International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR |Volume 7 | Issue 4 | Oct - Dec - 2019
www.ijamscr.com

Research article *Medical research*

Research on mouth dissolving tablet atorvastatin calcium using natural superdisintegrants

Sakshi Khandelwal*, Dr. Mayank Bansal, Jitendra Kumar

Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur (Rajasthan) India

***Corresponding Author**: **Sakshi Khandelwal**

Email id: sakshi.vapi96@gmail.com

ABSTRACT

The Purpose of the present research was to prepare Mouth Dissolving Tablet of Atorvastatin Calcium using natural superdisintegrant i.e. Plantago Ovata and Guar gum with the objective of patient compliance and the reduced onset of action due first pass metabolism. Tablet were prepared by direct compression method. The powder mixtures prepared were subjected to both pre and post compression evaluation parameters like micromeritics properties, tablet hardness, friability, wetting time, disintegration time and in vitro drug release. The results of micromeritics studies revealed that all formulations were of acceptable to good flow ability. On the basis of invitro studies F3 containing 16mg of Plantago Ovata was best formulation.

Keywords: Mouth Dissolving tablet, Atorvastatin Calcium, Plantago Ovata, Guargum, Superdisintegrants, In-vitro drug release.

INTRODUCTION

Oral dosages form is the most desirable and preferred dosages form. Oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of convenience in administration of drug and cost-effective manufacturing process. [1]

Hypolipidemic agent Atorvastatin Calcium is a selective and competitive inhibitor of HMG-CoA reductase. The rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme Ato mevalonate, a precursor of sterols, including cholesterol. Studies done clinical and pathologic reflected that raised-up plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are the risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk. As it has long half-life (14hrs), it is not suitable drug for controlled release formulation. Tablet dosage form is preferable because other dosage form don't have good shelf life in case of atorvastatin due to its degradation and impurity issue. Different processing parameters on final formulation & worst-case study were carried out for optimization of the best condition of the formulation. [1]

Atorvastatin calcium is highly receptive to heat, moisture, a low pH environment and light. Again, the amorphous form is many times unstable than its counterpart crystalline form. In acidic environment it degrades into corresponding lactone. The in-vitro

evaluation of an immediate release dosage form by using Atorvastatin calcium in amorphous form was used in tablets prepared by Dry granulation/Roller compaction techniques. The percent drug releases at 0, 5, 10, 15 and 30 mins were selected as responses. The release of Atorvastatin Calcium was immediate within 2-3 mins, indicating the usefulness of the formulations for once daily dosage forms. [2]

MATERIAL

Atorvastatin calcium was received as gift from R.K Enterprises, Meerut and other excipient used in work was obtained as gift from CDH Laboratory, New Delhi.

FORMULATION OF MOUTH DISSOLVING TABLETS

Weigh all the ingredients. Mix all the ingredients geometrically except Talc and Magnesium Stearate. After that add lubricant talc and magnesium stearate to the mixed material and passed through #60mesh.Then this mixture is compressed in multi stationary compression machine. Each tablet contains 10mg Atorvastatin calcium and other pharmaceutical ingredients such as Plantago ovata mucilage, Guar gum, Sodium starch, Crospovidone, Magnesium oxide, Sucralose, Aerosil, Talc, Magnesium stereate, Mannitol & Orange flavour.

EVALUATION PARAMETERS AND RESULT

Determination of λmax

The pure drug atorvastatin calcium was scanned by UV Spectrophotmeter at 200-400nm to determine λmax. The peak was observed at 253nm for atorvastatin calcium in 6.8 pH simulated salivary fluid.

Standard Calibration Curve

The standard calibration curve of atorvastatin calcium was obtained by plotting Absorbance V/s. Concentration. Table 1 shows the absorbance values of atorvastatin calcium. The standard curve is shown in Fig. no. 1.

Table 1: Standard calibration result of atorvastatin calcium:

S.No.	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	2	0.060 ± 0.034
3	4	0.131 ± 0.023
4	6	0.198 ±0.043
5	8	0.292 ±0.098
6	10	0.354 ±0.012

