International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (2): 1300-1309
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved
UGC Approved Journal

Formulation and Evaluation of Atorvastatin Matrix Tablets by Using Wet Granulation Method

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Received: 10 Jan 2019 / Accepted: 9 Mar 2018 / Published online: 1 Apr 2019
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Abstract
The objective of the study was to formulate and evaluate the matrix tablets of various concentrations of natural and synthetic hydrophilic polymers on in-vitro release rate from the prepared Atorvastatin matrix tablets. The Atorvastatin matrix tablets were developed by wet granulation method using natural polymers and synthetic polymers at various concentrations and its effect were compared. The formulations were evaluated for hardness, friability, weight variation, disintegration, and in vitro release study. Set of trials were formulated for which Atorvastatin evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 1.2 and pH 6. 8 phosphate buffers. From the results of the invitro study it appears that the release of the Atorvastatin was significantly influenced by the characteristics of the polymer used.

Keywords
Atorvastatin, wet granulation technique, natural and synthetic polymers, FTIR studies, in vitro drug release studies.

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1.INTRODUCTION
Oral drug delivery is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route.[1,2] Oral medication is generally considered as one of the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost effective manufacturing process.[3,4] The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product.[5] Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. [6] The advantages of sustained

release dosage forms over conventional forms include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction in overall health care costs.[7,8] The rate of drug release from solid dosage form may be modified by the technologies, which in general are based on modifying drug dissolution through the use of barrier coatings and controlling drug diffusion rates from dosage forms.[9]

2. MATERIALS AND METHOD

2.1 MATERIALS

Atorvastatin was collected as a gift sample from Hetero labs, Hyderabad, Natural and polymers and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY [11,12,13]

Preparation of Atorvastatin matrix tablets

Table-1: Formulation Table

S.NO.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Atorvastatin	20	20	20	20	20	20	20	20	20	20	20	20
2	HPMCk15M	50	75	100	-	-	-	-	-	-	-	-	-
3	HPMCk4M	-	-	-	50	75	100	-	-	-	-	-	-
4	Xantham gum	-	-	100	-	-	-	50	75	100	-	-	-
5	Sodium alginate	-	-	-	-	-	-	-	-	-	50	75	100
6	PVP k 30	20	20	20	20	20	20	20	20	20	20	20	20
5	Microcrystalline Cellulose	105	80	55	105	80	55	105	80	55	105	80	55
6	Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2	2	2	2	2
	Total Wt(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Preparation of matrix tablets by using wet granulation technique

The tablets of Atorvastatin were prepared by wet granulation method using PVP paste in the mixture of drug, polymers and PVP. PVP as a binding agent. Each formulation was composed of drug and excipients in various proportions. For formulation Atorvastatin, polymers and PVP, were sifted through the mesh (#10) and mixed well in a mortar. The paste of PVP in isopropyl alcohol was used as the granulating agent. Then the mass again passed through the mesh (#10) and dried in an oven at 60^0 C for 30 min. Magnesium stearate and talc were added as lubricants and compressed into a tablet.

Evaluation studies [14,15]

Pre compression parameters

Determination of bulk density and tapped density

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) were measured. Then the cylinder was dropped at 2-second intervals onto a hard-wooden surface three times, from a height of one inch. The volume was recorded, and the bulk density was calculated.

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed, and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6-inch height and was expressed in g/cm^3.

Bulk density= W/V_o; Tapped density= W/V_f

Where, V_o = initial volume; V_f = final volume.

Compressibility index

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the

bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

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

Post compression parameters

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Thickness

Twenty tablets were randomly selected form each batch and their thickness were measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked, and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

Weigh and powdered 10 tablets in a mortar. From this powder equivalent to 10 mg of Atorvastatin was taken in a volumetric flask to this 5 ml of methanol was added and then the solution was subjected to sonication for about 10min for complete solubilization of drug and the solution was made up to the mark with methanol, filtered and further appropriate dilutions were made with phosphate buffer pH 6.8 and the drug content was estimated by measuring the absorbance at 230nm spectrophotometrically.

