Zagazig J. Pharm. Sci. Jun, 2022 ISSN 1110-5089
Vol. 31, Issue 1, pp. 14- 24 ISSN (on-line) 2356_9786

Enhancement of Hypolipidemic Effect of Atorvastatin Calcium via Floating Microspheres

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Brief running title: Atorvastatin Calcium floating microspheres for enhanced hypolipidemic effect

Received:27 Feb 2022 /**Accepted**: 30 Mar 2022 /**Published online:** 30 June 2022

Abstract

The purpose of this study was to investigate the influence of hypolipidemic atorvastatin calcium (ATC) floating microspheres on the LDL and HDL levels in rabbit blood. ATC Floating microspheres were prepared via emulsion solvent evaporation method using Eudragit S100 as a polymer. The effect of certain variables including drug: polymer ratio, stirring rate, emulsifier concentration and internal: external phase volume ratio on the floating microspheres formulations were investigated. Evaluation of floating microspheres was done using particle size analysis, percentage yield, in-vitro buoyancy, entrapment efficiency determination, optical microscopy, in-vitro drug release studies, Thermal analysis (DSC) and Fourier transform infrared spectroscopy (FTIR). The prepared microspheres showed a good floating ability. The Floating microspheres formulation No (F5) revealed the highest drug release % which was 66% after 8 h. Furthermore, F5 significantly decreased the blood LDL and increased HDL levels in comparison to the market drug (ATOR ®) and it succeeded in lowering the blood total cholesterol level of rabbits by 74.42%.

***Key words*:** Atorvastatin calcium, Eudragit S100, floating microspheres, HDL, LDL and total lipid.

Introduction

Hyperlipidemia is considered a major cause of many diseases which may end up with sudden death syndrome (**Onwe et al., 2015**), it involves abnormal elevation of lipids in the blood stream (**Nouh et al., 2019**). World widely, 4.4 million deaths occurring each year as a result of hyperlipidemia(**Chaudhari et al., 2016**). On increasing serum cholesterol level they tend to aggregate on walls of blood vessels resulting in atherosclerosis which lead to many cardiac diseases ending up with death (**Shattat, 2014**). In Egypt, 80% of patients suffering from cardiovascular diseases are originally hyperlipidemic (**Ibrahim et al., 2013**), so treatment of hyperlipidemia is very important to protect people from most cardiovascular diseases. Many drug classes are used for treatmen of hyperlipidemia as niacin, statins, resins and their combinations (**Zodda et al., 2018**). Atorvastatin calcium (ATC) is the most common statin drug used for treatment of hyperlipidemia (**Khan and Dehghan, 2011**), it acts by inhibition of HMG-CoA reductase; an enzyme which prevents cholesterol formation by blocking the conversion of HMG-CoA to cholesterol precursor (mevalonic acid) (**Ray and Rege, 2002**). ATC possess low water solubility as a result of its poor bioavailability (14% only) (**Khan and Dehghan, 2011**) which be

increased by size reduction technique giving rise to high surface area, resulting in subsequent increase in ATC water solubility and bioavailability (**Ganesan et al., 2013**). Bioavailability of ATC can be also increased by increasing its residence time in GIT via preparation of floating microspheres. Floating microspheres are free flowing biodegradable powders, ideally have particle size less than 200 µm; they give sustained release effect of the drug, decreasing dosing frequency which leads to better patient compliance (**Mishra et al., 2018**). From the above-mentioned data our study is concerned with the formulation of ATC in floating microspheres to increase its residence time in GI tract and study the effect of this formula on total cholesterol, HDL and LDL levels in experimental animal.

Materials and methods

Materials

Atorvastatin calcium was obtained as a gift from Epico. Co., (Egypt). Eudragit S100 was purchased from Röhm pharma, Darmstadt (Germany). Liquid paraffin and span 80 were purchased from El-Naser Pharmaceutical Chemical Company (Egypt). Sodium Lauryl sulphate was purchased from Al Gomhouria Company, (Egypt). All solvents, methanol, methylene chloride, HCL and Acetone were of analytical grade.

Method of preparation

Floating microspheres were prepared by emulsion solvent evaporation method using liquid paraffin oil as a continuous phase. The drug and polymer (in different proportions) were weighed and dissolved into 20 ml methylene chloride at room temperature. The above organic phase was then added portion wise to the liquid paraffin oil containing different concentrations of span 80 with vigorous agitation for 3 h. After 2h and 45 min, 30 mls of n-hexane were added to the emulsion. Stirring was maintained until all the organic phase was evaporated. Then microspheres were separated by filtration, washed with two portions of n-hexane (200 ml) each. The washed microspheres were then dried at room temperature overnight (**Khan and Dehghan, 2011**). Eleven different microspheres formulas (F1-F11) were prepared by changing several factors as shown in **(Table 1):**

