CONTROLLED RELEASE 7-METHOXYTACRINE-POLYCAPROLACTONE NANOCAPSULES

DRUG-DELIVERY SYSTEM FOR ALZHEIMER'S DISEASE TREATMENT: SYNTHESIS AND PHYSICO-CHEMICAL CHARACTERIZATION

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Abstract
Alzheimer’s disease is the most prevalent cause of dementia in aging people. 7-Methoxytacrine (7-MEOTA) is one of the approved drugs for the treatment of this disease. In the current study, a 7-MEOTA delivery system was prepared based on the polycaprolactone nanocapsules (7-MEOTA@PCL), and its physico-chemical properties were investigated. The drug amount loaded in nanocapsules has been estimated 65%. The average particle size of the 7-MEOTA@PCL nanocapsules was around 237 nm with a polydispersity index of 0.31 and negative surface charge (−21.2 mV). The prepared nanoparticles are stable upon 40 days of storage at 25 °C, without any decomposition. The morphological analysis of the 7-MEOTA@PCL nanoparticles indicated that the nanoparticles are spherical and free of any aggregation. In vitro release experiments revealed the controlled release of the 7-MEOTA from the polycaprolactone nanocapsules. Application of the Korsmeyer–Peppas model to the release kinetics data showed that the release of the drug was by diffusion Fick’s law.

Keywords
Polycaprolactone · Nanocapsule · 7-Methoxytacrine · Alzheimer’s disease · Release profile

Introduction
Drug delivery is one of the most important and complex branches of pharmacology which has significantly expanded today with other scientific fields. These advances are particularly effective in the field of drug delivery mechanisms and systems. The drug delivery system (DDS) is a formulation or device capable of injecting a drug into the body and maintaining its effectiveness and safety by controlling the speed, time and place of its release. DDSs play a vital role in the pharmacological effects of drugs as they can affect the drug release and its speed, the drug distribution inside the body and even the occurrence of side effects. An effective DDS ensures that an active drug can be released at the right site at the right time and exert its effects while being present in the body [1]. During the common drugs taking, only a small part of the medicine reaches the proper site in the body, and most of it is excreted during the metabolism and enzyme secretion. Each drug has a treatment range in terms of the concentration. The maximum safe concentration above which is toxic, and the minimum effective concentration of the drug below this is ineffective [2]. The appropriate concentration of the drug lies between these two concentration levels. When an individual takes the drug regularly, the drug concentration in the blood suddenly increases up to near the maximum safe concentration and reaches its lowest effective one after a short period of time. In modern DDSs with various techniques, the appropriate drug concentration is continuously provided to the patient over a period of time [3–5]. A system with continuous drug release must be biodegradable and biocompatible to be able to release a therapeutic agent into the body and increase the degree of effectiveness and safety of the drug by controlling the rate, time and place of release. This system is used to transfer and store an appropriate amount of drugs for a period of time. It is expected to prevent the destruction of unreleased drugs in the body and reduce the side effects due to fluctuations in drug concentration or adverse effects of the damaged drug molecules. A drug delivery substance must have a suitable physical structure and time-invariant properties to be used.

