www.ijrps.pharmascope.org

ISSN: 0975-7538
Research Article

# Formulation and evaluation of Atorvastatin calcium sustained release matrix tablets

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**ABSTRACT**

In the present research, an attempt has been made to formulate sustained release matrix tablets of Atorvastatin Calcium, a novel statin reported to reduce the morbidity and mortality of cardiovascular diseases, which shows poor bioavailability (12%) and low aqueous solubility (BCS Class II). The matrix tablets were prepared by direct compression method using natural polymers (Xanthum gum -F1, F2, Guar gum -F3, F4, Carragenan -F5, F6) and synthetic polymers (HPMC-K100M -F7, F8 and HPMC- 50 cps -F9, F10) at various concentrations and its effect were compared. The tablets were subjected for weight variation, hardness, thickness, friability, drug content uniformity, *in vitro* dissolution and FT-IR studies. All the formulations showed compliance with pharmacopoeia standards and the FT-IR spectrum shows compatibility of the drug with excipients. The cumulative drug release for F2, F4 and F6 was 72%, 98% and85% up to 17 h indicating the retarded release due to higher concentration (60 mg) of natural polymers than the other batches and its $t_{50\%}$ values were found to be 12 ½ h and 8 h. The drug release mechanism was found to be Korsmeyers and Peppas model ($R^2$=0.9022) for F2 and zero order ($R^2$=0.9244) for F4 and ($R^2$=0.9348) for F6. The formulations F2, F4 and F6 which was prepared by natural polymers were optimized for the formulation of sustained release matrix tablets of Atorvastatin Calcium.

**Keywords:** Atorvastatin; Carrageenan; Guar gum; Sustained release; Xanthan gum

## INTRODUCTION

Hyperlipidimia is extremely common disorder where the lipids or lipoproteins are elevated in the blood stream prevalent in general population. It causes major risk factor for cardiovascular diseases due to influence of cholesterol. Statins are most commonly prescribed for dyslipidemia because they are effective, well tolerated, and easy to administrate and have relatively few adverse effects. Atorvastatin calcium (At.Ca) is a widely prescribed lipid lowering agent, belongs to the HMG-CoA reductase inhibitors it comes under BCS class II drugs. Drugs belonging to this class are expected to have a variable dissolution profile and affect the absorption (Gubbi 2003). At.Ca is rapidly absorbed after oral administration, with time to reach peak concentrations ($t_{max}$) within 1-2 hrs and attributed to presystemic clearance (Lennernas 2003, Corsini 1999). It is insoluble in aqueous solutions of pH 4 and below, slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol and freely soluble in methanol (PDR 2005). It undergoes high first pass metabolism, with 98% protein binding and posses' only 12% oral bioavailability after administration of 40mg oral dose (Patel 2010). In oral sustained release dosage form the natural polymers used for several decades because it is biodegradable and nontoxic in nature, which can hydrate and swell on contact with aqueous media (Nayak 2011). Xanthan gum is a high molecular weight extracellular polysaccharide, produced on the commercial scale by the viscous fermentation of a gram-negative bacteria *Xanthomonas campesteris* which are used to retard the drug release (Jain 2008, Thilak 2000). Guar gum a polysaccharide derivative with glycoside linkage, produced from the guar plant seeds i.e., *Cyampopis tetragonolobus* was also used as sustained release polymer (Thilak 2000, Chudzikowski 1971). Carrageenan a polysaccharide that are obtained commercially by extraction of certain species of red seaweeds of *Rhodophyceae,* which can be used for retarding the drug release (Chudzikowski 1971, Varshazaz 2006).

The synthetic hydrophilic polymer Hydroxy Propyl Methyl Cellulose (HPMC) is most widely used in the formulation of sustained release dosage form and its function was based upon its viscosity range (Fred 2005). Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release dosage form. The aim of the present work was to prepare sustained release matrix tablets of Atorvastatin Calcium by direct compression method using natural polymers such as Xanthan gum, guar gum and Carrageenan and synthetic polymers like

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Received on: 30-11-2012
Revised on: 12-01-2013
Accepted on: 16-01-2013

**Table 1: Formulation of Atorvastatin calcium SR Matrix Tablets**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Atorvastatin calcium | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Xanthan gum | 45 | 60 | - | - | - | - | - | - | - | - |
| Guar gum | - | - | 45 | 60 | - | - | - | - | - | - |
| Carrageenan | - | - | - | - | 45 | 60 | - | - | - | - |
| HPMC K-100 | - | - | - | - | - | - | 45 | 60 | - | - |
| HPMC 50CPS | - | - | - | - | - | - | - | - | 45 | 60 |
| Lactose | 71 | 56 | 71 | 56 | 71 | 56 | 71 | 56 | 71 | 56 |
| Avicel Ph 102 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

HPMC- 50Cps and HPMC- K 100M in varying proportions and its effects was studied.