Formul-ation code	Drug (mg)	Eudragit S100 (mg)	Internal phase volume (ml)	External phase volume (ml)	Internal: external phase ratio	Stirring rate (rpm)	Surfactant (span 80 %)
F1	300	300	20	100	1:5	1000	1
F2	300	600	20	100	1:5	1000	1
F3	300	900	20	100	1:5	1000	1
F4	300	300	20	100	1:5	1300	1
F5	300	300	20	100	1:5	1600	1
F6	300	300	20	100	1:5	1000	0.5
F7	300	300	20	100	1:5	1000	1.5
F8	300	300	20	50	1:2.5	1000	1
F9	300	300	20	150	1:7.5	1000	1
F10	300	300	15	100	1:4	1000	1
F11	300	300	25	100	1:6.6	1000	1

Table 1*: Composition of different microspheres formulations from F1-F11*

Characterization of floating microsphere

Fourier transform infrared spectroscopy

FTIR (Perkin-Elmer 1600 FTIR spectrophotometer) was performed to determine any possible interaction between ATC and Eudragit S100. About 2 mg of each of ATC, Eudragit S 100 and F5 were mixed separately with 200 mg KBr then compressed into discs which were scanned at 4 mm/sec with a resolution of 1 cm^{-1} at a range of 4000-400 cm^{-1}.

Thermal analysis

Thermal analysis experiments were performed using differential scanning calorimeter (DSC) (Shimadzu-DSC 50). Samples (2 mg) were heated in hermetically sealed aluminum pans over a temperature range of 0-3000 ˚C at a constant rate of 100 ˚C / min under a nitrogen purge (30 ml/min).

Evaluation of Atrovastatin Calcium loaded floating microspheres

Optical microscopy and Particle size analysis:

The characteristics of surface and particle size of floating microspheres formulae were examined with an optical microscope (Seizz MC 63 C-Germany) (**Avachat et al., 2011**).

Yield of Floating microsphere

The percentage yield of floating microspheres formulae were calculated according to the following equation (**Samirkumar et al., 2013**):

$$\text{Yield\%} = \frac{\text{Yp}}{\text{Yt}} \times 100$$

Where Yp is the practical microspheres yield, Yt is the theoretical microspheres yield.

In-vitro buoyancy

Floating microspheres (equivalent to 100 mg) were dispersed in 200 ml of 0.1 N hydrochloric acid solution (pH 1.2) containing sodium lauryl sulphate (1% w/v) at 37 ˚C. The mixture was stirred with a paddle at 100 rpm and after 12 h; the layer of buoyant microspheres was pipetted and separated by filtration. The buoyant microspheres were then dried overnight at room temperature. Their weight was measured and their buoyancy was calculated by the ratio between weight of the dispersed floating microspheres and their total weight at the beginning of the experiment (**Mukesh et al., 2012**).

Determination of Entrapment efficiency

Twenty milligrams of microspheres were dissolved completely in 10 ml methanol by means of a magnetic stirrer (Type MM5, Poland). Then 20 ml of 0.1 N HCL buffer were added while completing stirring and heating till solvents evaporation, filter then complete the volume to 100 ml in a volumetric flask with 0.1 N HCL buffer. The UV absorbance of the sample was determined at a wavelength of 246 nm against buffer as a blank (**Perumandla and Priya, 2014**)

$$Percentage\ Drug\ entrapment = \frac{Actual\ drug\ content}{Theoretical\ drug\ content}\ X100$$

In-vitro drug release

Dissolution was carried out using dissolution test apparatus USP type II (Pharma test, Germany) at 100 rpm at 37±2 ˚C for 8 h. Certain amount of microspheres equivalent to 20 mg of the drug were placed in 900 ml 0.1 N HCL buffer containing 1% SLS. An aliquot of 5 ml was withdrawn at different time intervals and it was replaced by an equal amount of freshly prepared buffer. Then it was measured spectrophotometrically at 246 nm against buffer as a blank (**Samirkumar et al., 2013**).

Hypolipidemic studies

Hypolipidemic studies focused on the measurement of serum lipids (total cholesterol, triglycerides, HDL and LDL) as it is the major pharmacological effects of ATC. *In-vivo* pharmacological studies were done for 3 groups (n=3 per group) of male rabbits weighing (2± 0.25 kg) each. Experimental design and animal handling were performed according to the guidelines of the Ethical Committee of the Faculty of Pharmacy, Zagazig University for animal use ‘’ECAHZU”. Hypercholesterolemia was induced by oral feeding of high fat diet with composition of (60% normal food, 20% margarine and 20% sugar) per day for one week in addition to oral feeding of cholesterol suspended in sesame oil in a dose of 60 mg of cholesterol suspended in 2ml of sesame oil for each rabbit daily for one week. The normal diet composition is (18% pure protein, 2.88% pure fats, and 10.5% pure fibers). Group A received ATC floating microspheres (F5) in capsules in a dose of 20 mg/kg/day (**Elseweidy et al., 2014**) for one week (**Ratnakar and Murthy, 1998**), group B received 20 mg/kg/day of market tablets ATOR® and group C (controlled group) received no treatment. After this week, blood samples were collected from each rabbit in each group and Serum cholesterol (TC) was determined according to (**Meiattini et al., 1978**), using diagnostic kits provided from Spinreact kits, Spain. Serum TGS was determined according to (**Fossati and Prencipe, 1982**), using diagnostic kits provided from Spin react, Spain. HDL-C (high density lipoprotein) was measured according to (**Grove, 1979**), procedures using commercial kit provided by Spin react, Co., Spain and LDL (low density lipoprotein) Serum LDL-C was determined according to

the following formula (**Friedewald et al., 1972**).

