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Formulation and Evaluation of Pluronic F127 Thermosetting Gels Containing Atorvastatin Calcium as Novel Ophthalmic Delivery Systems

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Aims: This study aims to formulate and evaluate ophthalmic thermo-sensitive gels containing atorvastatin calcium. The major problem of the drug is poor water solubility, and hence the ocular bioavailability, complexation with cyclodextrin is an attempt to solve this problem. The formulations based mainly on Pluronic F127 alone or combined with other viscosity-increasing polymers.
Methodology: Atorvastatin calcium the proved effective anti-inflammatory agent used in ocular diseases was prepared and characterised in the form of hydroxypropyl beta-cyclodextrin complex. In this study, the possibility to formulate thermosetting gels containing either the free drug, drug-cyclodextrin physical mixture or complex was investigated by using heat sensitive polymers pluronic F127 alone or combined with other viscosity-increasing polymers such as methyl cellulose, PVP K25.
All formulations were characterised physically for its colour, clarity, viscosity, pH, and drug contents. Also the effect of different polymeric composition on the in-vitro release profiles of Atorvastatin calcium from different preparations was investigated.

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Results: All preparations were found colourless, clear, and with accepted pH values, rheological properties and drug content. In vitro release studies of different formulations in Simulated tear, fluid indicated the possibility of altering the % drug release from thermosetting gels containing Atorvastatin calcium -HP-β-CyD complex relative to the free drug by modification the formulae prepared. Methyl cellulose in 2% was found to enhance the drug release profile of drug from Atorvastatin calcium -HP-β-CyD complex gels, while PVP K25 in 5% caused retardation of drug released from the prepared thermosetting gels.

Conclusions: Ophthalmic thermosetting gels formulations containing Atorvastatin calcium -HP-β-CyD complexes are considered good and promising delivery systems. They showed good physical properties. Depending on the type and concentration of the viscosity increasing polymer incorporated into the formulations, it can be applied either for improving or retardation of Atorvastatin calcium release profile.

Keywords: Ocular; thermosetting gels; atorvastatin calcium; HP-β-CyD; pluronic F127; methyl cellulose; PVPK25.

1. INTRODUCTION

The eye is one of the most important and sensitive organs in our body. Ocular Drug delivery systems are a still challenging problem due to physiological constraints imposed by the unique eye structure and efficient protective mechanism [1].

Eye drops are considered the most commonly used traditional ocular dosage form Ali and Lehmussaari [2]. However, the poor drug bioavailability caused by short pre-corneal residence time and rapid turnover of lacrimal fluid is considered a great problem [3]. Thus, frequent installation of eye drops is required to achieve a therapeutic effect which may lead to undesirable systemic drug absorption and harmful side effects [4]. Different approaches have been developed such as in-situ forming gel [5], Nan carrier systems [6], inserts [7] and vesicular systems [8].

The in-situ gelling system is one of the simplest, effective ocular delivery systems. It should be a low viscous, free-flowing liquid that allow administration as eye drops, and the gel formed following phase transition should be strong enough to withstand the shear forces in the cul de sac and provided long residence times in the eye. Depending on the method employed to cause sol to gel phase transition on the ocular surface, there are different systems either pH-triggered systems [9], temperature triggered in-situ gel [10], or Ion activated in-situ gels [11]. Over the last decades, an impressive number of novel temperature, pH, and ion-induced in-situ forming solutions have been developed each system has its own advantages and drawbacks. In temperature triggered in-situ gel, the system is designed mainly by using poloxamer 407 (pluronic F127) as a vehicle for ophthalmic drug delivery. It possesses many properties to make it particularly suitable for ophthalmic use such as its low toxicity, muco mimetic properties, and optical clarity [12].

Moreover, topical atorvastatin Calcium (ATC) Fig. 1 is proved to have a potential therapeutic effect for patients with dry eye and blepharitis (DEB) [13]. Lipid abnormalities in meibomian gland dysfunction, including an excess of free cholesterol in tears, resulting in the evaporative dry eye and chronic DEB [14]. Red, painful, irritated and itchy eyes, along with blurred vision, result from these disorders. Tear evaporation can lead to an increase in osmolality, which produces an inflammatory response [15]. One of the demerits of atorvastatin calcium is its low water solubility, several techniques have been developed to increase solubility as particle size reduction [16], nanoparticles [17] or using cyclodextrin as a complexing agent.