***In- Vitro* Release study**

The dissolution studies were performed using USP type II paddle apparatus, employing paddle stirrer rotating at 75 rpm, 900 ml of phosphate buffer pH 6.8 as a dissolution medium at 37 ± 0.5° C. 5 ml aliquots of dissolution medium was withdrawn at specified time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh dissolution medium. The absorbance of the withdrawn samples was measured at 230nm spectrophotometrically.

Stability studies

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data was selected

based on the correlation coefficient(R) value in various models. The models that have shown high 'R' value was considered as the best fit on the release data.

Various mathematical models are:

Zero Order Release Equation:

The equation for zero order release is

$$Q_t = Q_o + K_o t$$

Where ,

Q_o = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t"

K_o= Zero order release constant

T= Time in hours

The zero-order kinetics describes the systems in which the drug release rate is independent of its concentration of the dissolved substance. A graph was plotted between the time taken on x-axis and the cumulative percentage of drug release on y-axis.

First Order Release Equation:

The first order release equation is

$$\text{Log } Q_t = \text{Log } Q_o + K_t / 2.303$$

Where,

Q_o = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t"

K= First order release constant

Where,

F = fraction of drug released at time 't'

M_t = amount of drug released at time 't'

M = total amount of drug in dosage form

K_m= kinetic constant

n = diffusion or release exponent

t = time in hrs

'n' = Linear regression of log (M_t / M) versus log t

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared Matrix tablets of Atorvastatin were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°C and refrigerator 2-8°C for a period of 3 months.

T= Time in hours

Here, the drug release rate depends on its concentration. The first order kinetics describes the systems in which the drug release rate is concentration dependent.

Higuchi Release Equation:

The Higuchi release equation is

$$\mathbf{Q_t = K_H \sqrt{t}}$$

Where ,

Q = Cumulative amount of drug release at time "t"

K_H = Higuchi constant

T = Time in hrs

Hixson-Crowell release equation

The Hixson-Crowell release equation is

$$\sqrt[3]{Q_o} - \sqrt[3]{Q_t} =$$

Where,

Q_o = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t"

K_{HC} = Hixson -Crowell release constant

T= Time in hours

Korsmeyer -Peppas Release Equation:

Korsmeyer –Peppas equation is

$$F = M_t / M = K_m t^n$$

3.RESULTS AND DISCUSSION

Drug - excipient compatability studies

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

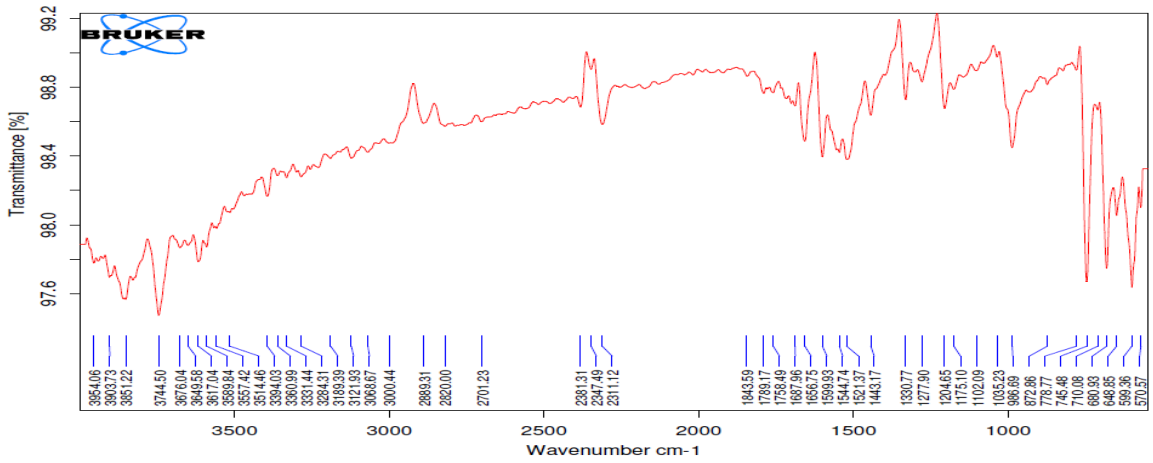

Fig-1: FTIR spectra of pure drug

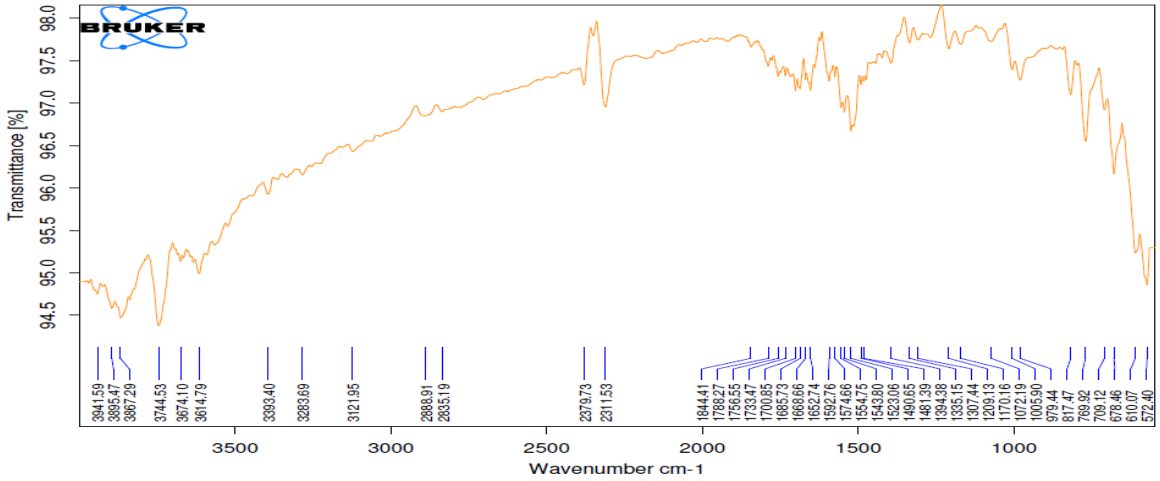

Fig-2: FTIR Spectra of optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation studies

Pre compression parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.369-0.373 g/cc.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.458-0.480 g/cc.

Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27 ^{0} to 30 ^{0}

Compressibility index: Compressibility index was carried out, it found between 10% to 22.8 % indicating the powder blend have the required flow property for compression.

Table-2: Characterization of Blends

S. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose (^{0})
F1	0.372	0.476	21.8	1.2	27^0
F2	0.373	0.468	20.5	1.2	28^0
F3	0.371	0.468	22	1.2	27^0
F4	0.369	0.478	22.8	1.2	29^0
F5	0.370	0.469	21.1	1.2	26^0
F6	0.371	0.480	22.7	1.2	27^0
F7	0.372	0.479	22.3	1.2	29^0
F8	0.369	0.476	22.4	1.2	28^0
F9	0.358	0.459	22	1.2	30^0
F10	0.361	0.458	21.1	1.2	29^0
F11	0.365	0.462	20.9	1.2	28^0
F12	0.368	0.465	20.8	1.2	27^0

Post compression parameters

Weight variation

The percentage weight variations for all formulations were tabulated in Table no .All the formulated (F1 to F12) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F12 formulations and were found to be in the range of 2.26 mm to 2.75mm.

Hardness:

The measured hardness of tablets of each batch ranged between 4.32 to 4.39 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F12 was found to be between 94.52 % and 98.53% of Atorvastatin, it complies with official specifications.

Table-3: Physical parameters of tablets of each batch

B. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	200	2.75	4.23	0.35	94.52
F2	199	2.72	4.30	0.38	95.22
F3	200	2.70	4.29	0.25	96.75
F4	198	2.69	4.30	0.28	97.69
F5	200	2.52	4.32	0.38	98.36
F6	198	2.25	4.29	0.42	96.65
F7	200	2.30	4.35	0.31	98.53
F8	198	2.26	4.26	0.23	96.26
F9	199	2.69	4.33	0.25	95.34
F10	198	2.32	4.37	0.26	96.60
F11	199	2.65	4.35	0.37	97.15
F12	200	2.70	4.36	0.36	94.62

***In-vitro* Dissolution Study**

The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table-: Drug release studies of all the formulations