LDL-C (mg/dl) = TC – [HDL-C + TAG/5]

Where, TAG did not exceed 400 mg/dl. Values of TC, TGS, HDL and LDL pre-cholesterol administration, after cholesterol administration and after treatment of rabbits in each group were compared.

Statistical analysis

All the means were presented with their standard deviation (mean± standard deviation, SD). Two-way ANOVA test was used to analyze the results statistically. p value <0.05 was considered significant.

Results and discussion

Characterization of ATC-loaded floating microspheres:

Particle size analysis

Table 2 shows that, increasing drug to polymer ratio from 1:1 to 1:3 led to an increase in the microspheres particle size from 330 to 606 µm respectively. The increasing in particle size is due to increasing the viscosity of the solution leading to formation of larger droplets giving rise to larger microspheres particles (**Patel and Patel, 2014**). On increasing the stirring rate from 1000 to 1600 rpm the particle size of microspheres was decreased from 330 to 150 µm respectively, so the particle size was decreased with increasing stirring rate. This result is agreement with **Demir et al., 2014.** On increasing the surfactant (span 80) concentration from 0.5 to 1.5% the particle size was decreased from 500 to 310 µm respectively (**Wadher et al., 2013**). On the other hand, increasing the internal: external phase volume ratio from 1: 2.5 to 1:4 to 1:5 to 1: 6.6 to 1:7.5 resulted in a decrease in floating microspheres particle size from 425, 400, 330, and 320 to 300 µm respectively. These findings may be explained on the basis of change in the viscosity of the emulsion formed during processing. Increased viscosity of the emulsion by alternation of aqueous/organic phase ratio resulted in high viscous resistance against the shear force during the forming of nanodroplets (**Quintanar et al., 1996**). These results could be explained by the fact that when the internal phase ratio increase, the shearing action of the mixer probably decreases resulting in formation of larger emulsion droplets and thereby creating relatively larger microspheres (**Abd El-Bary et al., 2012**). Additionally, the mean distances between the droplets could be decreased with increasing the internal phase ratio. Consequently, the chances of coalescence between the droplets are increased, leading to aggregation of the prepared microspheres (**Dinarvand et al., 2004**).

Formulation code	Particle size (µm)	Yield %	Duration of Buoyancy	Floating %	EE %
F1	330±3.12µm	75.00±2.2	14 h 10 min	75±0.94	71.15±0.77
F2	565±2.11µm	88.60±1.88	8 h 27 min	40±5.67	55.80±0.54
F3	606±1.87µm	99.40±0.77	8 h 26 min	40±2.99	55.60±0.12
F4	225±2.95µm	80.40±2.89	15 h 15 min	89±3.0	73.27±1.23
F5	150±1.45µm	60.80±5.87	15 h 15 min	89±2.5	75.00±1.87
F6	500±3.76µm	85.00±3.24	15 h 10 min	88±1.5	75.00±1.45
F7	310±2.98µm	65.00±2.63	12 h 20 min	64±2.7	63.63±0.33
F8	425±3.66µm	89.80±1.02	12 h 25 min	65±1.22	65.00±0.12
F9	300±2.58µm	65.00±2.48	18 h 13 min	95±2.5	89.00±1.98
F10	400±1.87µm	85.35±3.62	13 h 18 min	69±1.9	69.90±1.23
F11	320± 2.22µm	69.00±1.68	15 h 8 min	87± 1.0	85.00±2.22

***Table 2**: Particle size, yield %, duration of buoyancy, floating % and entrapment efficiency of floating microspheres of ATC*

Optical microscopy

The surface of the microspheres was evaluated by optical microscope; the microspheres were spherical in shape with smooth surface, **Fig. 1.**

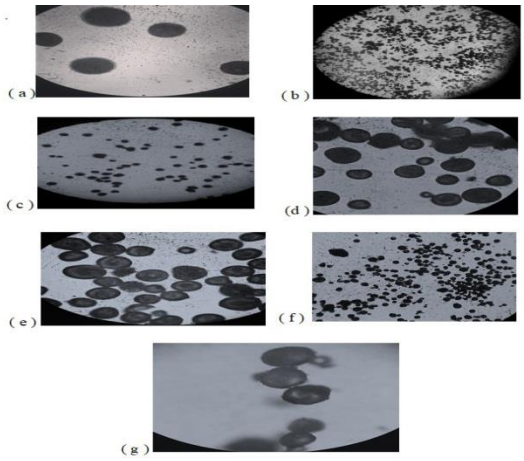

***Fig 1:** Photomicrograph of floating microspheres using magnification power 400. a) F6, b) F5, c) F11, d) F10, e) F3, f) F1 & g) F6.*