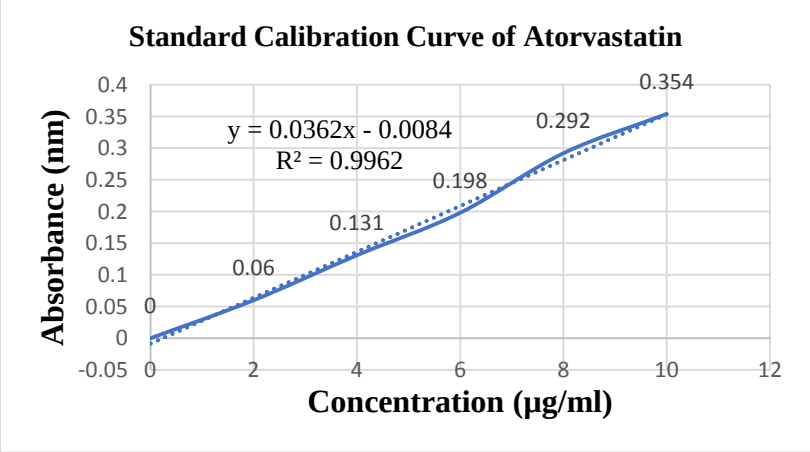

Fig. 1: Standard calibration curve of atorvastatin calcium

Pre-Compression Evaluation

Bulk Density

It may be defined as the mass of powder divided by the bulk volume. The bulk density were found between 0.28-0.34 g/cc.

Tapped Density

It may be defined as the mass of the powder divided by tapped volume. The tapped density were found between 0.34-0.42g/cc.

Compressibility Index

It is used to measure the porosity of the powder to be compressed to evaluate the interparticulate interactions. It was found between 11.11-21.95 which revealed that all powders had excellent to passable flow properties.

Hausner's ratio

It is used to know ease of flow of powder. Hausner's ratio were found between 1.17-1.25 which revealed that all powder blends had good flow properties.

Angle of Repose

It may be defined as the maximum angle possible between the surface of pile of powder and horizontal surface. The angle of repose were found between 28.20-32.29 which revealed that all powder blends had good to passable flow.

Table 2: Pre-compression studies of powder blend:

Formulations (code)	Bulk density (g/cc) ± S.D. n=3	Tapped den- sity (g/cc) ±S.D. n=3	Carr's index (%) ±S.D. n=3	Hausner's ratio ±S.D. n=3	Angle of re- pose (de-gree) ±S.D. n=3
F1	0.28±0.005	0.34±0.01	17.64	1.21	29.23±0.87
F2	0.34±0.005	0.42±0.01	19.04	1.23	28.20±1.11
F3	0.33±0.005	0.41±0.01	19.51	1.24	30.38±1.29
F4	0.31±0.001	0.39±0.01	20.51	1.25	31.1±1.40
F5	0.33±0.01	0.38±0.3	13.15	1.15	29.63±1.55
F6	0.32±0.01	0.38±0.005	15.78	1.18	31.93±1.56
F7	0.31±0.005	0.38±0.10	18.42	1.22	32.29±2.06
F8	0.32±0.021	0.36±0.03	21.95	1.12	30.24±2.54
F9	0.30±0.032	0.37±0.02	11.11	1.23	29.43±1.32
F10	0.28±0.005	0.33±0.01	15.15	1.17	30.04±1.39
F11	0.26±0.03	0.31±0.05	16.12	1.19	28.45±1.21

Thickness and Diameter

Thickness and diameter of tablets were calculated using the screw gauge. Thickness and Diameter of the formulations were found between 3.37mm-3.92mm and 7.76mm-8.31mm respectively.

Weight variation test

The weight of the tablet was routinely determined to ensure that a tablet contain proper amount of the drug. All the prepared formulations passed the weight variation test and the percentage deviation from average weight of tablets were found within the official limit ±7.5.

Hardness

It is the force which is required to break a tablet. Hardness for all the formualtions were found between 3.05-5.53 kg/cm^2.

Friability (%)

Friability may be defined as loss in weight of tablet during transportation. Friability for all formulations were found between 0.12-0.53%.

Table 3: In-process evaluation of tablets:

Formulations (code)	Diameter (mm) ± S.D., n=3	Thickness (mm) ± S.D., n=3	Weight variation	Hardness (kg/cm^2) ± S.D., n=3	Friability (%)
F1	8.05± 0.04	3.56 ±0.23	Pass	3.75±0.25	0.32
F2	8.21 ±0.32	3.48 ±0.31	Pass	3.46±0.25	0.46
F3	7.89 ±0.76	3.37 ±0.42	Pass	3.05±0.16	0.53
F4	8.04 ±0.23	3.64 ±0.13	Pass	5.12±0.32	0.15
F5	8.31 ±0.54	3.78 ±0.12	Pass	3.63±0.28	0.34
F6	7.87±0.11	3.54 ±0.31	Pass	3.43±0.14	0.37
F7	7.76 ±021	3.42 ±0.17	Pass	3.25±0.25	0.38
F8	8.25 ±0.98	3.92±1.02	Pass	5.33±0.21	0.12
F9	8.13 ±0.23	3.43±0.67	Pass	4.58±0.32	0.22
F10	8.02 ±0.12	3.56 ±0.76	Pass	3.11±0.14	0.43
F11	8.03 ± 042	3.62 ± 0.13	Pass	3.12 ± 0.23	0.44

Wetting time

Wetting time was determined because it mimics the action of saliva on tablet in oral cavity. It was found between 26-209 seconds for all formulations. On increasing in concentration of natural superdisintegrant, wetting time decreased which might be due to fast water uptake at low concentrations, but after a certain concentration wetting time increased on increasing the concentration of superdisintegrant which might be due to that beyond certain concentration, gel formation might be occur on initial contact of fluid with tablet due to which more fluid could not enter into the tablet and wetting time increases. Formulation F3 (16 mg mucilage) had least wetting time and formulation F8 (24 mg Guar gum) had highest wetting time among all formulations.