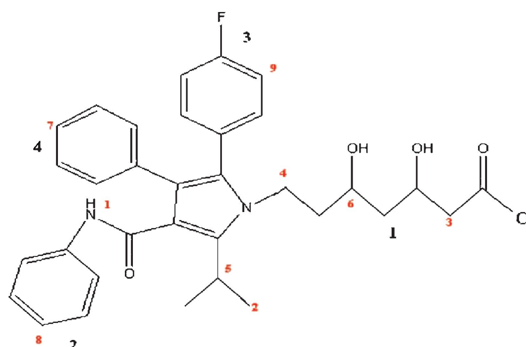

Fig. 1. Chemical structure of atorvastatin

Hydrophilic cyclodextrins, especially hydroxypropyl beta-cyclodextrin (HP-β-CyD) Fig. 2 is oligosaccharide often used as a medium for

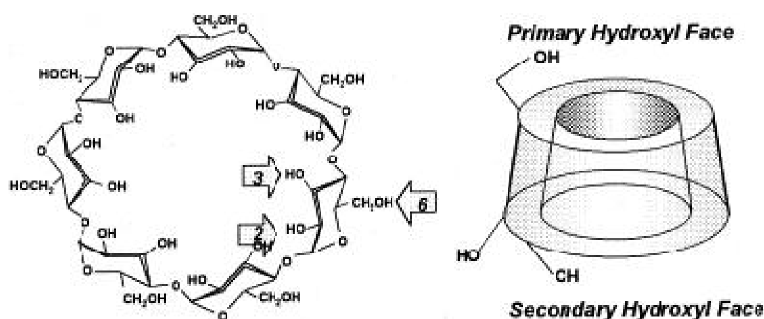

Fig. 2. The structure of HP-β-CyD

the encapsulation of active substances for medicines that will improve the water solubility, stability and bioavailability of the drug in the body by forming an active substance-cyclodextrin complex [18].

In this study, we have prepared and characterised the ATC as a complex with HP-β-CyD in 1:1 molar ratio using a common solvent evaporation technique. Then the prepared complex was incorporated into a poloxamer 407 based thermosetting gels. Also, gels were prepared using ATC alone and ATC- HP-β-CyD physical mixture in the same molar ratio for comparison. All prepared thermosetting gels were evaluated for their physical characters, as clarity, pH, viscosity, drug contents and in- vitro release profiles in simulated tear fluid as dissolution medium.

The aims of this work are 1) to investigate the possibility to formulate ophthalmic poloxamer 407 in-situ gelling formulations containing the ATC-(HP-β-CyD) complex 2) to evaluate in-situ gelling formulations containing ATC-(HP-β-CyD) complex, and compare that with gels prepared by the ATC-HP-β-CyD physical mixture or ATC alone.

2. METHODOLOGY

2.1 Materials

Atorvastatin calcium, 2-Hydroxypropyl-β-cyclodextrin (Epico Co., Egypt), methanol, propylene glycol, sodium chloride, calcium chloride dihydrate, sodium bicarbonate all of analytical reagents grade (Adwic, EL Nasr Pharmaceutical chemicals, Co., Egypt). Pluronic F127, PVP K25, methylcellulose (B.D.H. Chemicals, Liverpool - England). Cellulose membrane, spectrapore, M-W. cutoff: 12000-14000 (Fisher Sci. Co., Pittsburgh, U.S.A.).

2.2 Experimental

2.2.1 Estimation of ATC by UV spectrophotometer

A simple method is used for estimation of ATC based on UV spectrophotometric analysis using Spectro UV-VIS double beam spectro-photometer, Labomed Inc., USA.