## MATERIALS AND METHODS

### Materials

Atorvastatin calcium was obtained as a gift sample from Cadila Health care limited, Xanthan gum, guar gum, HPMC K100M, HPMC 50 cps, Lactose, Magnesium Stearate are purchased from Loba Chemie, Mumbai, Carrageenan was procured from Himedia laboratories, Mumbai, Talc was procured from Microfine chemicals, Mumbai, Microcrystalline cellulose was obtained as a gift sample from signet chemicals, Mumbai. All other chemicals used were of analytical grade.

### Methods

### Preparation of Matrix Tablets

The sustained release matrix tablets of Atorvastatin calcium were prepared by direct compression method. At.Ca (10 mg) and the polymers at two concentrations (45 mg and 60 mg) and microcrystalline cellulose were weighed accurately, sieved through a mesh size no.45 and were blended for 20 min in the blender. Magnesium stearate and talc were added at the last and blended for additional three minutes. The tablets were prepared using single punch rotary punching machine using 8 mm flat dies and weight of each tablet was adjusted to 150 mg. The composition of tablets was mentioned in the table 1.

### Evaluation of Tablets

The compressed At.Ca tablets were subjected for the physical characterization such as weight variation, thickness, hardness and friability. The weight uniformity of tablets was determined by taking 20 tablets randomly and weighed in the analytical weighing balance (Sartorius BT224S) and their percentage variation was determined. Tablet thickness was randomly measured for 10 tablets from the prepared formulations using Vernier Calipers and their average valves were determined. 10 tablets from the prepared formulations were subjected to hardness testing using Pfizer tester and the average hardness valves are determined in $kg/cm^2$. The friability test was performed in the Roche friabilator (Campbell electronics), by placing 20 tablets into the friability chamber and rotated for 4 min at a speed of 25 rpm. The percentage weight loss was calculated from the initial and final weight of the tablets. The measurements were conducted in triplicate for each formulation (Lachman 1990).

### *FT-IR Analysis*

The compatibility of excipients with At.Ca was studied by using Fourier Transform Infra Red spectrometer (Analytical FT-IR 2500 spectrometer). This is the powerful analytical technique to predict the existence of incompatibility. FT-IR spectrum was taken for At.Ca (drug), physical mixture of drug and polymer and the formulation. Here, the samples were taken and mixed thoroughly with KBr and the pellets were prepared by using hydraulic press. The prepared discs were scanned in the range of 4000 $cm^{-1}$ to 400 $cm^{-1}$ at a resolution of 4.

### *Drug content uniformity*

The drug content uniformity was determined by taking 10 tablets randomly weighed and finely powdered the tablets. The powder equivalent to 10 mg of Atorvastatin calcium was accurately weighed and transferred in a 100 ml volumetric flask, the content was dissolved by adding minimum quantity of methanol and pH 6.8 phosphate buffers and was subjected to sonication for 10 min to achieve good solubilization. The solution was made up to the mark using pH 6.8 phosphate buffer to obtain a concentration of 100 µg/ml. The subsequent dilution was prepared to get a concentration of 20 µg/ml. And the absorbance was measured at 246 nm using UV visible spectrophotometer (Techcomp UV 2310). The actual concentration of the sample was determined from the calibration curve of Atorvastatin calcium prepared by using pH 6.8 phosphate buffer.

### *In vitro release studies*

The *in vitro* release of Atorvastatin calcium from the prepared tablets was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution apparatus paddle type (Campbell electronic DR-6) at the stirring speed of 75 rpm with the temperature maintained at 37 ± 0.5ºC. An aliquot 5 ml of the sample was withdrawn at specific time intervals, filtered and