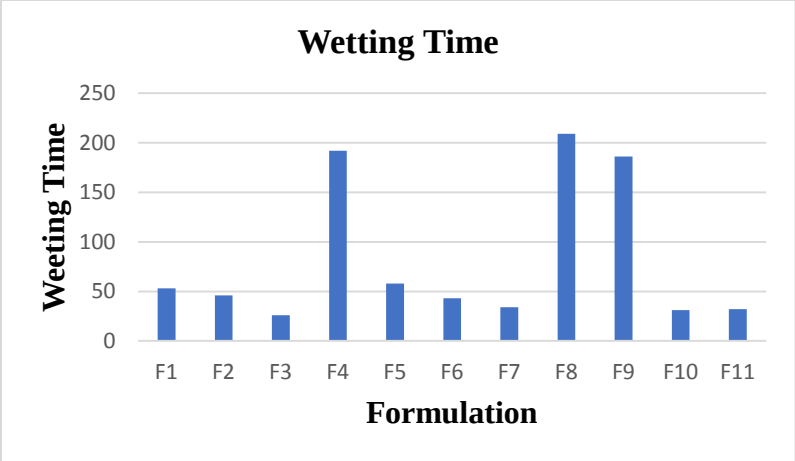

Fig.2: Wetting time of different formulations

Water absorption ratio

Water absorption ratio was found between 40.42-68.43% for all formulations of tablets. On increase in concentration of natural superdisintegrant up to a certain concentration, water absorption ratio increased which might be due to fast water uptake up to that concentration but after that water absorption ratio decreased which might be due to that gel formation occurred on initial contact of tablet with fluid and fluid could not further penetrate into the tablet. Formulation F3 (16 mg mucilage) had highest water absorption ratio because of higher porosity between the particles and F8 (24 mg Guar gum) had least water absorption ratio.

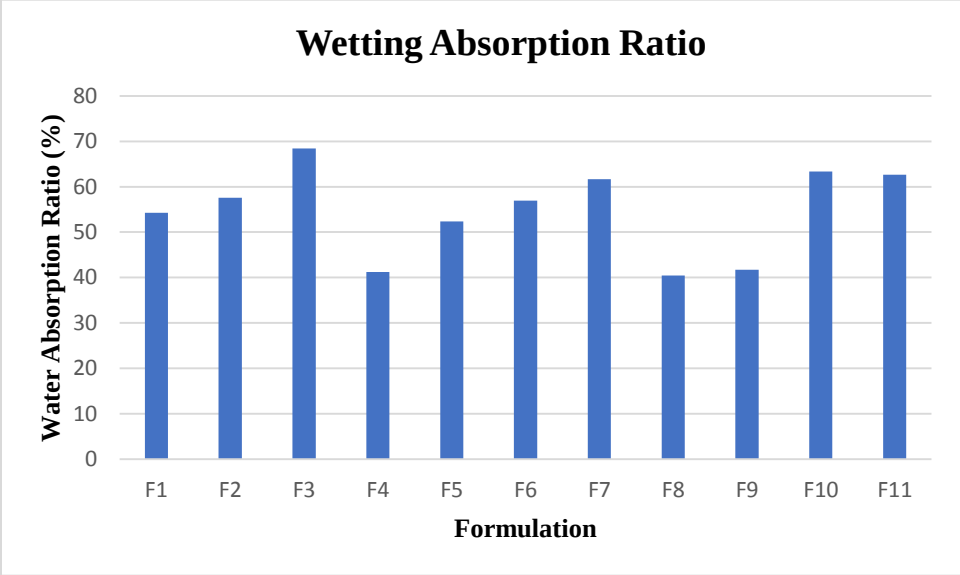

Fig. 3: Water absorption ratio for all formulations

In-Vitro disintegration time

It is the most important evaluation parameters which should be optimized in formulation of Mouth Dissolving Tablets. In-vitro disintegration time was found between 18- 198 seconds for all formulations. It was observed that disintegration time was decreased on increase in concentration of natural superdisintegrants up to a certain concentration, after that concentration disintegration time increased on increase in concentration. It might be due to that at higher concentrations, the natural superdisintegrants behaved like binding agents due to gelling property at high concentration. Formulation F3 (8% mucilage) had least disintegration time of 18 seconds because of higher porosity between the particles of mucilage and F8 (12% mucilage) had highest disintegration time of 198 seconds because of binding effect after a certain concentration. Formulation F0 (no superdisintegrants) had disintegration time.