Depending on the free solubility of ATC in methanol. The technique performed by dissolving accurately weighed 20 mg of Atorvastatin calcium in pure methanol, the solution was scanned from 200-400 nm to determine maximum wavelength. The standard calibration curve was performed in Methanol / STF (1:9) by serial dilution of the previously prepared stock solution, different drug concentration was prepared, their absorbance was determined, a calibration curve was drawn to determine slope.

2.2.2 Preparation of ATC- HP-β-CyD inclusion complexes by common solvent evaporation_method

ATC-and HP-β-CyD in the equimolar ratio of 1:1 were dissolved in a common solvent as extra pure methanol to get a clear solution. The prepared solution was allowed to evaporate overnight at the room temperature. The collected drug-cyclodextrin complex was pulverised and passed through sieve number 80 [19].

2.2.3 Preparation of ATC- HP-β-CyD physical mixture

To prepare the physical mixture, Atorvastatin Calcium and H-P-ß-CD in equimolar proportion (1:1 molar concentrations) were mixed in a mortar for one hour without applying any pressure [20].

2.2.4 Characterisation of Atorvastatin calcium inclusion complexes

2.2.4.1 Differential scanning calorimetry (DSC)

The thermal behaviour of drug, H-P-β-cyclodextrin, Physical mixture and the complex was studied to confirm the formation of the complex. Thermal analysis was carried out by using Differential scanning calorimeter, Pyris 6 DSC, Perkin Elmer, USA. The samples were heated from 20 -300°C at 10°C heating rate.

2.2.4.2 Scanning electron microscopy (SEM)

The surface morphology of Atorvastatin Calcium was determined using a scanning electron microscope (JSM- 6510LV, JEOL, Japan).

2.2.4.3 FT-IR studies

All pure drug, cyclodextrin, Physical mixture and complexes were subjected to IR studies to check whether interaction occurs between pure atorvastatin drug and added ingredients. The instrument used was Fourier transform infrared spectrophotometer (FT-IR), Thermo Fisher Scientific, Inc., Waltham, MA, USA [21].

2.2.5 Formulation of medicated *in-situ* gels

Different polymers were selected as a viscosity increasing agents to prepare the thermosetting gels based on pluronic F127 for ophthalmic application such as and methyl cellulose and PVP K25. All preparations compositions are indicated in Table 1.

All *in-situ* gels were prepared by the cold method. For preparations containing methyl cellulose or PVP K25. The polymer solution was prepared by dispersing the calculated weight of methyl cellulose or PVP K25 in double distilled water with continuous stirring until it had completely dissolved. Then polymer pluronic F127 solution was prepared by dispersing the weighed amount of Pluronic F127 in the previously prepared polymeric solution after cooling to 4°C, then stirring for 1 hour in an ice bath. The final preparation was kept in the refrigerator for at least 24 hours to ensure the complete dissolution.

For medicated formulae, three preparations were made from each formula either by incorporating free atorvastatin calcium (F1A, F2A, F3A), or Atorvastatin Calcium/ H-P-β-cyclodextrin physical mixture (F1B, F2B, F3B), or Atorvastatin Calcium/ H-P-β-cyclodextrin complex (F1C, F2C, F3C).

To prepare the medicated ophthalmic gels, atorvastatin calcium 0.5% (W/W) or its equivalent weight of Atorvastatin Calcium/ H-P-β-cyclodextrin Physical mixture, and complex was dissolved firstly in propylene glycol and added to the previous mixture drop by drop by stirring using magnetic bars till complete dissolution. The weight of gel was adjusted to final prepared weight and then packaged in clean, dry and sterile glass containers until use.

2.2.6 Physical evaluation of *in- situ* thermosetting systems

2.2.6.1 Determination of the viscosity of prepared formulations

The ophthalmic gels were subjected to viscosity determination using rotary viscometer which has been calibrated before use. The temperature was maintained at 37 ± 0.5°. One gram of each formulation containing was placed on the plate of viscometer (with a diameter of 2.9 cm) and cone with 2.8 cm in diameter. The torque value "S" was determined for each "N" value (speed), the viscosity is calculated using the following equation:

$$Y = \frac{G.S}{N} \text{ (mpa.S)}$$

Where;

Y : Viscosity in mpa.s (mpa.s = 1 centipoise)
G : Instrumental factor (14200 mpa.s/scalagrad. min)
S : Torque (scale grad.)
N : Speed (rpm)

2.2.6.2 Determination of the pH of prepared formulations

One gram of each formulation was dispersed in 25 ml of double distilled water, and the pH was measured using pH-meter (U.S.P.) [22].