Fourier transform infrared spectroscopy

FTIR were performed to investigate the possible type of interaction between ATC and ES100 as shown in the **Fig. 2.** The results showed that the characteristic shoulders of ATC were traced as follows: 3360 and 3365 cm^{-1} (N-H stretching), 3406 cm^{-1} (O-H), 3057 cm^{-1} (c=c),1315 and 1216 cm^{-1} (C-OH), 1433 cm^{-1} (C-C), 1216 cm^{-1} (C-O), 1650 cm-1 (C=O), 3057 cm^{-1}(C-H Aromatic), 2923 and 2967 cm^{-1} (C-H Aliphatic) and 694 cm^{-1} (para-flourophenyl). The acidic
O-H group of ES100 appearing at 3451 cm^{-1} was shifted in microspheres to 3421 cm^{-1} due to formation of hydrogen bonds with O-H group of atorvastatin calcium which appeared at 3406 cm^{-1}. An intermolecular hydrogen bond was formed between NH of ATC which appeared at 3260 cm^{-1} and 3365 cm^{-1}, and C=O group of acid in ES100 and both groups disappeared. Aliphatic hydrogen in ATC appeared at 2923 cm^{-1} and 2967 cm^{-1}, and aliphatic hydrogen of ES100 appeared at 2952 cm^{-1} and 2997 cm^{-1} while aliphatic hydrogen in microspheres appeared at 2949 cm^{-1}. C-OH group of ES100, which appeared at 1264 cm^{-1}, appeared in microsphere at 1246 cm^{-1}. C-C which appeared in ATC at 1433 cm^{-1} and appeared in ES100 at 1447 cm^{-1} and 1481 cm^{-1} appeared in microsphere at 1439 cm^{-1}. C-O, which appeared in ATC at 1216 cm^{-1} and appeared in ES100 at 1191 cm^{-1} disappeared in microspheres. C=C of ATC appeared in microsphere at 1560 cm-1 and 1597 cm^{-1}. C=O of ester group of ES100 appeared in microspheres at 1729 cm^{-1}. C=O of amide group of ATC appeared in microspheres at 1646 cm^{-1}. So intermolecular hydrogen bonds were formed between the drug and ES100 indicating formation of microspheres.

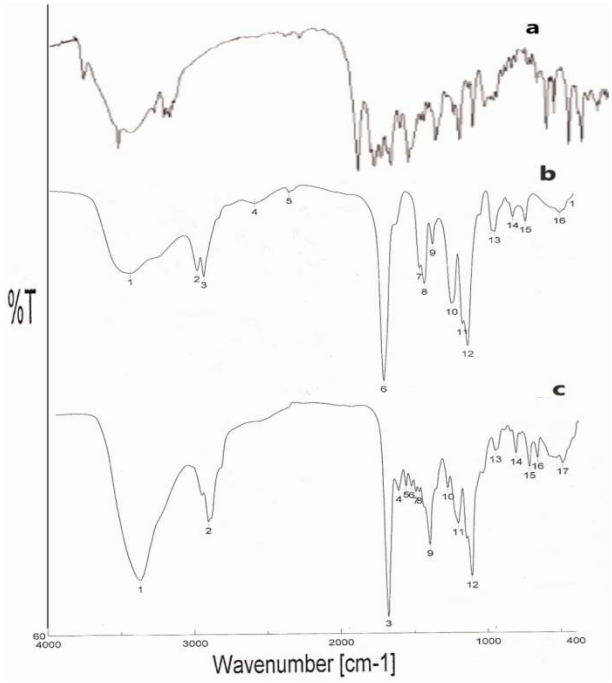

Fig 2: *FTIR spectrum of (A) ATC, (B) ES100, (C) Microspheres.*

Differential scanning calorimetry

By heating the microspheres over a temperature range of 0-400°C it didn't melt, indicating that its melting point was higher than 400°C, this is due to the formation of a sphere from polymer (ES100) around the drug (ATC), The endothermic peak of ATC appearing at 154.37°C corresponding to its melting point was disappeared in microspheres which indicate complete entrapment of ATC inside the microspheres, **Fig. 3.**