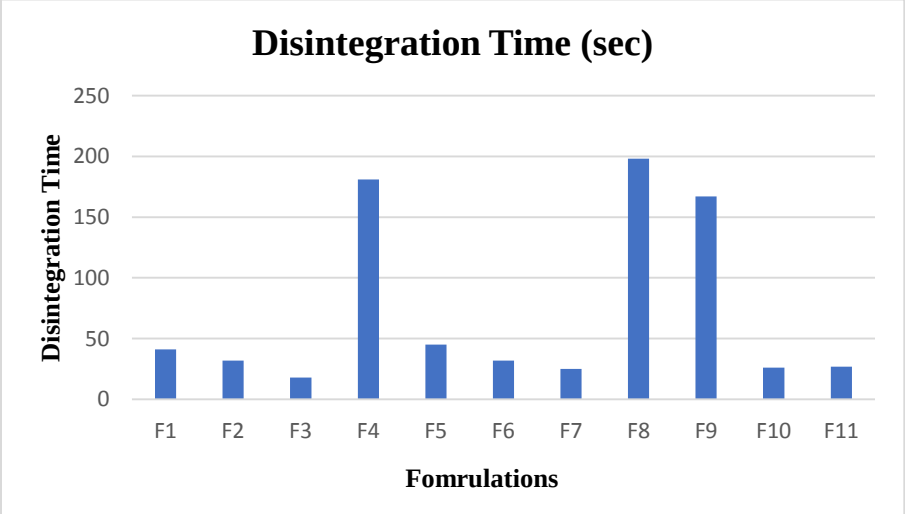

Fig. 4: Disintegration Time for all formulations

Drug content (%)

Drug content was found between the 93.76-98.76% for all the formulations. F3 formulation had highest drug content that was98.76% and formulation F4 had least drug content that was 93.24%. F3 formulation was selected as best formulation on basis of drug content.

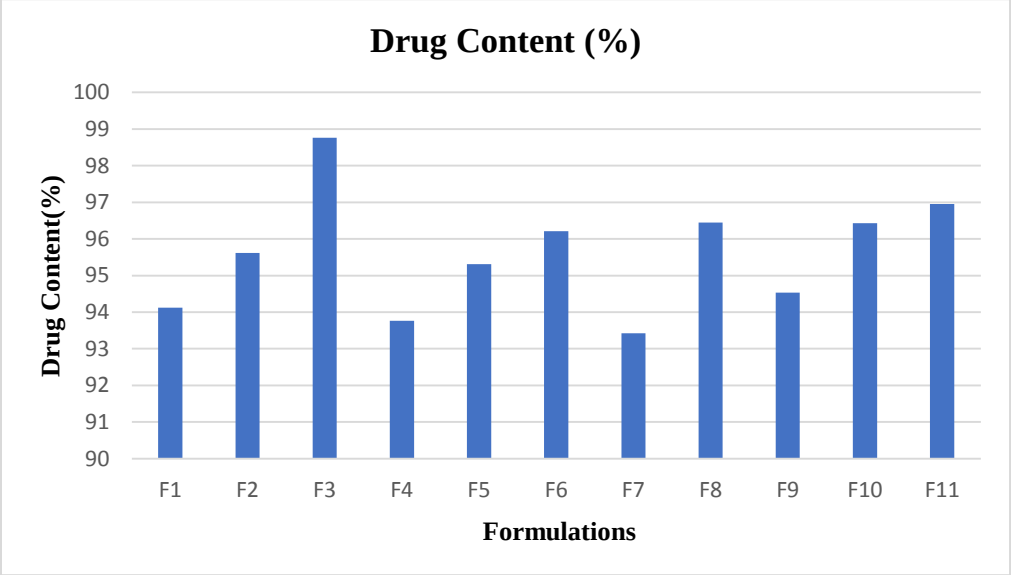

Fig. 5: Drug Content (%) for all formulations

Table 4: Post-compression studies of tablet:

Formulations (code)	Wetting time (sec), ±S.D.	Water absorption ratio (%) ± S.D., n=3	D.T. (sec) ± S.D., n=3	Drug content (%) ± S. D., n = 3
F1	53±1	54.23±0.12	41 ± 1.5	94.12±1.12
F2	46±0.5	57.56±0.19	32 ± 1.5	95.62±1.04
F3	26±0.5	68.43±0.06	18 ±1	98.76±1.56
F4	192±1.73	41.21±0.12	181 ± 2.51	93.76±2.12
F5	58±1.15	52.34±0.15	45±1.15	95.31±1.63
F6	43±0.5	56.91±0.66	32±0.5	96.21±1.09
F7	34±1.5	61.63±26	25±2	93.42±0.87
F8	209± 0.4	40.42 ± 0.12	198±2	96.45±2.12
F9	186±0.5	41.71 ± 0.03	167±1	94.53±1.92
F10	31 ± 2.6	63.32 ± 0.29	26±2.5	96.43±1.05
F11	32 ± 0.5	62.64 ± 1.12	27±2	96.95±0.76