2.2.6.3 Determination of drug content in the prepared formulations

One gram from each formulation containing the drug was accurately weighed and placed in tightly closed 100 ml volumetric flask containing 50 ml of methanol or STF pH 7.4.

Table 1. Compositions of ATS Ca ophthalmic thermosetting gels

Ingredients	Formulations								
	F1A	F1B	F1C	F2A	F2B	F2C	F3A	F3B	F3C
Atorvastatin calcium	0.5%	---	---	0.5 %	----	----	0.5 %	----	----
Atorvastatin/ HP-β-CyD physical mixture equivalent to Atorvastatin	----	0.5%	---	---	0.5%	----	----	0.5%	----
Atorvastatin/ HP-β-CyD complex equivalent to Atorvastatin	----	---	0.5%	---	---	0.5%	----	----	0.5%
Pluronic F127	20%	20%	20%	20%	20%	20%	20%	20%	20%
Methyl cellulose	----	-----	---	2%	2%	2%			
PVP K25	-----	----	---	---	----	----	5 %	5 %	5 %
Propylene glycol	20%	20%	20%	20%	20%	20%	20%	20%	20%
Distilled water	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S

The content of each flask was shaken for 2 hours and then, 10 ml were centrifuged. The supernatant was filtered through 0.45 m membrane filter and measured spectro-photometrically at 242 nm for drug content [23].

2.2.7 *In-vitro* release study of in- situ gelling systems

The method was performed by filling 1 ml of the cold in-situ gel formulation into the dialysis tube with care to avoid air bubbles inside the preparation. Standard cellophane membrane (previously immersed in STF, pH 7.4, for 24 hrs.) was stretched over the dialyser tube. Then, it was placed at 35°C inside an oven for 30 mints to ensure the complete gelation. whole dialysis unit was then immersed in a 100 ml beaker containing 50 ml of the STF (pH=7.4) in such a manner that the membrane was located just below the surface of the sink solution. (Simulated tear fluid, STF, was prepared by Na Cl (0.67 g), Na HCO3 (0.2 g), Ca Cl_2.2H2O (0.008 g), and purified water to 100 g, pH was adjusted to 7.4) [24].

The beaker was placed in a thermostatically controlled incubator system (GFL Germany shaking incubator type 3033 with orbital motion incubator) adjusted at 37± 0.5°C with a constant stirring at 100 rpm to avoid any development of a concentration gradient.

At appropriate sampling intervals an aliquot of 1 ml, was collected and replaced by equal volume of the STF at the same temperature to keep the volume of the sink solution constant during the experiment. Samples were then assayed spectrophotometrically at λ_{max} 242 nm. Each experiment was repeated three times and the average was calculated. The concentration of ATC in each sample was determined from the standard curve previously constructed after suitable dilution. Blank gel samples were carried out simultaneously to check for any interference [25].

2.2.8 Kinetic analysis of *in vitro* drug release

To determine the drug release kinetics, the in-vitro release data were analysed according to different kinetic models, Zero-order kinetics, First-order kinetics and Higuchi diffusion mechanism (Fickian and non-Fickian) [26].

3. RESULTS AND DISCUSSION

3.1 Estimation of ATC by UV Spectro-photometer

The absorption maximum was found to be at 242 nm.

The results were the average of three values. The curve indicates that Atorvastatin calcium obeys Beer's law on the tested concentration range with slope equals 0.035

3.2 Characterisation of Atorvastatin Calcium Inclusion Complexes

The different methods DSC, FT-IR, and SEM, used to estimate the complex formation indicated the formation of ATC- HP-β-CyD inclusion complexes of distinctive characteristics compared with that of the pure drug or HP-β-CyD. This was explained with details in our previously published paper [27].

