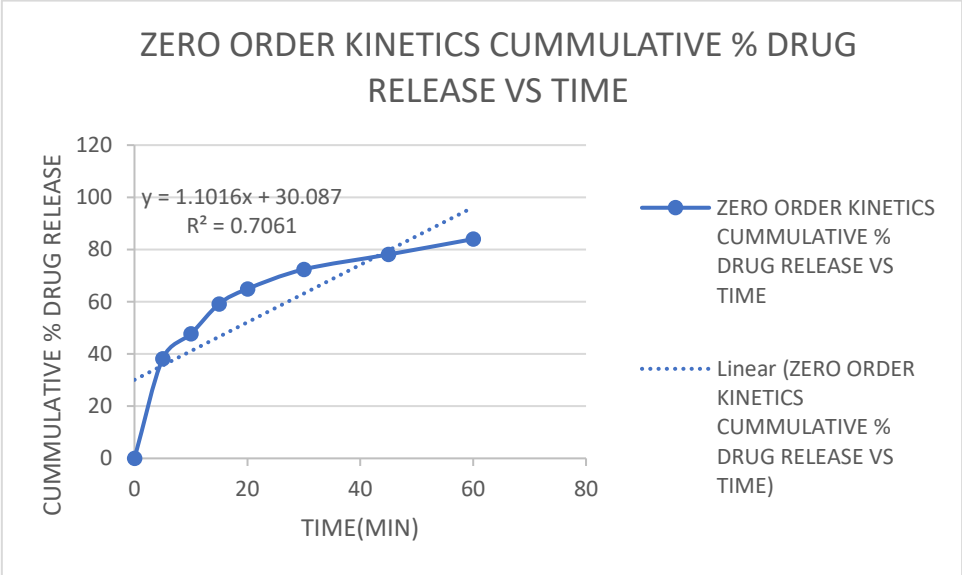
Batch Code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	% Friability
F1	Pass	4.57 ± 0.047	3.30 ± 0.08	0.40 ± 0.02
F2	Pass	4.67 ± 0.037	3.22 ± 0.06	0.42 ± 0.05
F3	Pass	4.54 ± 0.015	3.18 ± 0.03	0.48 ± 0.03

Table :14 Dissolution profile for amlodipine

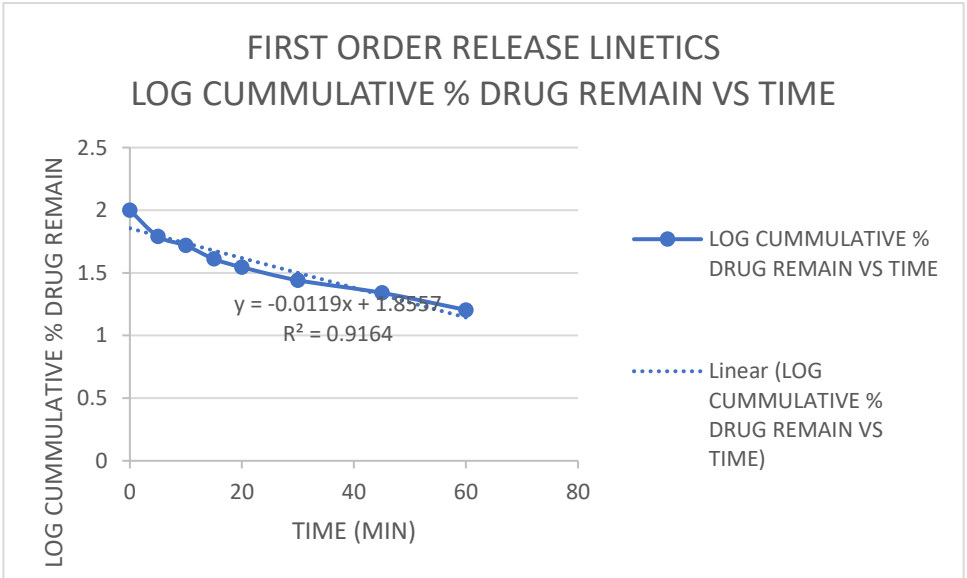
Time	F3	F2	F1
0	0	0	0
5	38.2	37.8	49.8
10	47.7	51.6	58.6
15	59.2	56.6	69.4
20	64.9	59.1	79.8
30	72.4	63.2	85.6
45	78.1	65.5	87.9
60	84	70.9	88.2