**Table 2: Characterization of Atorvastatin calcium SR Matrix tablets**

| Formulation code (F) | Weight Variation (mg) | Thickness (mm) | Hardness (kg/cm2) | Friability (%) | Drug content uniformity (%) |
|---|---|---|---|---|---|
| **F1** | 146.97±1.20 | 2.17±0.05 | 4.66±0.57 | 0.33±0.06 | 98.68±2.35 |
| **F2** | 147.02±1.21 | 2.16±0.05 | 4.83±0.28 | 0.35±0.07 | 98.36±1.95 |
| **F3** | 146.99±1.12 | 2.31±0.03 | 4.33±0.28 | 0.32±0.040 | 96.15±2.36 |
| **F4** | 147.43±1.66 | 2.26±0.04 | 4.16±0.28 | 0.40±0.14 | 99.51±1.95 |
| **F5** | 146. 6±1.38 | 2.29±0.03 | 4.50±0.50 | 0.42±0.12 | 96.78±1.65 |
| **F6** | 146.97±1.16 | 2.31±0.02 | 4.33±0.28 | 0.32±0.040 | 99.34±1.89 |
| **F7** | 146.95±1.088 | 2.13±0.09 | 4.83±0.21 | 0.38±0.15 | 98.19±1.25 |
| **F8** | 146.94±1.26 | 2.26±0.030 | 4.3±0.22 | 0.42±0.12 | 99.29±1.02 |
| **F9** | 146. 8±1.36 | 2.26±0.04 | 4.66±0.28 | 0.68±0.05 | 98.78±1.65 |
| **F10** | 146.93±1.31 | 2.16±0.04 | 4.50±0.50 | 0.52±0.16 | 99.34±1.89 |