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in the DDSs. Furthermore, it must be pure and chemically inert. Structurally diverse carriers such as gels, liposomes, microspheres, foams and films have been introduced for DDSs, the most significant advantages of including the improved therapeutic effect, reduced toxicity, etc. [6–15]. The controlled drug release is the process through which a carrier such as polymeric, metal, protein or lipid nanoparticles is purposefully combined with the active drug to release it in the body in a predetermined and desired manner. In recent years, much attention has been paid to the use of nanoparticles as pharmaceutical carriers. Nanoparticles are colloidal carriers of natural or synthetic origin whose sizes range from 1 to 1000 nm. Also, nanocarriers may be composed of polymeric or mineral materials. These carriers, in the form of nanocapsules and nanospheres, can absorb and encapsulate various drugs, thus protecting them against enzymatic and chemical degradation and directing them towards various tissues and cells. As one of the best DDSs, polymeric nanoparticles have been extensively explored in recent years [16–20]. These substances can carry a wide range of drugs to the specific parts of the body within a certain period of time. Biodegradable polymers have gained great importance due to the easy excretion of their metabolites by the body. Many polymers have been employed in the DDSs due to their unique properties [21–27]. There are many ways to combine drugs with polymeric nanoparticles. For example, the drugs can be trapped in the polymeric matrix, encapsulated in the nucleus of nanoparticles or surrounded by shell-like polymeric membranes. Drugs are also combined with nanoparticles by creating chemical bonds to polymers or adsorption on the surface of nanoparticles. The nanocarrier-based DDSs have been entered the global pharmaceutical market, and their use in drug delivery is increasingly growing. Future research prospects will be on the development of multifunctional pharmaceutical nanoparticles, such as those with targeted drug delivery capabilities and simultaneous imaging. Having biodegradable, biocompatible and non-carcinogenic properties, polycaprolactone (PCL) is an excellent choice for the DDSs. PCL is a hydrophobic semi-crystalline polymer. In addition to the non-toxicity of the product resulting from its degradation, PCL also has excellent mechanical properties (mechanical flexibility), good biocompatibility and a low melting point [28]. The U.S. Food and Drug Administration (FDA) has approved PCL as a biodegradable polyester. Earlier, the PCL nanoparticles have been widely used as pharmaceutical nanocarriers in the DDSs [29–36].

Alzheimer’s disease (AD) is one of the leading causes of death among the elderly in the world [37]. It is considered a progressive neurodegenerative disorder that leads to dementia and has several symptoms such as cognitive dysfunction, psychiatric and behavioural disorders, and difficulties in performing daily activities associated with depression. This disorder has indicated an increase of more than 66% in mortality [38]. Methoxystacrine (7-MEOTA) is one of the three approved drugs by the FDA to treat AD [39, 40]. However, this drug has a short biological half-life of 2–3 h, and its high doses are associated with gastrointestinal, cholinergic and hepatic side effects. Given the experience of the present research group related to the use of PCL nanocapsules in the pharmaceutical and agricultural industries [41–43], in the present study, it has been attempted to load 7-MEOTA drug on PCL nanoparticles as a useful release system and investigate its physicochemical properties using various analytical techniques.

### Experimental

#### General Information

All chemicals required to prepare 7-MEOTA@PCL, including PCL, span 60, tween 80 and necessary solvents, were purchased from Sigma-Aldrich, Merck and local companies. The amount of drug loaded into the nanocapsules was measured using liquid chromatography-tandem mass spectrometry (LC–MS/MS) with an Agilent 6410 spectrometer with electrospray ionization source and Ultraviolet–Visible spectroscopy (UV–Vis), using a spectrophotometer.

It should be noted that before analyzing the nanocapsules solution, standard drug samples with different concentrations should be examined with UV–Vis device to obtain a calibration curve. The following formula has been used to measure the amount of drug loaded into the nanocapsule:

\[
\text{The amount of drug loaded into the nanocapsule} = \frac{\text{the amount of the initial drug} - \text{the amount of free drug in the nanocapsules solution}}{\text{the amount of the initial drug}}
\]

To measure the amount of free drug in the nanocapsule solution, special cellulose filters were used with a porosity of 30,000 kDa (0.22-µm Millipore membrane, 30 kDa). This membrane pore size ensures that the free drug passes through the filter while the encapsulated drug remains in the solution. The dynamic light-scattering technique was employed to measure the particles’ average size (hydrodynamic diameter) and their dispersion. The suspension was diluted to the volume of 1:100, and its parameters were measured at 25 °C using a Zeta Plus analyzer (Malvern Zetasizer ZEN3600 model) with the detector at a constant angle of 90°. The FT-IR spectra were prepared using the Spectrum 65-Perkin-Elmer device. The TEM images of 7-MEOTA@PCL were provided using Scanning Probe Microscope-DME-95-50 device. Moreover, the
SEM images of 7-MEOTA@PCL were prepared by Philips EM2085 100 kV instrument.