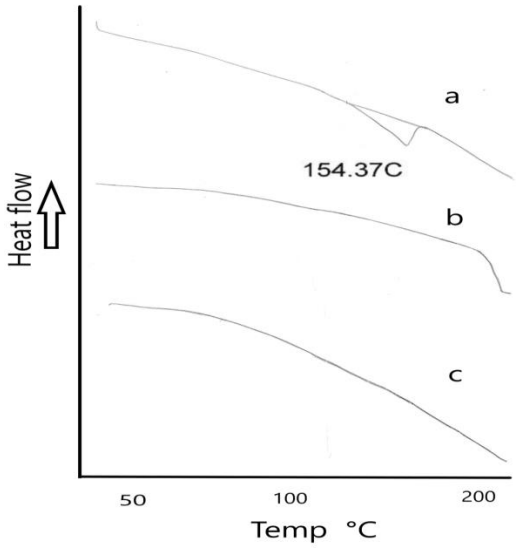

Fig 3: *DSC Spectrum of (A) ATC, (B) ES100, (C) Microspheres.*

Percent Yield of Floating microsphere

Increasing the drug: polymer ratio from 1:1 to 1:3 resulted in an increase in the microspheres yield % from 75 to 99.4, respectively, this may be due to the increase in throughput of the polymer slurry and rapid evaporation of the solvent (**Shah et al., 2011**). Increasing the stirring speed from 1000 to 1600 rpm led to a marked decrease from 80.4 to 60.8, this is attributed to the adherence of the polymer to the paddle by the turbulence created within the external phase leading to a reduction in the yield% (**Abdallah et al., 2012**). As the span 80 concentration increased from 0.5 to 1.5% the yield% was decreased from 85 to 65 respectively (**Wadher et al., 2014**). Increasing the internal: external phase volume ratio from 1: 2.5, 1:4, 1:5, 1:6.6 to 1:7.5, the yield % was decreased from 89, 85.35, 75, 69 to 65 respectively (**Tyagi and Kori, 2014**), this can be attributed to the fact that larger volumes of continuous phase resulted in less collisions between emulsion droplets and fine droplets of emulsion, giving rise to small and uniform microspheres (**Saravanan et al., 2003**).

In-vitro buoyancy

As shown in **table 2**, It was found that the buoyancy and floating % of microspheres was affected by the preparation variables, both were increased by increasing stirring rate, internal: external phase volume ratio and decreased by increasing drug to polymer ratio and surfactant concentration (**El Nahas and Hosny., 2011**).

Determination of Entrapment efficiency

Table 2 shows the effects of different factors on the entrapment efficiency of ATC microspheres. The entrapment efficiency was increased from 71.15, 73.27 to 75 with increasing the stirring rate from 1000, 1300 to 1600 rpm respectively, increased from 65, 71.15 to 89 with increasing the external phase volume from 50, 100 to 150 ml respectively and increased from 62.9, 71.15 to 85 with increasing the internal phase volume from 15, 20 to 25 ml respectively, while on increasing the drug to polymer ratio from 1:1,1:2 to 1:3 the entrapment efficiency was decreased from 71.15, 55.6 to 55.8%.

In-vitro drug release

Fig. 4 shows the cumulative % drug released from different formulations after 8 h. It was found that, F5 (prepared at stirring rate of 1600 rpm) had the highest % drug released (66 %) after 8 hours, because higher stirring rate produce smaller microspheres of faster drug release %. Increasing drug to polymer ratio from 1:1 to 1:3 (F1-F3), the % drug released decreased from 50.18 to 25.00 %, respectively, this was attributed to that, the increasing in the drug to polymer ratio led to increase in particle size. This could be ascribed to the increase in viscosity of the medium with increasing polymer concentration resulting in enhanced interfacial tension and diminishing shearing efficiency which resulted in formation of larger particles of slower drug release (**Najmuddin et al., 2010; Punitha et al., 2010**). Increasing the stirring rate from 1000 to 1600 rpm resulted in a marked increase in the % drug released from 50.18 to 66, respectively, because increasing the mixing speed generally resulted in decreased microsphere mean size (**Tiwari and Verma, 2011**). Increasing span 80 concentration from 0.5 to 1.5 % led to an increase in the % drug released from microsphere from 40.5 to 58, respectively due to stabilization of small droplets which resulted in smaller microspheres with faster drug release (**Dhakar et al., 2010**). On increasing the internal: external phase volume ratio from 1: 2.5, 1:4, 1:5, 1: 6.6 to 1:7.5, the % drug released was increased from 48.29, 49, 50.18, 59 to 60.6 respectively, as a result of the porosity decrease occurred with increasing aqueous/organic phase ratio, so lower aqueous/organic phase ratio is needed to

obtain more porous nanoparticles with faster release rates (**Choi et al., 2002**).

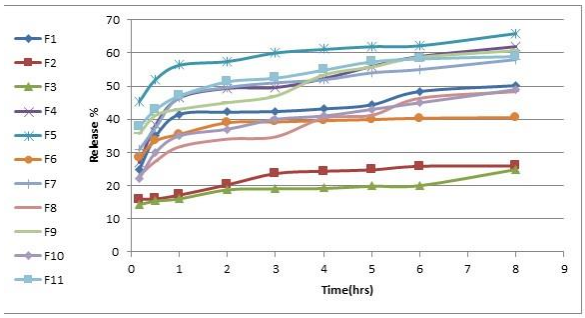

Fig. 4: *In vitro release studies of different floating microsphere formulas from F1-F11.*

Hypolipidemic effect of ATC floating microspheres

The ability of ATC floating microspheres to decrease the blood total cholesterol level (TC), the blood triglycerides level (TGS) and the blood LDL level of rabbits was (74.42 %, 66% and 92.51%), its effect was significantly higher than market drug ATOR ® (56%, 19.11 % and 74.32%) at (P<0.01) (**Fig. 5)**. The ability of floating microspheres to increase the blood HDL level of rabbits was (11.94%), it was significantly higher than market drug ATOR ® (4.8) at (P<0.001). In case of control group there was no significant difference after placebo treatment for all data. Similar findings were reported by **Husseiny et al., 2018** who investigated that floating microsphere loaded Meclizine HCL as anti-vomiting drug might represent an alternative oral dosage forms via decreasing the frequency of dosing, enhancing the compliance of patient and, more importantly, increasing the therapeutic efficacy of the drug during pregnancy.