*above values shows Mean ± S.D

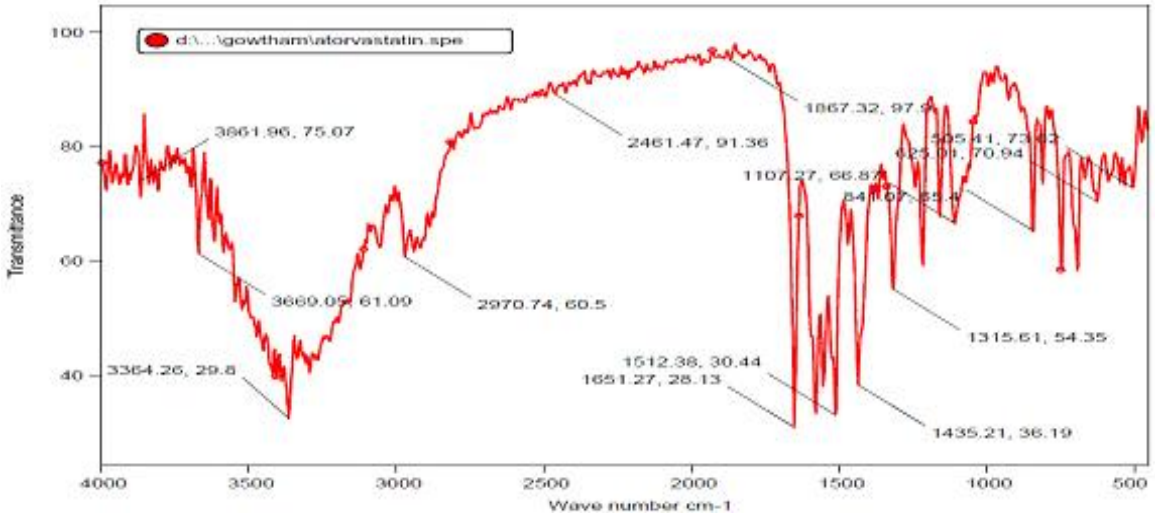


**Figure 1: FT-IR spectrum for Atorvastatin Calcium**

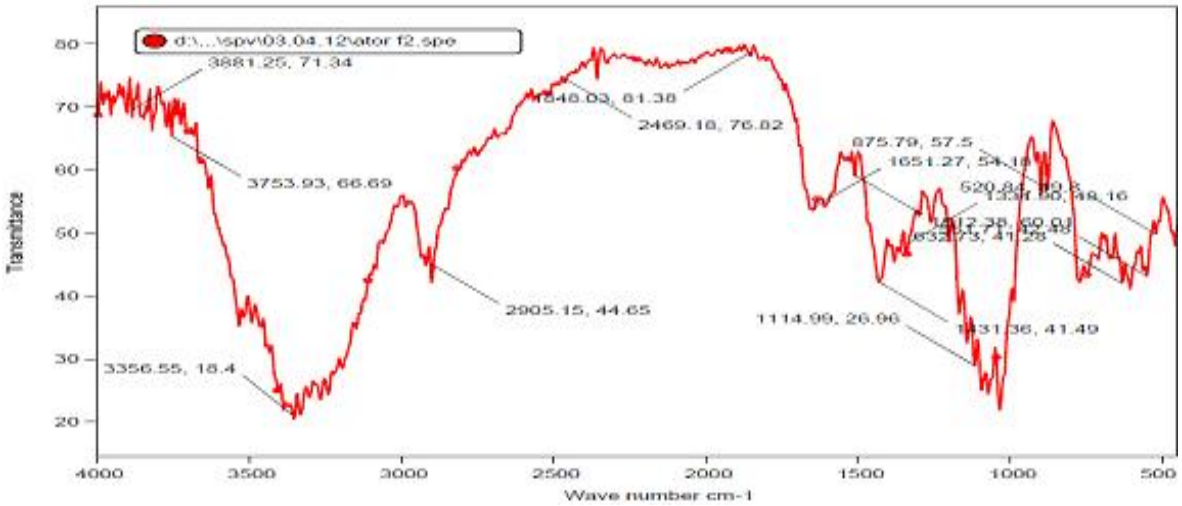


**Figure 2: FT-IR spectrum for formulation F2**

the drug content was determined by UV-Visible spectrophotometer (Techcomp UV 2310) at 246 nm. An equal volume of fresh dissolution medium was replaced to maintain the sink condition. Cumulative percentage of drug release was calculated. All the tests were carried in triplicate and the average of three valves were taken.

## RESULTS AND DISCUSSION

### *Physical characterization of prepared tablets*

The Atorvastatin calcium sustained release matrix tablets (150 mg) were prepared by direct compression method. The prepared tablets were appeared as white to off-white, smooth, and flat shape. The various phys-