In-Vitro Drug Dissolution Studies

In-vitro dissolution study for formulated Mouth Dissolving Tablets of Atorvastatin calcium was carried out in 6.8pH simulated salivary fluid because the tablet was intended to dissolve in oral cavity. The percentage cumulative drug release was found between 58.25-98.08% for all the formulations. Formulation F3 had highest % cumulative drug release that was 98.08% and F8 had least %cumulative drug release that was 57.65% among all formulations.

Table 5: In-vitro drug release for all formulations

Time (min)	% Cumulative drug release

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
5	48.19 ±0.08	53.08 ±0.18	44.06 ±1.02	16.56 ±0.19	49.26 ±0.17	51.32 ±0.76	51.38 ±0.15	17.08 ±0.18	21.32 ±0.76	52.34 ±0.52	54.34 ±1.05
10	60.6 ±0.16	70.15 ±0.14	64.35 ±1.05	30.32 ±0.13	70.61 ±0.13	71.97 ±0.21	68.98 ±0.14	31.15 ±0.14	32.97 ±0.21	70.98 ±0.32	71.64 ±0.98
15	72.77 ±0.19	76.87 ±0.06	84.64 ±0.46	39.09 ±0.24	80.80 ±0.22	82.21 ±0.63	77.97 ±0.10	38.87 ±0.06	40.21 ±0.63	82.93 ±0.91	81.03 ±0.54
20	84.52 ±0.52	87.98 ±0.06	94.68 ±0.97	42.89 ±0.13	89.80 ±0.22	90.23 ±0.32	87.78 ±0.15	43.98 ±0.06	45.23 ±032	94.21 ±0.67	93.24 ±0.12
25	93.21 ±0.05	94.87 ±0.12	96.78 ±0.24	55.24 ±0.15	91.88 ±0.29	92.02 ±0.10	91.60 ±0.19	55.87 ±0.12	56.02 ±0.10	96.05 ±1.01	95.78 ±0.24
30	94.67 ±0.10	95.65 ±0.10	98.08 ±1.58	58.25 ±0.21	92.88 ±0.25	94.82 ±0.14	92.23 ±0.18	57.65 ±0.10	59.67 ±0.14	96.93 ±0.62	96.85 ±0.07

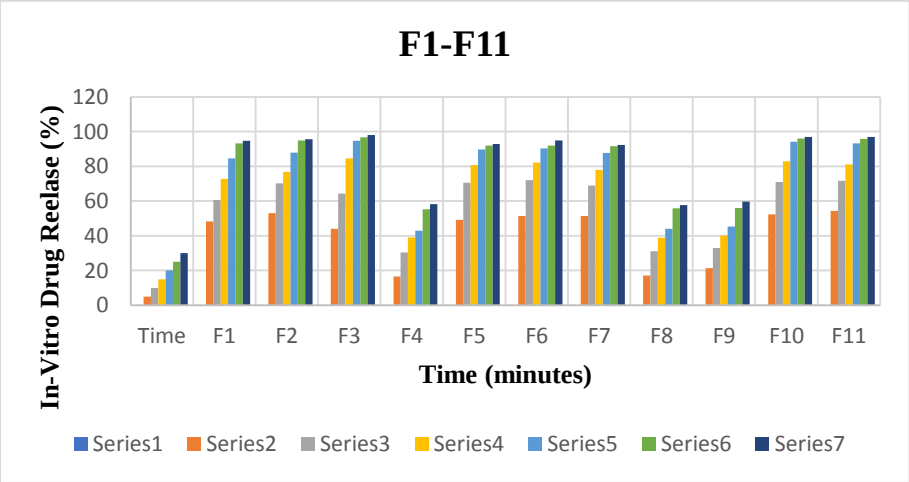

Fig. 6: In-vitro drug release for all formulations

By analysing all the above datas the formulation F3 was found to be the best formulation.

Drug Kinetics

- Drug release kinetics of F3 (best formulation)
- Drug release kinetics studies for best formulation (F3) were done using software KinetDS3 and it was observed that F3 formulation followed Korsmeyer-peppas drug kinetic model for drug release.

