



EVALUATION AND PREPARATION OF ATENOLOL-LOADED FLOATING MICROCAPSULES

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The aim of this investigation is to prepare Atenolol (AT) floating microcapsules with sustained release profiles utilizing ethyl cellulose (EC) as a matrix former. EC is frequently used as a hydrophobic polymeric material for extended drug release applications. Emulsion-solvent evaporation technique was utilized to fabricate the floating microcapsules. The ratios of EC and AT utilized were 1:1, 1:2, 1:3, 1:4, and 1:5, with the amount of EC used being constant and the amount of AT being variable depending on the polymer ratio/AT ratio. The prepared microcapsules were assessed for entrapment efficiency (EE%), drug loading, percent yield (% yield), buoyancy percentage (%), particle size analysis, and in-vitro drug release study after 12 h. After that, the best-achieved microcapsule was characterized using scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The best formula (M1) demonstrated a spherical morphology. Further, M1 released about $91.23 \pm 3.21\%$ after 12 h. Moreover, the FTIR showed that there is no chemical interaction between the formulation components. In addition, DSC showed the ability of microcapsules to enclose AT inside its constructs. Further, XRD studies showed that microcapsules had an amorphous form. The previous findings demonstrated the good capability of M1 as a floating dosage form for sustained and continuous drug delivery of AT.

Keywords :Atenolol, Floating dosage form, microcapsules, XRD, SEM

INTRODUCTION

Microencapsulation technology involves the incorporation of different types of encapsulants into polymeric microparticles, this technology was employed successfully in the encapsulation of a wide range of cargo including drugs; cosmeceuticals; insecticides; fragrances, and flavors¹. A microcapsule is a small sphere. Its wall is called a shell/ coating and the material inside the microcapsule is termed a core/an internal phase. The most important application of microcapsules is to store compounds inside them. Furthermore, they could be employed to control the release of the compounds, to prevent the core material from environmental influences (like temperature, light, oxygen, and moisture), and to enhance the shelf-life of the compounds².

Ethyl cellulose (EC) is a non-biodegradable and biocompatible polymer and is an extensively studied encapsulating material for the controlled release of pharmaceuticals³. The use of EC-based microcapsules has been reported by several authors for the encapsulation of a variety of drugs, such as the sustained release of amoxicillin, theophylline, and 5-fluorouracil prepared by solvent evaporation. In addition, fabrication of EC microcapsules using chitosan as a stabilizer has been reported⁴.

Atenolol (AT) is a cardio selective β_1 -adrenergic receptor blocking agent widely prescribed for the treatment of hypertension, cardiac arrhythmia and angina. The recommended adult oral dosage of conventional tablets of atenolol (AT) is 25–100 mg twice daily for the effective treatment of hypertension. Additionally, it can be taken as a

migraine headache preventative measure⁵. However, fluctuations of drug concentration in plasma may occur, resulting in side effects (nausea, stomach pain, low fever, loss of appetite, dark urine, jaundice, anxiety, depression, etc.) or a reduction in drug concentration at receptor side⁶. Due to changes in AT tissue distribution and pharmacokinetics, sustained release has been proven to be a highly effective method for increasing medicinal efficacy and/or decreasing drug toxicity⁷.

Therefore, an efficient oral drug delivery system is needed to overcome the drawbacks associated with conventional AT tablets and improve the clinical treatment process which is capable of maintaining the therapeutic concentration of the drug at the desired absorption site over a longer period of time.

There have been a number of studies to develop AT as sustained-release dosage forms. As previous investigation developed a delayed release of AT from these pellets was prepared by coating them with a gastro-resistant polymer⁸. Another study developed floating AT microspheres as a prolonged release multi particulate system and assessed it using an innovative multicompartiment dissolving system⁹.

The goal of this investigation's study is to prepare floating microcapsules by emulsion solvent evaporation method using EC that might impart a controlled release properties to the prepared microcapsules. The produced microcapsules were assessed for their flow characteristics, entrapment effectiveness (EE%), particle size analysis (PS), percent yield (% yield), *in-vitro* drug release, and buoyancy percentage. The optimized microcapsule formula was also chosen and evaluated by SEM, FTIR, DSC diffraction, XRD assessment.