**General Preparation Process of 7-MEOTA@PCL Nanocapsules**

The interfacial deposition of the pre-formed polymer was used to prepare 7-MEOTA@PCL [44]. The organic phase comprises 100 mg of PCL, 30 mL of acetone, 200 mg of oil (capric/caprylic acid triglycerides), 40 mg of sorbitan monostearate surfactant (Span 60) and 10 mg of 7-MEOTA. Also, the aqueous phase is composed of 30 mL of a solution containing 60 mg of polysorbate surfactant (Tween 80). After dissolving the components of both phases, the organic phase was slowly added into the aqueous one by a magnetic stirrer. The suspension was shaken for 10 min, and then the organic phase was evaporated at low pressure. The suspended nanoparticles were concentrated up to a final volume of 10 mL, resulting in a concentration of 1 mg/mL of 7-MEOTA.

**In vitro Release Studies**

The release of 7-MEOTA from PCL nanocapsules was investigated by dialysis method in phosphate buffer with pH 7.4 [45]. The suspension of 7-MEOTA@PCL nanocapsules was centrifuged at 4000 rpm for two hours. The residue as 7-MEOTA@PCL nanocapsules was washed twice to remove the unentrapped 7-MEOTA. The supernatant for the content of the drug free PCL nanocapsules was spectrophotometrically examined by measuring the absorbance at 246 nm [46]. The residue bearing 6.5 mg of 7-MEOTA was placed in a cellulose dialysis bag (Sigma-Aldrich), sealed at both ends. The dialysis bag was immersed in 20 mL of phosphate buffer at pH 7.4, maintained under gentle agitation. 2 mL of samples were withdrawn at regular time intervals, and the same volume was replaced with fresh dissolution medium up to 72 h. The content of 7-MEOTA in samples was analyzed spectrophotometrically by measuring the absorbance at 246 nm. The cumulative percent release was calculated using the standard curve.

**Results and Discussion**

7-MEOTA was synthesized by following the known and optimized procedure [47, 48] in the laboratory (Scheme 1) with a purity of higher than 95%. The chemical structure of 7-MEOTA was characterized using $^1$HNMR, $^{13}$CNMR and FT-IR techniques. Spectral data were in good agreement with the literature. The condensation reaction of 4-methoxyaniline 1 with ethyl 2-oxocyclohexanecarboxylate 2 in the presence of $p$-toluenesulfonic acid (pTsOH) as an acidic catalyst and refluxing toluene yielded 7-methoxy-1,2,3,4-tetrahydroacridin-10H-9-one 3 up to 80% yield. The reaction of phosphorus oxychloride (POCl$_3$) with 3 gave 9-chloro-7-methoxy-1,2,3,4-tetrahydroacridine 4 with excellent yield. The compound 4 is converted into 7-MEOTA with ammonium carbonate in phenol at 120 °C.

Spectral data of 7-MEOTA (9-Amino-7-methoxy-1,2,3,4-tetrahydroacridine): m.p. = 211–215 °C; FT-IR (KBr, υ/cm$^{-1}$): 3458.70, 2932.54, 1650.98, 1573.71,
1501.89, 1460.29, 1379.65, 1234.99, 1032.39; $^1$HNMR (500 MHz, CD$_3$Cl) δ: 1.89 (m, 4H), 2.57 (t, $^3$J = 11.5 Hz, 2H), 2.98 (t, $^3$J = 11 Hz, 2H), 3.79 (s, 3H, OCH$_3$), 4.68 (s, 2H, NH$_2$), 6.95 (s, 1H), 7.22 (d, $^3$J = 10 Hz, 1H), 7.81 (d, $^3$J = 10 Hz, 1H); $^{13}$CNMR (500 MHz, CD$_3$Cl) δ: 22.99, 23.08, 24.01, 34.03, 55.58, 98.90, 110.94, 117.73, 120.46, 130.54, 142.66, 145.66, 156.28 ppm.

The amounts of 7-MEOTA present in the PCL nanocapsules suspensions were determined by UV–Vis technique at $\lambda_{\text{max}} = 246$ nm and liquid chromatography-tandem mass spectrometry, after filtration through a 0.22-µm Millipore membrane, 30 kDa. According to the concentration and chromatographs of the standard drug samples and analysis of nanocapsules solution, the amount of free 7-MEOTA in suspensions has been obtained as 35%. Thus, 65% of the initial drug amount has been associated with PCL nanocapsules. Examining the PCL suspensions after one month, no significant change is observed in the initial free drug concentration (Fig. 1).