Table 6: Drug kinetic of F3 formulation

Time (Minutes)	Cumulative % Drug Release (Zero Order Kinetics)	Log Remaining Cumu- lative % Drug Release (first Order Kinetics)	Cube Root of Remaining Cumulative % Drug Re- lease (Hixson Crowell Ki- netics)
00	0	0	0
05	44.06	1.74	55.94
10	64.35	1.55	35.65
15	84.64	1.92	15.36
20	94.68	1.97	5.32

25	96.78	1.98	3.22
30	98.08	1.99	1.92

Table 7 : Calculated Values by Higuchi and Krosmeyer- Peppas Models

Higuchi Model		**Krosmeyer- peppas model**	
Square root of time	**Cumulative % Drug Release**	**Log time**	**Log Cumulative % Drug release**
0	0	0	0
2.23	44.06	0.69	1.644
3.16	64.35	1	1.808
3.87	84.64	1.17	1.92
4.47	94.68	1.30	1.97
5	96.78	1.39	1.98
5.47	98.08	1.47	1.99

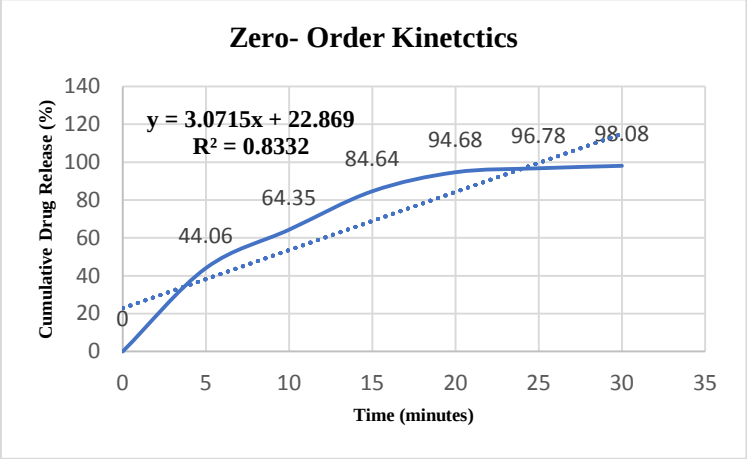

Fig. 7 Zero order kinetic

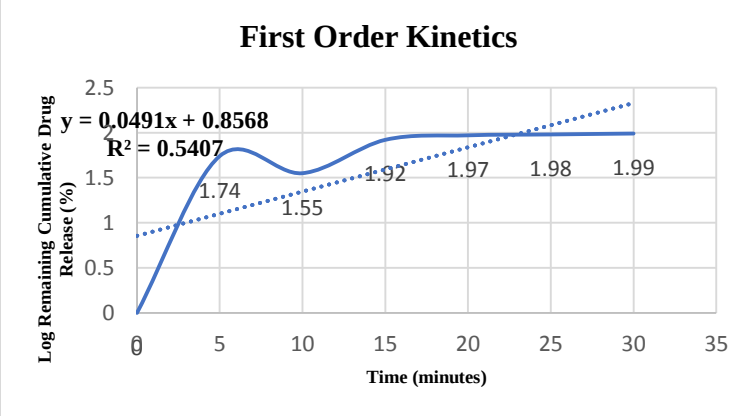

Fig. 8: First order kinetics

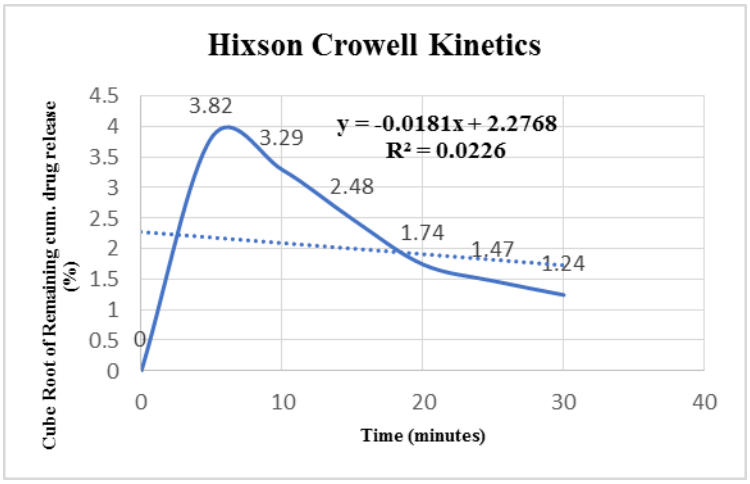

Fig. 9: Hixson crowell kinetics

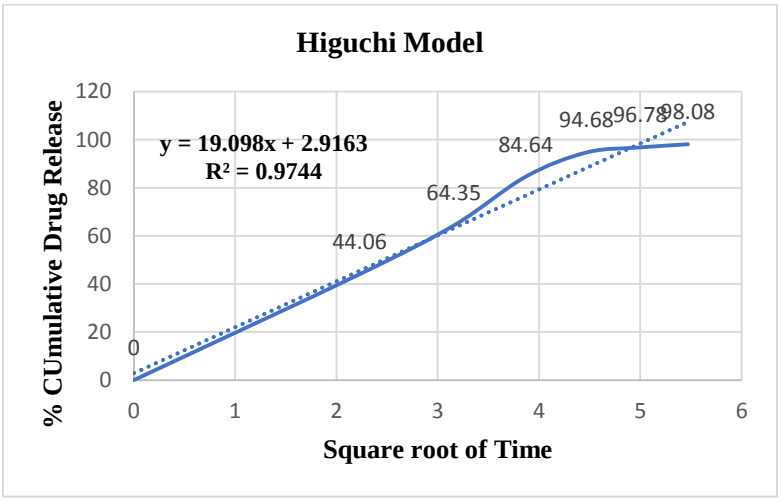

Fig. 10: Higuchi Kinetics

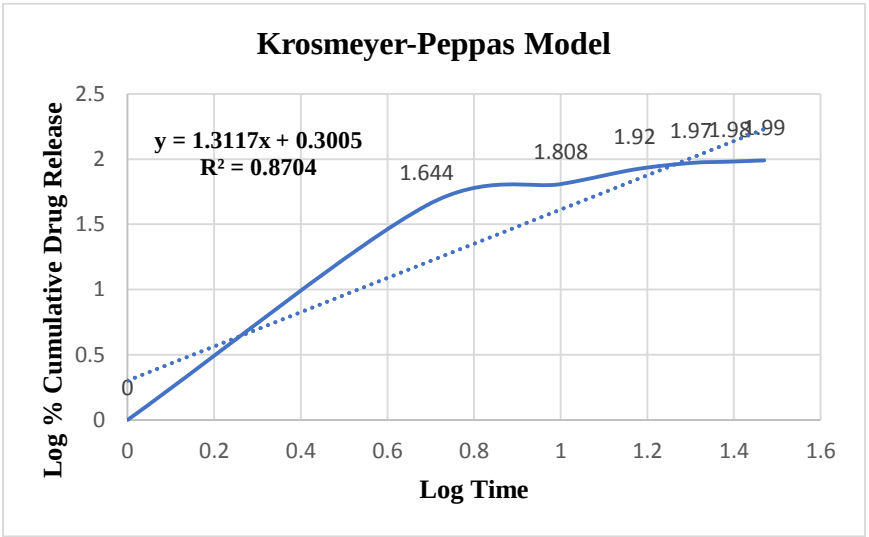

Fig. 11: Krosmeyer- peppas kinetics

Table 8: Drug kinetic model

Sr. no.	Drug kinetic models	R^2 value
1	Zero order	0.8332
2	First order	0.5407
4	Korsmeyer- peppas model	0.8704
5	Higuchi model	0.9744
6	Hixson-crowell model	0.0226

Stability studies for best formulation