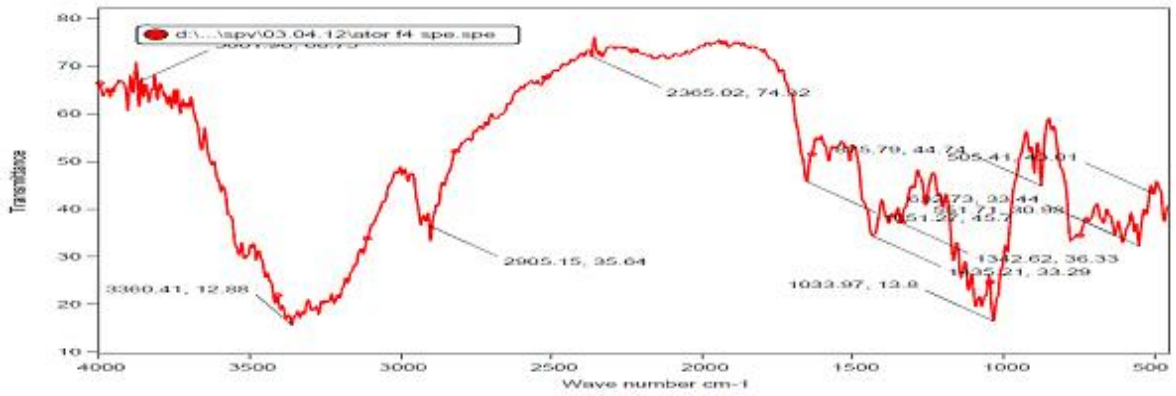


**Figure 3: FT-IR spectrum for formulation F4**

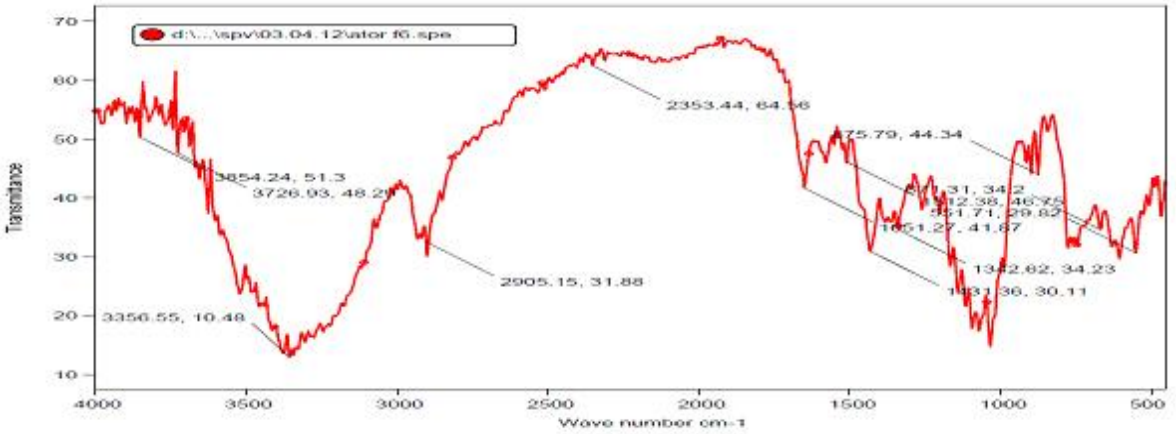


**Figure 4: FT-IR spectrum for formulation F6**

ical characterizations parameters of tablets were performed and the data was shown in the table 2. The weight variation among the each batch was found to be in the percentage deviation of 1.08 to 1.66 mg showing satisfactory results as per the U.S.P 2009. The thickness of the At.Ca SR tablets was measured by Vernier calipers and was ranged between 2.13±0.09 to 2.31±0.03 mm. The hardness was measured by Pfizer hardness tester and the valves are in the range between 4.16±0.28 to 4.83±0.28 kg/cm$^2$. The percentage friability was determined to be below 1% for all the prepared batches, which is an indication of good mechanical resistance of the tablet. The percentage drug content uniformity was found to be in between 96.78 ± 1.65 to 99.34 ± 1.89, which was complies with the official specifications (Lachman 1990).

***FT-IR studies***

The FT-IR spectrum of At.Ca (Fig no:1) shows the characteristic absorption spectrum in the region 3364 cm$^{-1}$ (O-H str, H-bonded) may due to presence of alcohols, At the wave number 3100-3000 cm$^{-1}$(C-H str) due to the aromatic group. At the wave number 2970 cm$^{-1}$ (C-H str) may indicate the presence of alkanes. The region 1651 cm$^{-1}$ (C=O str) were indicates for carbonyl group. The wave number at 1435 cm$^{-1}$ (C-H bend) may indicate for alkanes. The peak at 1161 cm$^{-1}$ may represent for (C-H wag) halides and at 675 cm$^{-1}$ may indicates for =C-H bend. The above represented groups were confirmed with the standard spectrum. The FT-IR spectrum for prepared formulations (Fig no: 2, Fig no: 3, Fig no: 4.) were also exhibits above characteristic peak with negligible shift in wave numbers, thus it concludes At.Ca were compatible with the selected polymers.

***In vitro drug release study***

The *in vitro* drug release was studied in the USP paddle type apparatus using pH 6.8 phosphate buffer. The formulations F1-F6 are prepared with the natural polymers like xanthan gum, guar gum, Carrageenan gum and the formulations F7-F10 are prepared with the synthetic polymers like HPMC K100M and HPMC 50 cps with various concentrations of polymers 45 mg and 60 mg. The formulations prepared with 45 mg of natural polymers F1, F3 and F5 were showing the drug release for up to 8 h. Whereas at 60mg concentration the drug release was retarded significantly and was found to be 72% (F2), 99% (F4) and 84% (F6) up to 17 h. It also indicates that, for F2 batch (containing 60mg of xanthan gum) more lag time was takes place to release 52% of drug as compared to other polymers.

In the case of synthetic polymers HPMC K100M (F7 and F8) both at 45 mg and 60 mg concentrations the drug release was takes place up to 10 hours (97% and 99%). Similarly for F9 and F10 containing HPMC 50 cps were