Graph : 3 DISSOLUTION PROFILE OF IMMEDIATE RELEASE

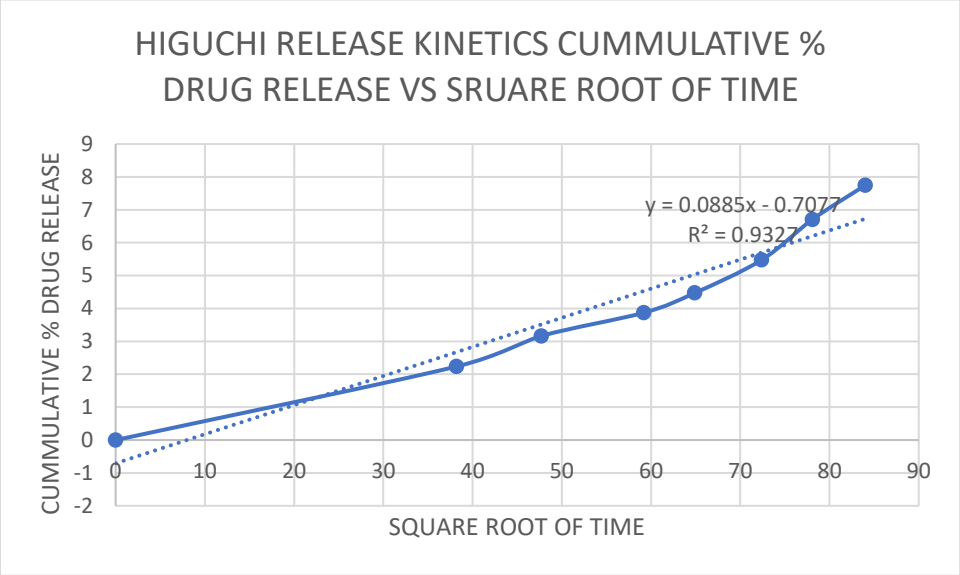


Graph :4 ZERO ORDER KINETICS CUMMULATIVE % DRUG RELEASE VS TIME



Graph :5 FIRST ORDER RELEASE LINETICS

LOG CUMMULATIVE % DRUG REMAIN VS TIME



Graph :6 HIGUCHI RELEASE KINETICS CUMMULATIVE % DRUG RELEASE VS SRUARE ROOT OF TIME

Evaluation Parameters of Rosuvastatin

Pre-compression Evaluations of Batches F1 to F3

The Powder blend for all 3 formulations were evaluated for bulk density which ranged from 0.252 ± 0.25 to 0.385 ± 0.21 gm/ml, tapped density ranged from 0.285 ± 0.20 to 0.442 ± 0.39 gm/ml, Carr's index ranged from 11.32 ± 1.85 to 14.37 ± 1.19%, Hausner's ratio from 1.128 ± 0.012 to 1.168 ± 0.007 and Angle of repose ranged from 22.52 ± 1.32 to 28.60 ± 2.12. All these results indicate that, the power blend possess excellent to good flow ability and compressibility properties.

Table : 15 Pre-compression Evaluations of Batches F1 to F3

Batch Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.270 ± 0.25	0.310 ± 0.25	12.90 ± 1.26	1.148 ± 0.057	25.03 ± 2.52
F2	0.285 ± 0.33	0.325 ± 0.40	12.30 ± 1.2	1.140 ± 0.015	26.24 ± 2.25
F3	0.321 ± 0.35	0.362 ± 0.37	11.32 ± 1.85	1.128 ± 0.012	25.02 ± 1.58

Post-compression Evaluations of Batches F1 to F3

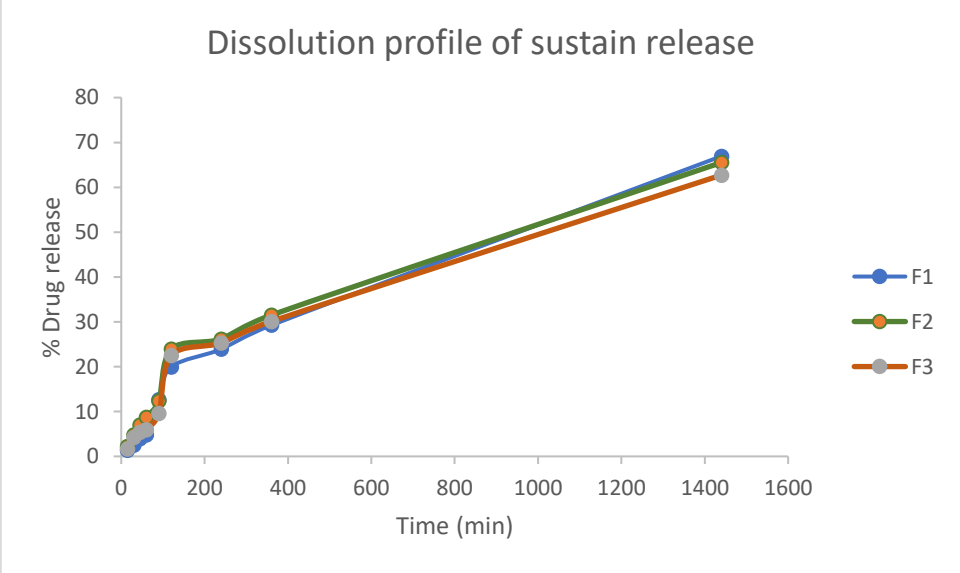
All the tablet preparations were evaluated for various physical parameters before proceeding further. Table includes the values (mean ± SD) of weight variation, hardness, thickness, friability, % drug content, disintegration time. All the formulated (F1 to F3) tablets passed weight variation test as the % weight variation was within the pharmacopeia limits of ± 7.5% of the weight. Thickness of all tablets was in the range between 2.57 ± 0.047 mm to 2.84 ± 0.015 mm. Hardness of tablets was in range between 3.14 ± 0.058 to 3.52 ± 0.032 kg/cm^2. Friability was in range between 0.32 ± 0.03 to 0.78 ± 0.032 %. Friability values were less than 1 % in all cases shows good mechanical strength at the time of handling and transports. Disintegration time from 22 ± 0.032 sec to 38 ± 0.021 sec. Thus, all the physical parameters of the manually compressed tablets were quite within control