3.3 Physical Evaluation of *In-situ* Thermosetting Systems

The obtained results are illustrated in Table 2. It was observed that the prepared ocular gels were colourless and with good clarity. Also, the pH

values of all formulations were within the acceptable range (4-9) which the eye can tolerate, without any irritation.

Finally the viscosity values and drug contents of all formulations were found to be in the acceptable range.

3.4 *In- vitro* Drug Release from Different Formulations

Percentages released of ATC from Pluronic F127 different thermosetting gels containing free drug (F1A), drug- HP- β-CD physical mixture (F1B), and drug- HP- β-CD complex (F1C) through semipermeable cellophane membrane were shown in Fig. 3. The hydrophilic membrane was used to simulate the release towards a hydrophilic surface such as the ocular mucosa.

From the results, it was found that percent released of ATC from F1C gel was 95.6% after 6 hours while that from F1A, F1B was 71.1% and 72.6% respectively. This improvement in the drug release may be due to the ability of the incorporated cyclodextrin in the complex to enhance the aqueous solubility and hence the bioavailability of the drug. This is in accordance with Guo and Cooklock [28] who proved that cyclodextrins have the potential to enhance drug release from polymeric systems by increasing the concentration of diffusible species within the matrix.

In addition, % released of ATC from Pluronic F127 and 2% MC gels were represented in Fig. 4. Both thermosetting gels containing drug- HP- β-CD physical mixture (F2B), and drug- HP- β-CD complex (F1C) also showed a high increase in % drug release compared with thermosetting gels containing free drug (F2A) from 46.5% to nearly 60% after 6 hours.

On the other hand, drug release profiles of the third group of thermosetting gels of different polymers composition (containing Pluronic F127 and 5% PVPK25) representing in Fig. 5 showed some differences. There was an observed reduction in % drug release of formulae containing ATC- HP- β-CD complex (F3C) to 67% compared with F3A, F3B with 80% after 5 hours release period. This may be explained on the basis of the thermosetting gel composition and also measured viscosity values on these formulations.

Moreover, another explanation is that the capability of HP- β-CD o complex with the thermosetting gel polymer itself (PVPK25). The physical presence of polymers capable of inclusion within the HP-β-CD cavity would be expected to hinder the ability of HP-β-CD to complex with the drug itself, which results in de-complexation free drug and hence a decrease in % release [29].

Filipović-Grčić et al. [30] also stated that drug release from polymer matrices containing drug inclusion complexes may be retarded. They verified a reduced release of the poorly water-soluble nifedipine complexed with HP-β-CD in case of chitosan microspheres, compared to those contained the only free drug. It was explained on the basis that during the release, drug rapidly dissociated from the complex, resulting in an increased concentration of free HP-β-CD within the polymer matrix. A more hydrophilic, polymer: HP-β-CD matrix was created which in turn decreased permeability and slowed the release of the drug.

So, hydrophilic Cyclodextrins are found to produce an increase or decrease in drug release profile depending on the polymer type incorporated in the gel. They have been used extensively to enhance the bioavailability of poorly water-soluble drug [31].

3.5 Kinetics of Drug Release

The kinetics studies of in-vitro drug release of different types of prepared thermosetting gels were demonstrated in Table 3.

It was found that the release of atorvastatin from both F2A, F2B and F2C showed Higuchi diffusion kinetics model with r2 of 0.992, 0.988 and 0.989 respectively. On the other hand, F1C exhibited controlled first order release kinetics with r2 of 0.991. It was reported that the incorporation of HP-β-CD into polymeric drug delivery systems can influence the mechanisms by which a drug is released. Additionally, drug-HP-β-CD complex can modify drug solubility, drug diffusivity and hydration of the polymer matrix [32].

In addition, the release from all other different formulations showed a good fit to Korsmeyer-Peppas models. The analysed results indicated n values either located between 0.5, 1 for F2A, F2B, F2C, and F3C or some other formulations with n values less than 0.5.