The results extracted from the UV–Vis method were also in line with the LC–MS/MS data. It should be mentioned that a five-point calibration curve based on the peak area ratio 7-MEOTA versus the 7-MEOTA concentration showed a good linear relationship over the range of 0.002–0.01 mg/mL, with a regression coefficient $r^2 = 0.990$ (Fig. 2).

The stabilities of the 7-MEOTA@PCL suspensions were evaluated using measurements of their diameter, polydispersity index, and zeta potential as a function of time over a 40 days (0, 10, 20, 30 and 40 days). The average sizes of the 7-MEOTA@PCL nanocapsules were 237 nm (Fig. 3a).
The values represent the average of three experiments performed at room temperature. No significant difference was observed in the nanocapsule size throughout the 40 days of the experiment. Size distribution of the 7-MEOTA@PCL nanocapsules after 10 days was shown in Fig. 3b. As can be seen, a narrow particle size distribution of 7-MEOTA@PCL nanocapsules was obtained with the interfacial deposition of pre-formed polymer method (experimental section).

The polydispersity index (PI) in different directions, including the particle sizes dispersion, was used to evaluate the stability and uniformity. The values of PI of 7-MEOTA@PCL nanocapsules at the beginning of the period was determined as 0.31. The PI value smaller than 0.5 is ideal for colloidal suspension. Good particle homogeneity was observed from the polydispersity results. After 40 days, the 7-MEOTA@PCL nanocapsules remained stable, but PI value for the nanocapsules increased slightly, showing

![Calibration curve based on the peak area ratio 7-MEOTA versus the 7-MEOTA concentration](image)

**Fig. 2** Calibration curve based on the peak area ratio 7-MEOTA versus the 7-MEOTA concentration

![Stability of 7-MEOTA@PCL nanocapsules as a function of time (0, 10, 20, 30 and 40 days) (a) and size distributions of the 7-MEOTA@PCL nanocapsules after 10 days (b)](image)

**Fig. 3** Stability of 7-MEOTA@PCL nanocapsules as a function of time (0, 10, 20, 30 and 40 days) (a) and size distributions of the 7-MEOTA@PCL nanocapsules after 10 days (b)
greater instability, due to aggregation of the nanocapsules (Fig. 4).

Zeta potential of 7-MEOTA@PCL nanocapsules at the beginning of the period was estimated as $-21.2$ mV (Fig. 5). This potential shows the charge present on the particle surface. The zeta potential in the nanocapsules is negative due to the presence of carboxylic groups ($-\text{COO}^-$) in the PCL chemical structure since PCL is a polyester. The zeta potential value with an amount of $\pm 30$ mV is considered to be suitable for the suspension. In addition, the zeta potential of the 7-MEOTA@PCL nanocapsules remains negative after 40 days, pointing out their complete stability and lack of any aggregation. This is mainly due to the fact that the charge of particles is sufficient so that electron repulsion prevents particle aggregation.

The FT-IR spectra of 7-MEOTA, pure PCL, and 7-MEOTA@PCL nanocapsules are plotted in Fig. 6. Comparing the FT-IR spectra' absorption frequencies is considered as a good benchmark for interaction investigating between the 7-MEOTA and PCL nanocapsules interaction. As can be seen from Fig. 6a, the bands at 3458 and 3320 cm$^{-1}$ correspond to stretching of the N–H bond present in the primary amine group of the 7-MEOTA structure, while bands at 2826–3063 cm$^{-1}$ are related to stretching of the alkyl (sp$^3$) and aromatic (sp$^2$) C–H bonds. Aromatic C=C stretching frequencies of 7-MEOTA can be observed at 1501–1600 cm$^{-1}$. Bending absorption of methylene and methyl groups occur around 1460 and 1379 cm$^{-1}$, respectively. The absorption frequencies of the C–N bonds also appear at 1650 cm$^{-1}$. The FT-IR spectra confirm the formation of 7-MEOTA@PCL nanocapsules as absorption frequencies of particles is sufficient so that electron repulsion prevents particle aggregation.