Table : 16 Post-compression Evaluation Parameters of Batches H1 to H10

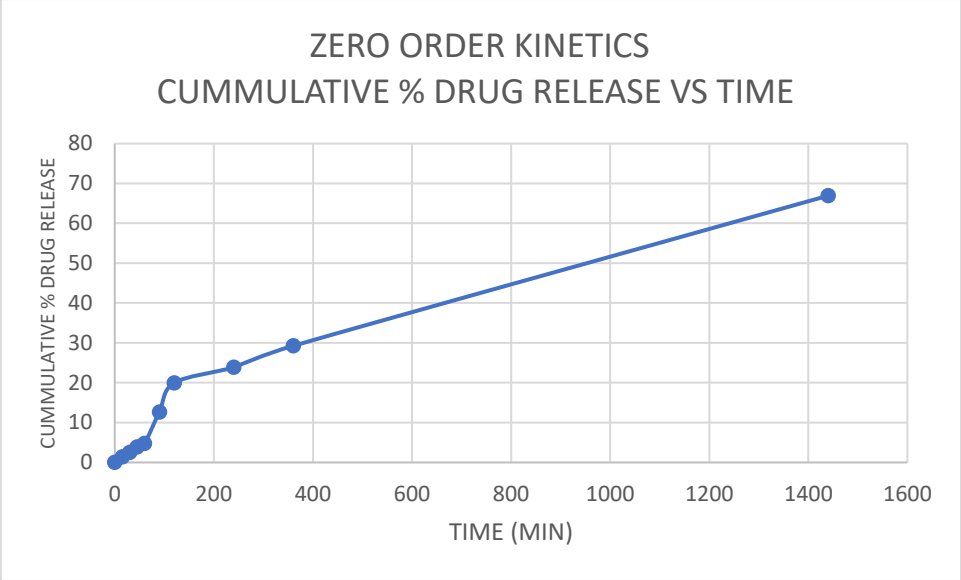
Batch Code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	% Friability	Disinteg ration time (sec)
F1	100.70 ± 0.14	2.55 ± 0.04	3.50 ± 0.05	0.43 ± 0.02	37 ± 1
F2	100.70 ± 0.05	2.54 ± 0.02	3.10 ± 0.04	0.46 ± 0.15	36 ± 2
F3	100.70 ± 1.07	2.54 ± 0.04	2.98 ± 0.14	0.46 ± 0.03	38 ± 1

Table : 17 Dissolution profile for Rosuvaststin

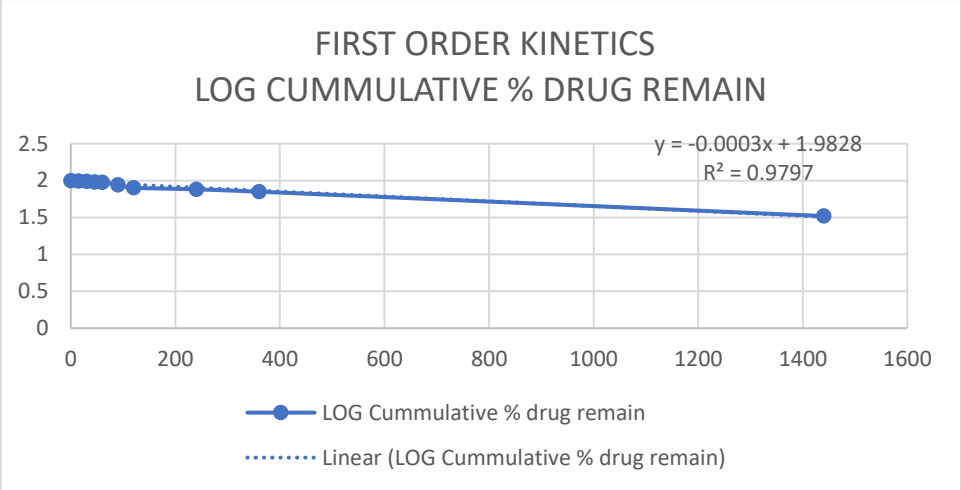
Time (mins)	F1 (%Release)	F2 (%Release)	F3 (%Release)
15	1.4	2.25	1.69
30	2.53	4.78	4.22
45	3.93	7.03	5.34
60	4.78	8.72	5.91
90	12.65	12.38	9.56
120	19.96	23.91	22.5
240	23.9	26.16	25.31
360	29.25	31.5	30.09
1440	66.93	65.53	62.72