The tablets of best formulation were sealed in amber-colored bottle and kept it in stability chamber which was maintained at 40±2°c / 75±5% RH. The study was carried out for one month. At the end of study, tablets were removed from bottle and analyzed for Physical evaluation, disintegration time, wetting time, drug content and in-vitro dissolution studies. Similarity (f2) factor was calculated using the software DD Solver for the tablets after stability studies and before stability studies. The formulations have no significant difference in dissolution.

CONCLUSION

Mouth Dissolving Tablets were formulated using natural superdisintegrant after evaluating the increasing demand for natural excipients due to advantages like biocompatibility, biodegradability, price effective and better activity than synthetic excipients.

Several formulations were formulated using Mucilage of Plantago ovata and Guar gum in concentration of 2-11% and 3-12% respectively, one formulation formulated without any superdisintegrant and two formulations were formulated using synthetic superdisintegrant for comparison with natural super disintegration. Good result occurred from 3 natural and 2 synthetic agents.

On the basis of in-vitro study it was found that formulation F3 containing 8% mucilage was best formulation. It was also observed that on increasing the concentration of mucilage beyond 8% and guar gum beyond 9%, super disintegration property was destroyed because disintegration time of tablets formulated with 11% mucilage and 9% guar gum was more than tablet formulated without any superdisintegrant.

The stability studies revealed that F3 (best formulation) remain stable after exposure to elevated conditions of temperature and moisture.