This indicated that the atorvastatin release mechanism from these formulations was non-Fickian diffusion which suggested both diffusion and erosion mechanisms controlling the drug release.

Table 2. Physical characters of ophthalmic gels

Formula	Colour	Clarity	pH	Viscosity (m pa.s)	drug content
F1A	colourless	clear	6.6	1002.5±1.2	106%±0.2
F1B	colourless	clear	6. 8	1000.2±4.22	94%%±0.5
F1C	colourless	clear	6.53	1005±12.6	96%%±0.5
F2A	colourless	clear	4.65	1181.25±19.42	102%%±0.1
F2B	colourless	clear	4.55	1181.25±1.2	88%%±0.42
F2C	colourless	clear	4.85	1200.25±4.9	94%%±0.81
F3A	colourless	clear	4.79	1195.25±8.8	104%%±1.2
F3B	colourless	clear	4.8	1212.5±6.82	108%%±0.82
F3C	colourless	clear	5.02	1406.25±9.12	92%%±0.52

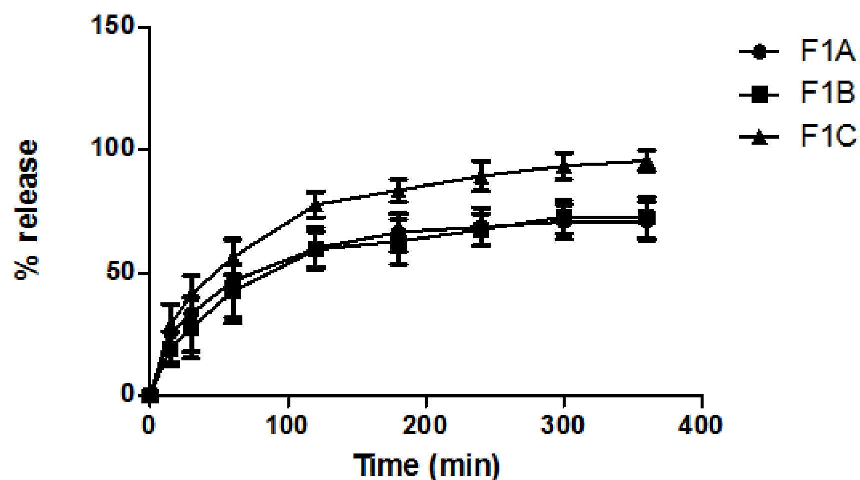

Fig. 3. ***In vitro*** **release profile of ATC from Pluronic F127 thermosetting gel in STF**

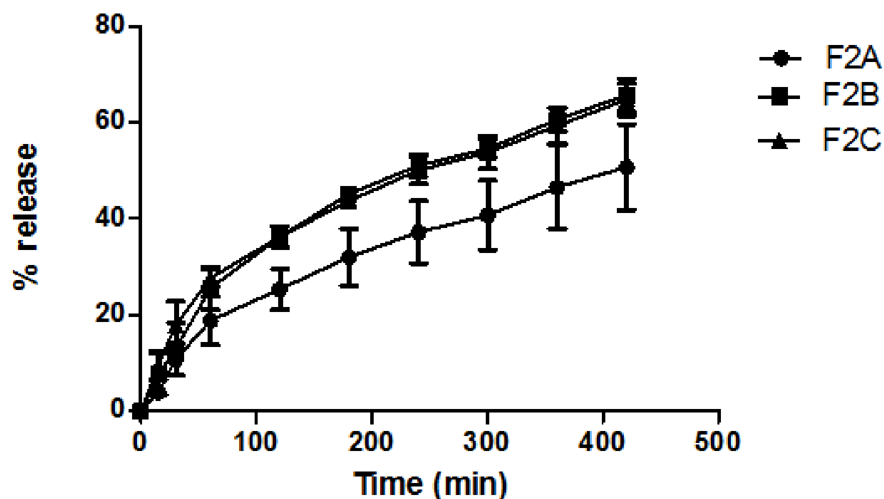

Fig. 4. ***In vitro*** **release profile of ATC from Pluronic F127 and MC thermosetting gel in STF**