The oral route of drug administration represents one of the most convenient and attractive routes for the drug administration because of the ease of administration. Therefore, the formulation of oral drug delivery systems that maintain higher drug absorption is of great importance to enhance drug pharmacological efficiency. In this study, floating microsphere was used as a carrier for the controlled and/or sustained release of ATC. Therefore, these results indicate that ATC floating microspheres may be a promising technique for effective treatment of hyperlipidemia.

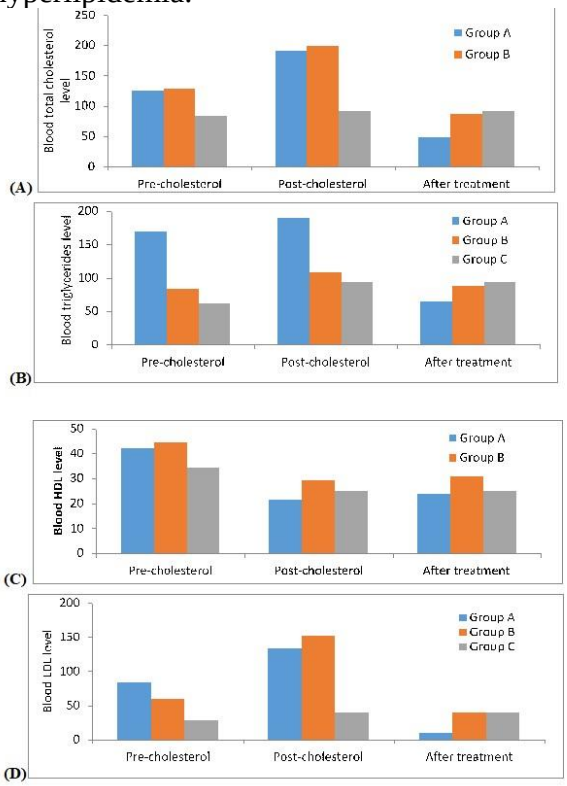

Fig 5: *Statistical analysis of blood levels of a) Total cholesterol, b) Triglycerides, c) LDL & d) HDL.*

Conclusion

The present study investigated the possibility of enhancement of oral hypolipidemic effect of atorvastatin calcium via formulation of floating microspheres. F5 gave the highest % drug released (66%) after 8 h. The floating microspheres were able to decrease the rabbit's blood TC, TGS and LDL levels by 74.42%, 66% and 92.51% respectively and to increase the HDL level by 11.94% which is more effective than the market drug ATOR®.

Acknowledgments

The authors want to thank the Egyptian International Pharmaceuticals Industries Co. (EIPICO) for granting samples of Atrovastatin Calcium.

Financial support

None

Conflict of interest

The authors report no conflicts of interest in this work

Reference

Abd El-Bary, A.; Aboelwafa, A.A.; and Al Sharabi, I.M. (2012). Influence of some formulation variables on the optimization of ph-dependent, colon-targeted, sustained-release mesalamine microspheres. AAPS Pharm Sci Tech 13(1): 75-84.

Abdallah, M.H.; Sammour, O.A.; El Ghamry, H.A.; El Nahas, H.M.; and Barakat, W. (2012). Development and characterization of controlled release ketoprofen microspheres. J Appl Pharma Sci 2(3): 60-67.

Avachat, A.M.; Bornare, P.N.; and Dash, RR. (2011). Sustained release microspheres of Ropinirole hydrochloride: Effect of process parameters. Acta Pharm 61: 363–376.

Chaudhari, S.Y.; Galib, R.; and Prajapati, P.K. (2016). Association of Dietary Factors in Hyperlipidemia - A Review. J Ayurveda Medical Sci 1(2): 51-54.

Choi, H.S.; Seo, S.A.; Khang, G.; Rhee, J.M.; and Lee, H.B. (2002). Preparation and characterization of fentanyl-loaded PLGA microspheres: in vitro release profiles. Int J Pharm 234: 195‑203.

Demir, G.M., Karaküçük, A. and Zelihagül, D. Stirring speed effects on physical characteristics of theophylline microsphere 41, (2014).

Dhaka, R.C.; Mauryal, S.D.; Sagar, B.; Bhagat, S.; Prajapati, S.K.; and Jain, C.P. (2010). Variables influencing the drug entrapment efficiency of microspheres: A Pharmaceutical Review. Sch Res Lib 2(5): 102-16.