REFERENCES

[1]. Altuntas, T. G., Journal of liquid chromatography & related technologies. 2004, 83-93.
[2]. Dale Martin., 35th International edition, the complete drug reference, pharmaceutical press, London, Chicago, 1094.
[3]. Allen, L.V., and Wang, B., Particulate support matrix for making a rapidly dissolving tablet, US Patent 1997, 5595761.
[4]. Pebley., WS., Jager., NE, and Thompson SJ, Rapidly disintegrating tablets, US Patent No.5, 1994, 298, 2.
[5]. Bogner, R.H., and sWilkosz, MF., Fast-dissolving tablets: new dosage convenience for patients, U.S. Pharm. 27, 2002, 34–43.
[6]. Sanket K., Shiv K. G., "Mouth dissolving tablet (FDTs): Current status, new market opportunities, recent advances in manufacturing technologies and future prospects". Int. J. Pharm. Pharm. Sci, 6(7), 2014, 22-35.
[7]. Shukla, D., Chakraborty S., Singh S., Mishra B., Science Pharm. 2009, 309-326.
[8]. Leuner, C., DressmanJ, European J of Pharm and Biopharm, 50, 2000, 47-60.
[9]. Pahwa, R., and Gupta, N., Superdisintegrants in the Development of Orally Disintegrating Tablets: A Review. International Journal of Pharmaceutical Science and Research, 2, 2011, 2767-2780.
[10]. Reddy, LH.,Ghose B and Rajneesh, Indian J. Pharm. Sci., 64(4), 2002, 331-336.
[11]. Devrajan, P.V., and Gore, SP. Express Pharma Pulse, 7(1), 2000.
[12]. Dong, W., Su, X.,Xu, M., Hu, M., Sun, Y., Zhang, P., Asian Journal of Pharmaceutical Sciences 13(6), 2018, 546-554.

[13]. Wicaksono, Y., Wisudyaningsih, B., Siswoyo, T., Tropical Journal of Pharmaceutical Research, Aug. volume 16(7), 2017, 1497-1502
[14]. Ali, J., Shamsuddin, Fazil, M., Ansari, S.,J Adv Pharm Technol Res. 7(1), 2016, 22–26.
[15]. Ahmed, M., Choudhari, R., Acharya, A., J Pharm Sci., 5(2), 2015, 53-60
[16]. Balaji, B., Krishnaveni, V., Goud,. Int J Pharm PharmSci, Jan. 6(2), 2014, 332-337.
[17]. Belhadj, Z., Zhang, S., Zhang, W., Wang, J. Formulation development and bioavailability evaluation of a Self-nanoemulsifying Drug Delivery System (SNEDDS) of Atorvastatin Calcium. Int. J. Pharm. Jan. 29, 2013, 2051-5782.
[18]. Jahan R, Islam M, Tanwir A, Chowdhury JA. In vitro dissolution study of atorvastatin binary solid dispersion. J Adv Pharm Technol, 2013, 18-24.
[19]. Geethalakshmi, A., Divya, V., Mahalingan, K., Rao, N., Pandey, H., World Journal Pharmacy and Pharmaceuticalscience 2013, 205-209.
[20]. Kumare, M.M., Marethe P.R., Kawade, M.R., Ghante, H.M., and Shendarkar R.G., Asian Journal of Pharmaceutical and Clinical Research, 6, 2013, 81-85.
[21]. Jain, K., Suresh, R., Sood, S., K. Gowthamarajan. J. Pharm. Sci. & Res. 5(1), 2013, 18 - 25
[22]. Tangri, P., Satheesh, N., Drug Development and Delivery 2012.
[23]. Khan, F., Islam, M., Roni, M.,Jalil, R.,.Sci Pharm. 2012, 1027–1043.
[24]. Hardik, S., Kumavat T.,, Yadav K., Bhatt C., Shah C., Ramani V., International Journal of Pharmacy Research and Technology, 2(4), 2012, 35-40
[25]. Rajpurohit, H., Sharma, P., Sharma, S., Purohit, s., Bhandari A., Journal of Young Pharmacists 3(3), 2011, 211-215.
[26]. Malik, K., Arora, G., Singh, I., Arora, S., Int J Pharm Investig. 1(3), 2011, 192–198
[27]. Khan, N., Hassan,M., Dehghan, Sci Pharm. 80(1), 2011, 215–228.
[28]. Abed, Khalid, K., Hussein, Ahmed, A., Ghareeb, Mowafaq, M., Abdulrasool, Alaa, A., AAPS PharmSciTech. 11(1), 2010, 356–361.
[29]. Sharma, V., Pathak. K., and Philip, A., AAPS Pharma Science and Technology. 9(1), 2008, 87-94.
[30]. Gohel,M., Patel,M., Amin,A., Agrawal, R., and Bariuya, N., AAPS Pharma Sciences Tech, 5(3), 2004, 1-6.

How to cite this article: Sakshi Khandelwal, Dr. Mayank Bansal, Jitendra Kumar. Research on mouth dissolving tablet atorvastatin calcium using natural superdisintegrants. Int J of Allied Med Sci and Clin Res 2019; 7(4): 1193-1203.
Source of Support: Nil. **Conflict of Interest:** None declared.