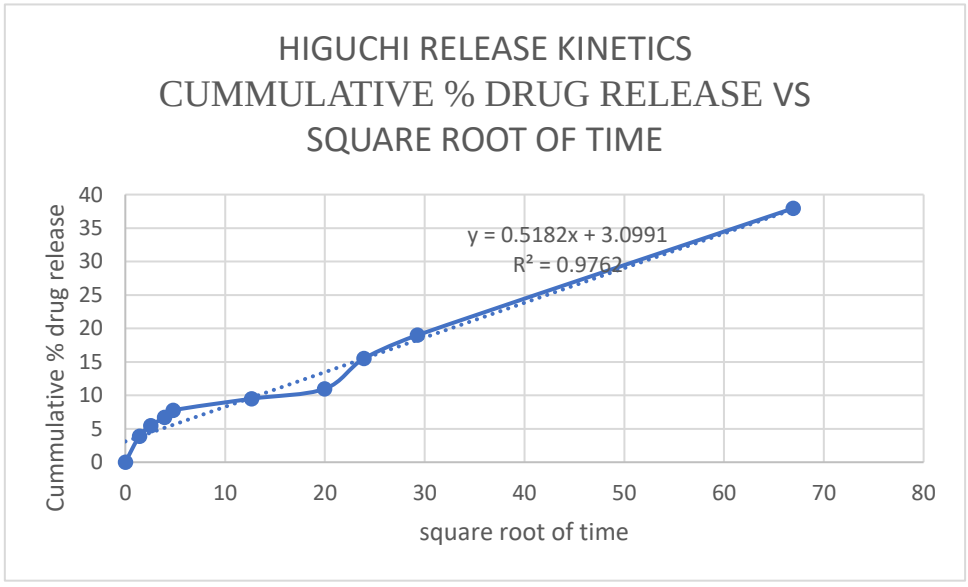
Graph :7 Dissolution profile of sustain release



Graph :8 ZERO ORDER KINETICS CUMMULATIVE % DRUG RELEASE VS TIME



Graph :9 FIRST ORDER KINETICSLOG CUMMULATIVE % DRUG REMAIN



Graph :10 HIGUCHI RELEASE KINETICS CUMMULATIVE % DRUG RELEASE VS SQUARE ROOT OF TIME.

DISCUSSION :

The bilayer tablet of the Amlodipine and the Rosuvastatin, the immediate release layer was Amlodipine and the Sustain release layer was Rosuvastatin both the layers can be prepared by the Direct compression technique. The Sustain release layer containing the Tamarind seed mucilage powder as a natural polymer which can helps the drug to desired sustain release action upto12 hrs. The immediate release layer containing sodium starch glycolate which act as the super disintegrant which release the drug at faster rate. Formulation F1 can be shows desired action of the immediate action of amlodipine and the sustain action of the rosuvastatin.

CONCLUSION :

The present study was undertaken with an aim formulation and evaluation of Bilayer Tablets containing Amlodipine and Rosuvastatin by Direct compression technology was to formulate a stable, safe and convenience dosage form for the better management of most common blood pressure and the cholestrol. The formulations of bilayer tablets showed good results in case of Amlodipine immediate release layer physicochemical parameters and prepared using concentration of superdisintegrant sodium starch glycolate for the fast release layer and sustained release layer of Rosuvastatin containing Tamarind seed mucilage powder for the delay the drug release up to 10-12 hrs. The FTIR analysis indicates that there were no drug-drug and drug-excipients interactions. Pre compression and post compression parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayer tablets. Formulation batch of Amlodipine and Rosuvastatin was finally optimize in which F1 (Amlodipine) batch is selected as immediate release layer and F1(Rosuvastatin) batch is selected as sustained release layer as final selected formulation. The F1 batch of both drugs provides better drug release profile.

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