	% Drug Release											
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	13.25	18.36	19.65	20.65	28.94	23.15	19.95	17.56	18.55	18.50	17.99	16.40
2	28.94	29.92	31.85	33.68	39.75	34.75	30.78	32.40	35.56	36.80	37.75	35.45
3	34.65	47.93	51.25	57.91	46.90	48.41	41.25	42.26	46.80	46.45	47.50	46.50
4	44.10	64.72	63.92	63.25	53.96	52.36	52.38	51.28	51.40	50.28	51.75	51.30
5	56.55	75.92	79.90	72.18	62.25	63.28	61.28	60.54	62.70	62.68	63.71	63.70
6	68.92	82.83	82.15	82.90	73.29	71.36	72.29	71.15	72.87	73.85	74.70	74.25
7	72.26	89.39	89.36	89.56	83.65	80.27	81.25	83.50	83.31	82.29	80.10	83.50
8	89.36	92.68	93.64	92.29	94.56	91.36	96.28	92.25	93.90	93.89	94.90	95.56

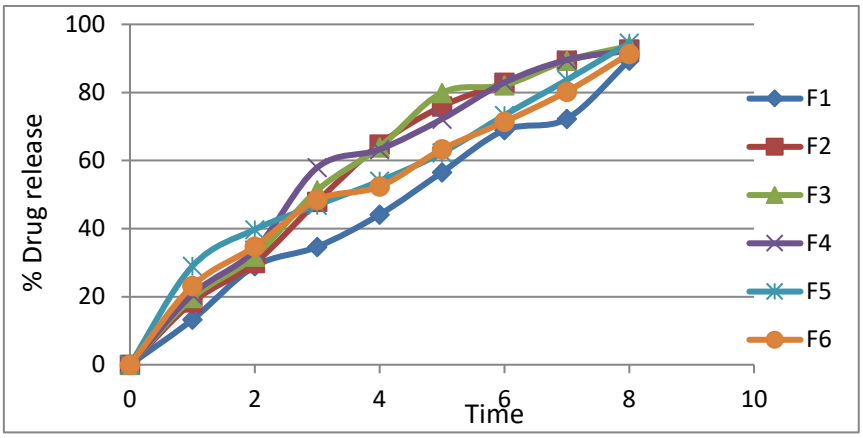

Fig-3: In vitro drug release studies of F1- F6 formulation

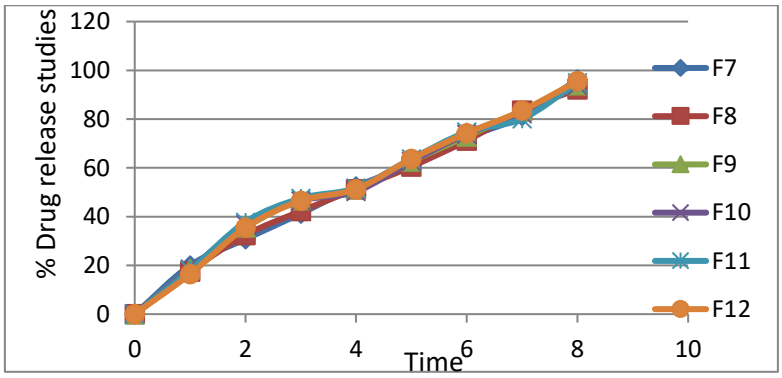

Fig-4: In vitro drug release studies of F6- F12 formulation

Drug release kinetics:

All the 12 formulation of atorvastatin tablets prepared were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 10 ml of Standard buffer pH 6.8 period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

- Cumulative percent drug released vs. time (zero order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential)

Table-4: Drug Release Kinetics of Formulation F7

TIME	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
1	19.95	1	0	1.299943	80.05	80.05
2	30.78	1.414214	0.30103	1.488269	69.22	69.22
3	41.25	1.732051	0.477121	1.615424	58.75	58.75
4	52.38	2	0.60206	0.30103	47.62	47.62
5	61.28	2.236068	0.69897	1.787319	38.72	38.72
6	72.29	2.44949	0.778151	1.859078	27.71	27.71
7	81.25	2.645751	0.845098	1.909823	18.75	18.75
8	96.28	2.828427	0.90309	1.983536	3.72	3.72