Dinarvand, R.; Mahmoodi, S.; and Farboud, E. (2004). Effect of process variables on particle size of gelatin microspheres containing lactic acid. Pharma Dev Tech 9: 291–29 9.

El-Nahas, H.M.; and Hosny, K.M. (2011). Chitosan-based floating microspheres of Trimetazidin dihydrochloride; preparation and in vitro characterization. Indian J Pharm Sci 73(4): 397–403.

Elseweidy, M.M.; Abdallah, F.R.; Elswefy, S.E.; Eldahmy, S.I.; Shaheen, M.A.; and Elnagar, G.M. (2014). Protective role of 10-dehydrogingerdione as modulator for CETP activity and HDL metabolism in cholesterol fed rabbits. Biomed Eng Res 3(2): 28-36.

Fossati, P.; and Prencipe, L. (1982). Serum triglycerides determined calorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem J 28: 2077-2080.

Friedewald, W.T.; Levy, R.I.; and Fredrickson, D.S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem J 18: 499-502.

Ganesan, P.; Soundararajan, R.; Shanmugam, U.; and Ramu, V. (2013). Development, characterization and solubility enhancement of comparative dissolution study of second generation of solid dispersions and microspheres for poorly water soluble drug. Asian Jicrospheres containing Duloxetine hydrochloride. Int J Res Pharm Biomed Sci 4(2): 568-572.

Grove, T.H. (1979). Effect of reagent pH on determination of high-density lipoprotein cholesterol by precipitation with sodium phosphotungstate-magnesium. Clin Chem J 25: 560-564.

Husseiny, R.A.; Abu Lilaa, A.S.; Abdallah, M.H.; Hamed, E.E.; and El-Ghamry H.A. (2018). Design, in vitro/in vivo evaluation of meclizine HCl-loaded floatingmicrospheres targeting pregnancy-related nausea and vomiting. J Drug Deliv Sci Tech 47: 395–403.

Ibrahim, M.; Ibrahim, A.; Shaheen, K.; and Nour, M. (2013). Lipid profile in Egyptian patients with coronary artery disease. Egy Heart J 65: 79-85.

Khan, F.N.; and Dehghan, M.H.G. (2011). Enhanced bioavailability of Atorvastatin calcium from stabilized gastric resident formulation. AAPS Pharma Sci Tech 12(4): 1077-1086.

Meiattini, F.; Prencipe, L.; Bardelli, F.; Giannini, G.; and Tarli, P. (1978). The 4-hydroxybenzoate/4-aminophenazone chromogenic system used in the enzymatic determination of serum cholesterol. Clin Chem J 24(12): 2161-2165.

Mishra, A.; Rathore, S.; Marothia, D.; and Chauhan, C.S. (2018). Formulation and Evaluation of Floating Microspheres of an Anti-Diabetic Agent. Int J Drug Dev & Res 10: 38-42

Mukesh, P.; Ratnaparkhi, S.B.; Dhiwar, K.E.; Dhage, S.S.; Bhore, P.M.K.; and Pradeep, SP. Formulation and in-vitro characterization of floating microspheres of Metfomin HCl". Der Pharmacia Letter. 2012;4(5):1390-1400.

Najmuddin, M.; Shelar, S.; Ali, A.; Patel, V.; and Khan, T. (2010). Formulation and in vitro evaluation of floating microspheres of ketoprofen prepared by emulsion solvent diffusion method. Int J App Pharm 2(1):13-17.

Nouh, F.; Omar, M.; and Younis, M. (2019). Risk Factors and Management of Hyperlipidemia (Review). Medicine 2(1): 1-10.

Onwe, P.; Anyigor-Ogah, C.s.; Okorocha, A. and Afoke, Ao. (2015). Hyperlipidemia: Etiology and Possible Control. IOSR J Dent Medical Sci 14(10): 93-100.

Patel, K.S.; and Patel, M.B. (2014). Preparation and evaluation of chitosan microspheres containing Nicorandil. Int J Pharm Inves 4(1): 32–37.

Perumandla, P.K.; and Priya, S. (2014). Formulation and in vitro evaluation of floating microspheres of Dextromethorphan hydrobromide. Int J Pharm Pharm Sci 6(4): 206-210.

Punitha, K.; Khadhir, S.; Ravichandiran, V.; Umadevi, S.K.; Vaijayanthi, V.; Padmapriya, S.; and Kumar, S. (2010). Intragastric floating drug delivery system of Ranitidine hydrochloride: Formulation and evaluation. Int J Pharm Pharm SCi 2(4): 106-108.

Quintanar-Guerrero, D.; Fessi, H.; Allémann, E.; and Doelker, E. (1996). Influence of stabilizing agents and preparative variables on the formation of poly(d,l-lactic acid) nanoparticles by an emulsification-diffusion technique. Int J Pharm 143: 133-141.

Ratnakar, P.; and Murthy, R.S. (1998). Rabbit model for studying hypocholesterolemic effect of drugs and hypocholesterolemic effect of extracts of Garlic (allium sativum). Indian J Clin Biochem 13(1): 8-11.