The FT-IR spectra of pure PCL indicate the absorption frequencies at 3436 cm$^{-1}$ (O–H bond stretching), 2949 cm$^{-1}$ (C–H bond stretching) and a characteristic stretching absorption at 1731 cm$^{-1}$ for the carbonyl group of ester. The spectrum of the 7-MEOTA@PCL is almost similar to that of pure PCL. Due to a very small amount of the 7-MEOTA with respect to PCL nanocapsules, the frequencies related to the nanocapsules usually cover the absorption associated with the 7-MEOTA. FT-IR spectra confirm the formation of 7-MEOTA@PCL nanocapsules as absorption frequencies.
were shifted after interaction of PCL nanocapsules with 7-MEOTA (Fig. 6b and 6c).

The morphological characteristics of the 7-MEOTA@PCL nanocapsules were studied using transmission electron microscopy (Fig. 7) and scanning electron microscopy (Fig. 8). The TEM images showed that the 7-MEOTA@PCL nanocapsules were nearly spherical with a uniform size distribution, and there was no tendency for aggregation. The average size was in the range 200–300 nm. The SEM micrograph confirmed solid dense nanocapsules with a fully polymeric structure.

The release profile of the encapsulated 7-MEOTA from the PCL nanocapsules is shown in Fig. 9. It should be mentioned that the release profile was obtained by dialysis bag technique [45]. The profile shows the release of 7-MEOTA in 3 steps with different slopes. At first step, the initial explosive release of the drug occurs, and about 50% of the initially encapsulated 7-MEOTA was released
from the PCL nanocapsules after one hour. The initial fast release of 7-MEOTA was observed into buffer probably due to the dissolution of 7-MEOTA attached to the surface of the PCL nanocapsules and the beginning of the drug release process due to the water penetration into PCL nanocapsules and escape of the drug through the concentration gradient. The second stage includes a range of 1 h after the start to 3 h. The slope of the chart is reduced at this step, and can be seen the gradual release of the drug from inside the PCL nanocapsules. In the last step, the slope of the diagram is almost fixed. The release percentage of around 90% was obtained after 24 h, while the release of the drug reached 95% after 72 h.

To evaluate the release mechanism of the drug from PCL nanocapsules, the drug release results were matched with the mathematical model proposed by Korsmeyer and Peppas [49, 50], described by:

\[
\frac{M_t}{M_\infty} = k t^n
\]

where \(M_t\) quoted the amount of 7-MEOTA released in time \(t\), \(M_\infty\) is the quantity of 7-MEOTA associated with the PCL nanoparticles at time \(t=0\), \(k\) is the kinetic release constant, and \(n\) is the release exponent. The value of exponent \(n\) is used to provide a hint of the release mechanism. By plotting the graph between \(\ln(M_t/M_\infty)\) and \(\ln(t)\), the values of \(n\) and \(k\) can be found [51]. Application of the Korsmeyer-Peppas model to the release kinetics data resulted in values for the release constant (\(k\)) and the release exponent (\(n\)) of
3.86 min\(^{-1}\) and 0.25, respectively. The value of the release exponent was in the range \(n \leq 0.43\), indicating that a diffusion mechanism controlled the release process according to Fick’s law.

**Conclusions**

The PCL nanocapsules were tested as a matrix for loading 7-MEOTA by the interfacial deposition of the pre-formed polymer. The efficiency of 7-MEOTA incorporation in the final matrix was 65% as quantified by LC–MS/MS and UV–Vis methods. The size of the 7-MEOTA@PCL nanocapsules was in the range 200–300 nm, the polydispersion value was below 0.31, and zeta potential was \(-21.1\) mV. The data of FT-IR spectra confirmed that the 7-MEOTA interacted with the PCL nanocapsules. The TEM and SEM analyses revealed that the nanocapsules were spherical, dense, and had no apparent aggregation. Application of Korsmeyer and Peppas mathematical model showed that the kinetics of 7-MEOTA release was consistent with a Fickian diffusion mechanism. It is concluded that the formulation is expected to be useful for sustained delivery of 7-MEOTA in drug delivery and the PCL nanocapsules could be a suitable solution to increase drug’s action on the target site.

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**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

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