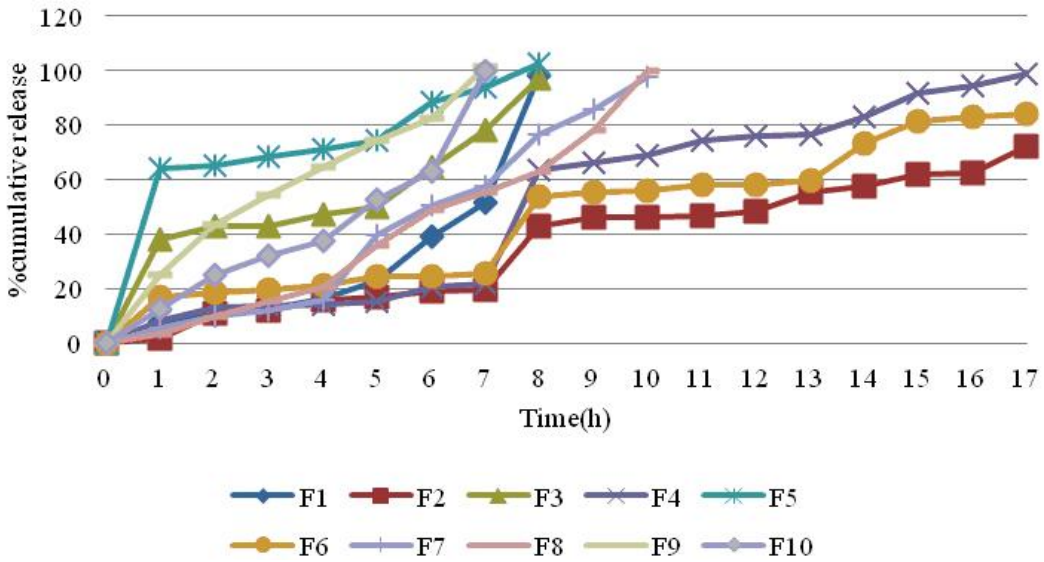


**Figure 5: Comparative *in vitro* dissolution studies (F1-F10)**

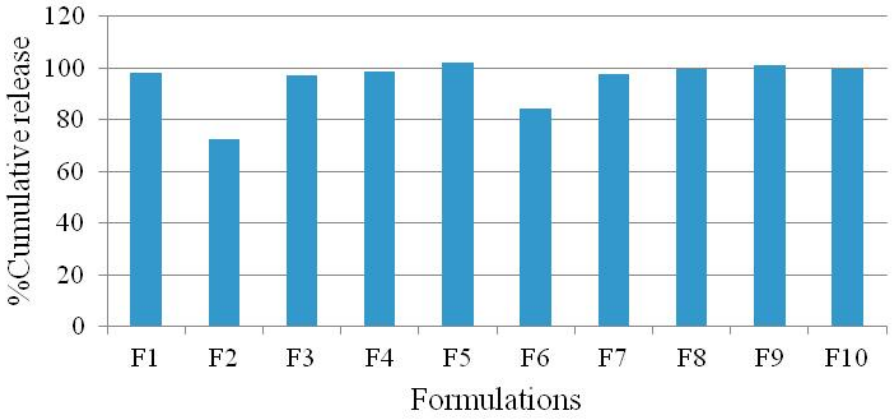


**Figure 6: *In vitro* release profile of Atorvastatin calcium formulations from various batches (F1-F10)**

also exhibits the release retarding effect for up to 7 h. Among the natural polymers used in the formulation, with respect to $t_{50\%}$ valves F1 and F2 containing xanthan gum were showed higher drug release rate than the guar gum and Carrageenan and was found to be 7 h and 12 h for 45 mg and 60 mg concentrations. It was followed by guar gum where exhibits the drug release rate 5 h and 8 h for releasing 50% of drug (for 45 mg and 60 mg) where as Carrageenan within 5 min, 50% of At.Ca was released and 60 mg it takes 8 h. The dose dumping may found to be takes place at lower concentration of Carrageenan.

In case of synthetic hydrophilic polymer the higher viscous grade HPMC K100M were produce the release retarding effect in moderate range with respect to $t_{50\%}$ valves and was found to be 6 h and 7 h for 45 mg and 60 mg.

At 45 mg and 60 mg concentration of HPMC 50 cps the $t_{50\%}$ valve was found to be 3 h and 5 h. Based on $t_{50\%}$ valves we can observe that the concentration variations of synthetic polymer were not producing the significant effect as like that of natural polymers.

This above results depicts that the drug diffusivity occurs slowly in higher concentration of natural polymers than that of the synthetic polymer.

***Analysis of release kinetics***

The obtained in vitro dissolution data were fitted in different models and for F2 batch (higher concentration of xanthan gum) the highest correlation was found to krosmeyer-peppas ($R^2$>0.9022), which indicates the drug release diffusion may takes by erosion mechanism. Formulation F4 and F6 (higher concentration of guar gum and Carrageenan) the data were fitted in to zero order profile where $R^2$ valves were found to be 0.9244 and 0.9348 indicates the diffusion mechanism of drug release.

**CONCLUSION**

The present work was aimed to study the effect of various concentrations of natural and synthetic hydrophilic polymers on in vitro release rate from the prepared Atorvastatin calcium tablets. Natural polymers were showing good release rate up to 17 h as compared to synthetic polymer in which the xanthan gum at higher concentration can exhibit drug release rate in predict-

able manner. Further research was focused to precede with the stability studies as per ICH guidelines.

**ACKNOWLEDGEMENTS**

The authors are thankful to Faculty of Pharmacy, PRIST University, Thanjavur, for providing laboratory facilities and Signet chemicals Pvt. Ltd. Mumbai, for providing gift sample of microcrystalline cellulose.

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