Ray, S.K.; and Rege, N.N. (2002). Atorvastatin: in the management of hyperlipidaemia. J Postgrad Med 46(3): 242-243.

Samirkumar, P.; Chand, T.; and Maulik, T. (2013). Formulation development and evaluation of microspheres containing Duloxetine hydrochloride. Int J Res Pharm Biomed Sci 4(2): 568-572.

Saravanan, M.; Bhaskar, K.; Srinivasa, R.G.; and Dhanaraju, M.D. (2003). Ibuprofen-loaded ethylcellulose/polystyrene microspheres- An approach to get prolonged drug release with reduced burst effect and low ethyl cellulose content. J Microencap 20: 289-302.

Shah, V.A.; Shinde, M.L.; Patil, S.B.; Nikam, M.B.; Ghodke, D.S.; and Shah, R.R. (2011). Impact of selected variables on the preparation of Aceclofenac microspheres by spray drying using full factorial design. Int J Pharma Tech and Res 3(2): 1066-1072.

Shattat, G.F. (2014). A Review Article on Hyperlipidemia: Types, Treatments and New Drug Targets. Biomed Pharma J 7(2): 399-409.

Tiwari, S.; and Verma, P. (2011). Microencapsulation technique by solvent evaporation method (Study of effect of process variable. Int J Pharm Life Sci 2(8):998-1005.

Tyagi, L.K.; and Kori, M.L. (2014). lornoxicam loaded ethyl cellulose microspheres prepared by emulsion solvent evaporation method. African J Pharm Pharm 8(9): 277-288.

Wadher, K.J.; Nagarkar, A.; Sahare, D.; and Umekar, M.J. (2013). Formulation and evaluation of sustained release Ciprofloxacin hydrocloride microspheres using synthetic polymers. Int J Pharm Tech Res 5(2): 773-780.

Zodda, D.; Giammon, R.; and Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel) 6(1): 10.

Zagazig J. Pharm. Sci. Jun, 2022 ISSN 1110-5089
Vol. 31, Issue 1, pp. 14- 24 ISSN (on-line) 2356_9786

إستخدام تقنية الحويصلات الدقيقة الطافية لعقار أتورفاستاتين كالسيوم لتحسين قدرته علي خفض مستوي الدهون

تم تحضير 11 تركيبة من الحويصلات الدقيقة الطافية (ف1-ف11) بإستخدام بوليمرالأدراجيت اس 100 و بتغيير بعض العوامل مثل نسبة العقار و البوليمر,معدل التقليب,تركيز المادة ذات النشاط السطحي والنسبة بين حجم المحلول الداخلي و الخارجي . قيمت الحويصلات الدقيقة الطافية المحضرة عن طريق التحليل الحجمي للجزيئات , الحجم و الكفاءة الأحتوايه و الأنتاجية ,الطفو المعملي و إنحلال الدواء المعملي و التحويل الطيفي بالأشعة تحت الحمراء و التحليل الحراري التفاضلي. تتراوح حجم جزيئات الحويصلات الدقيقة الطافية من (150-606 مم) و كان لزيادة نسبة العقار للبوليمر أثر علي زيادة حجمها, كما أدي زيادة معدل التقليب و تركيز المادة ذات النشاط السطحي والنسبة بين حجم المحلول الداخلي و حجم المحلول الخارجي الي صغر حجمها. كانت مدة الطفو المعملي أكثر من 8-18 ساعة و تراوحت نسبة الحويصلات الدقيقة الطافية من 40% الي 95% و يتأثركلاهما بالمتغيرات التي تحدث في عملية التحضير فقد أزدادوا بزيادة معدل التقليب والنسبة بين حجم المحلول الداخلي و الخارجي و نقصوا بزيادة نسبة العقار للبوليمر و تركيز المادة ذات النشاط السطحي . تراوحت الكفائة الأحتوائية من 55.6 الي 89 % و قد أزدادت بزيادة معدل التقليب والنسبة بين حجم المحلول الداخلي و الخارجي و قلت بزيادة نسبة العقار للبوليمر و تركيز المادة ذات النشاط السطحي . كان معدل الإنحلال المعملي للعقار من الأقراص ف5 التي تم تحضيرها بإستخدام معدل تقليب 1600 لفة في الدقيقة 66% بعد مرور 8 ساعات و هو أعلي معدل إنحلال في كل الأقراص.كما أوضح التحليل الطيفي التحويلي بالأشعة تحت الحمراء للحويصلات الدقيقة الطافية تكوين روابط هيدروجينية بين جزيئات العقار و البوليمر و هذا يؤكد تكوين حويصلات دقيقة تحتوي علي مجموعات تقع في أطياف مختلفة عن العقار و البوليمر..عند عند إجراء التحليل الحراري التفاضلي للحويصلات الدقيقة تم تعريضها لدرجات حرارة متفاوتة من 0-400 درجة مئوية و لكنها لم تنصهر مما يؤكد أن درجة إنصهارها أعلي من 400 درجة مئوية و يرجع ذلك إلي تكوين حويصلات من البوليمر حول العقار

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