Table 3. Kinetic analysis of the release data of Atorvastatin from different thermosetting gel formulations

Parameter	Formulation	F1A	F1B	F1C	F2A	F2B	F2C	F3A	F3B	F3C
Zero- order	k (min^{-1})	7.48	8.81	10.85	6.7	8.8	7.9	11.2	12.4	14.74
	r^2	0.798	0.82	0.83	0.94	0.92	0.93	0.91	0.96	0.98
First- order	k (min^{-1})	0.161	0.18	0.46	0.09	0.138	0.115	0.529	0.529	0.368
	r^2	0.86	0.90	0.99	0.97	0.97	0.974	0.7	0.73	0.82
Higuchi Model	k (min^{-1})	23.8	27.8	34.2	20.6	27.1	24.5	34.06	37.4	43.7
	r^2	0.916	0.93	0.94	0.992	0.988	0.989	0.93	0.98	0.972
	k (min^{-1})	39.8	31.6	50.1	14.4	19.9	19.9	39.8	31.6	12.5
	r^2	0.96	0.96	0.97	0.953	0.97	0.976	0.94	0.989	0.989
Korsmeyer-Peppas	n	0.33	0.42	0.37	0.70	0.64	0.54	0.40	0.49	1.04
	Transport mechanism	Fickian	Fickian	Fickian	Non-Fickian	Non-Fickian	Non-Fickian	Fickian	Fickian	Non-Fickian

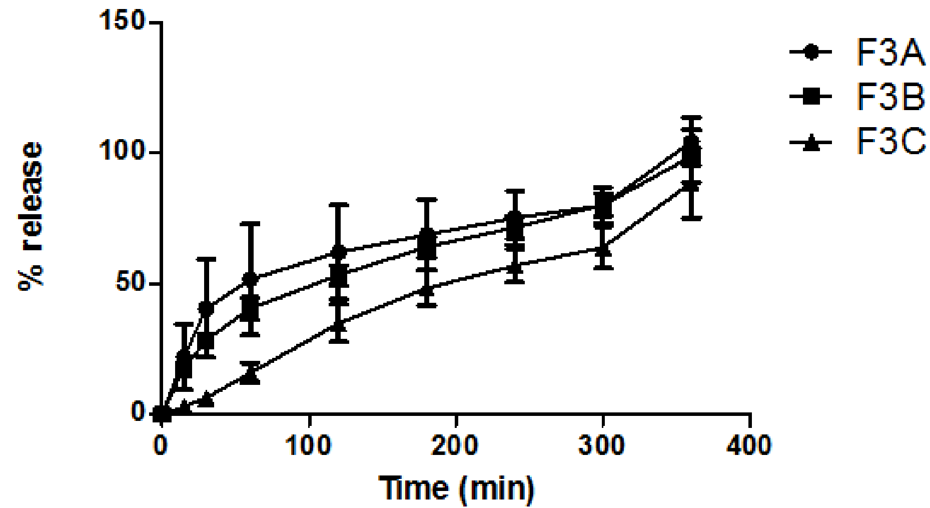

Fig. 5. ***In vitro*** **release profile of ATC from Pluronic F127 and PVPK 25 thermosetting gel in STF**

4. CONCLUSION

So, Percentages released of ATC from thermosetting gels through cellophane membrane were found to be dependent mainly on the composition of the formulae itself. HP-β-CD succeeded to increase the cumulative ATC release % in case of thermosetting gel containing only 20% Pluronic F 127 or 20% Pluronic F 127 in addition to the low concentration of additional polymer (2%) MC. On the other hand, in case formulation containing 20% Pluronic F 127 and a high concentration (5%) PVPK 25, incorporation of ATC-HP-β-CD complex in the gel caused marked retardation of drug release.

We can conclude that the type and percentages of polymer used in thermosetting gel formulation are considered the main effective factor controlling the % released of ATC from thermosetting gels incorporated with Atorvastatin calcium -HP-β-CyD complex.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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