Zero order kinetics

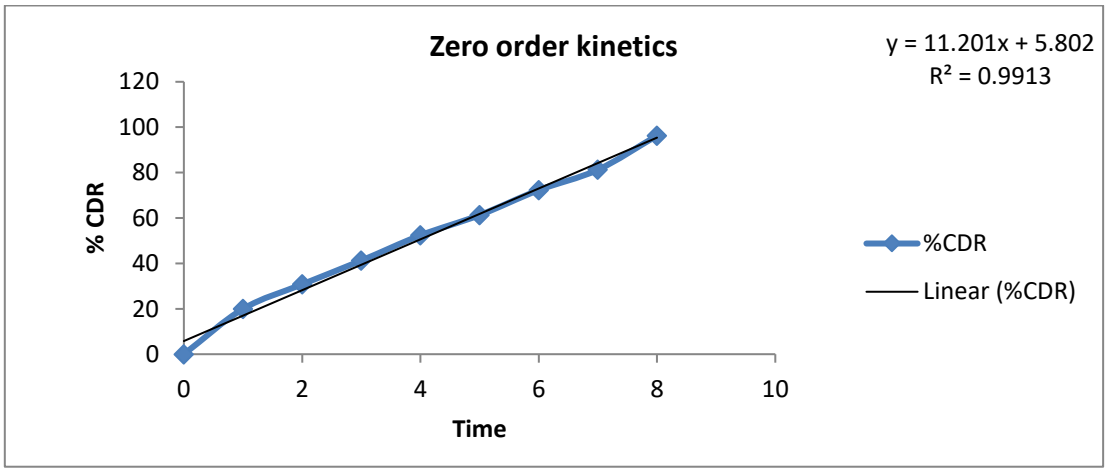

Fig-5: Zero order kinetics of optimized formulation

First order kinetics

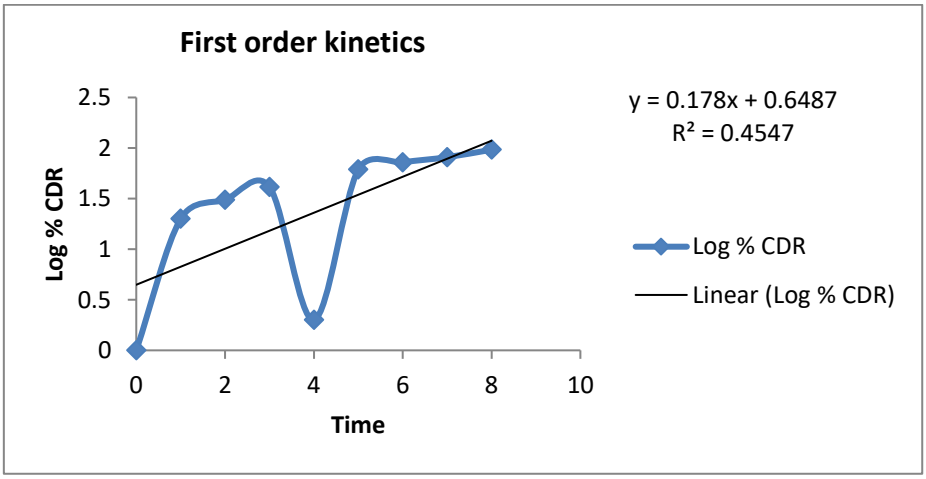

Fig-6: First order kinetics of optimized formulation

Higuchi model

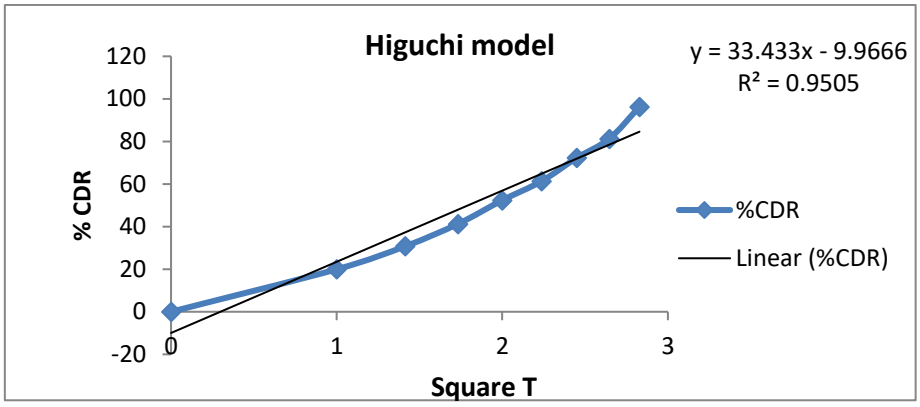

Fig-7: Higuchi model of optimized formulation

Korsmayer peppas

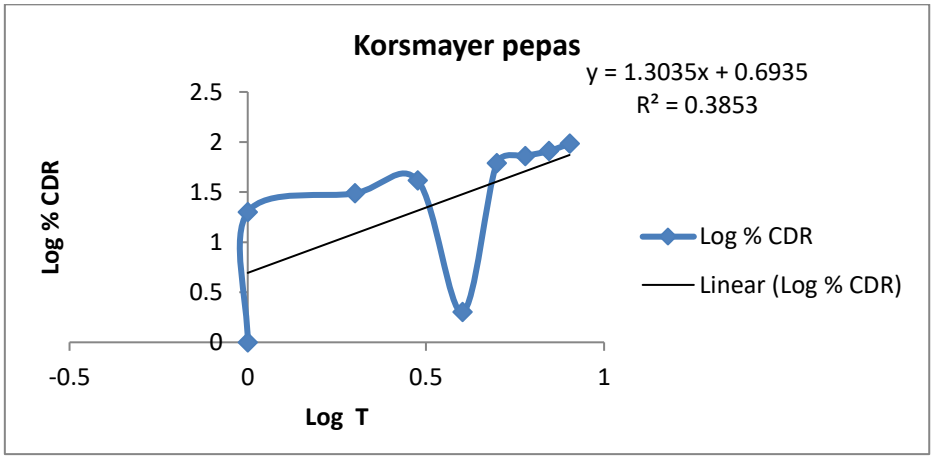

Fig-8: Korsmayer pepas of optimized formulation

Stability studies

Sustained release matrix tablets of Atorvastatin formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°C and 2-8°c for a period up to 180 (6 months) days. The samples were withdrawn after periods of 15 days, 30, 60, 90, 120,150 and 180 days and were analyzed for its appearance, hardness, friability, drug content and in vitro release. The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for F7 formulation. When it was stored at the three storage conditions. However, there was slight variation in in vitro release when it is stored at 2-8°C, there was no change when it is stored at 40°C and room temperature.

Table-5: Stability Studies of Optimized Formulation

S.no	Time in days	Physical changes	Mean % drug content		
			Atorvastatin		
			25°C/60%	30°C/75%	40°C/75%
1	01	No Change	96.28	96.28	96.28
2	30	No Change	96.25	96.24	96.18
3	60	No Change	96.12	96.13	96.16
4	90	No Change	96.09	96.10	96.15
5	120	No Change	96.25	96.24	96.18
6	150	No Change	96.12	96.13	96.16
7	180	No Change	96.09	96.10	96.15

4. CONCLUSION

Present work was done with an aim to formulate tablet dosage form of Atorvastatin and to evaluate the tablets for various parameters including in vitro drug release studies. Atorvastatin was subjected to preformulation studies; based on the results obtained, Atorvastatin fast dissolving tablets were successfully formulated. 12 Formulations were prepared by using natural and synthetic polymers, magnesium stearate as lubricant, microcrystalline cellulose as filler. These formulated powder blends were evaluated for physical parameters such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose and were found to lie within the specifications. The powdered blends were compressed into tablets by direct compression method and were evaluated for the parameters such as average weight, weight variation, thickness, friability, hardness, disintegration time, drug content and dissolution rate. All the parameters viz: Friability, Hardness, Thickness, Weight variation and drug content were also found to be within limits.

Drug release profiles of F7 were found to be satisfactory comparative to other formulations. The formulation F7 was found to be most effective as it has shown faster disintegration and maximum drug release among all the four formulations. Stability studies of the optimized formulation were done and found that there was no significant change in the physical properties. It was also observed that to further increase the drug release from matrix tablets, solubility enhancement of Atorvastatin is required and is under investigation.

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