MATERIALS AND METHODS

Materials

Atenolol (AT) was supplied from M/s Provizer Pharma, (Gujarat, India). Ethyl cellulose (EC) was provided from (Acros, Belgium). Span 80, tween 80, and light liquid were supplied from sigma Aldrich (St. Louis, MO, USA). Acetone, hexane, and methanol were supplied from El-Nasr Pharmaceutical Chemicals Co., (Cairo, Egypt).

Fabrication of AT microcapsules

The emulsion-solvent evaporation method was used for preparing AT microcapsules¹⁰. **Table (1)** illustrates the different ratios of EC and AT utilized, which were 1:1, 1:2, 1:3, 1:4, and 1:5, respectively. The amount of EC used was constant, however the amount of drug used varied depending on the polymer/drug ratio. First, 3 gm of EC were dissolved in 70 milliliters of acetone using a magnetic stirrer at 750 revolutions per minute for 20 minutes. For 10 min at 25°C, different concentrations of AT (3, 1.5, 0.75, 0.375, and 0.187 gm) were stirred into the polymeric solution at the same speed. The finished dispersion was then gradually put into 200 ml of light liquid paraffin that included span 80 (1.5% w/v) as an emulsifying agent, while being stirred at room temperature using a homogenizer (three-blade propeller) (Diax 900 homogenizer, Heidolph, Germany). The resulting emulsion was continually stirred at 1250 revolutions per minute until all solvent had evaporated. The produced microcapsules were collected after the liquid paraffin had been decanted, and the remaining oil was washed off of them three times each with 100 ml of n-hexane¹¹.

Table 1 : Composition of the floating AT-loaded microcapsules.

Formula code	M1	M2	M3	M4	M5
AT (gm)	3	1.5	0.75	0.375	0.187
EC (gm)	3	3	3	3	3

Abbreviation: AT; atenolol, and EC; ethyl cellulose.

Characterization of the prepared AT microcapsules

Entrapment efficiency (EE%), and drug loading evaluation

Accurately weighed portions of the produced microcapsules from each batch were taken and thoroughly dissolved in methyl alcohol (10 ml) using a magnetic stirrer (Model MSH-20D, GmbH, Germany) for two hours. A millipore filter (0.45 μ) was used to filter the resulting solution. Samples were spectrophotometrically analyzed at 274 nm using spectrophotometer (model UV-1601 PC; Shimadzu) after being appropriately diluted with methyl alcohol, and the actual drug content was determined¹². The measurement was carried out three times. These subsequent equations were used to calculate the EE% and drug loading:

$$\text{EE\%} = \frac{\text{Actual drug loaded in microcapsules}}{\text{Theoretical drug loaded in microcapsules}} \times 100$$

$$\text{Drug loading \%} = \frac{\text{Weight of drug in microcapsules}}{\text{Weight of microcapsules}} \times 100$$

The results were represented as mean \pm SD.

Particle size (PS) assessment

An optical microscope (Axiostar Plus; ZEISS, Oberkochen, Germany) was employed to measure the PS of the microcapsules. A calibrated ocular micrometer was used to measure 100 microspheres in order to determine the mean particle size¹³. The results were represented as mean \pm SD.

Determination of percent yield (yield %)

Weighing the total weight of dried microcapsules and comparing it to the initial weight of the drug and polymer mixture allowed us to estimate the percent yield of the fabricated microcapsules¹⁴ by using the subsequent equation:

$$\text{Percent Yield (\%)} = \frac{\text{Total weight of dried microcapsules}}{\text{Initial Total weight of drug and polymer}} \times 100$$

The results were represented as mean \pm SD.

In-vitro drug release study

USP dissolution apparatus II, Pharma Test (Hainburg, Germany) was utilized to determine the amount of AT released from the produced microcapsules. 500 ml of 0.1N HCl was used for the release investigation as media, and the temperature was kept at 37 \pm 0.5°C for 12 hrs

at 100 rpm. To keep the volume constant of the release media, aliquots of 5 ml were taken out at predefined intervals up to 12 hrs and replaced with fresh medium. The samples were diluted, filtered using a millipore filter (0.45 m), and then subjected to UV/VIS spectrophotometer analysis at 274 nm using spectrophotometer (model UV-1601 PC; Shimadzu)¹⁵.

In-vitro buoyancy study

The floating microcapsules (50 mg) were added to a 250 ml vessel containing 100 ml of 0.1N HCl (0.02% w/v tween 80) and swirled at 100 rpm for 12 hrs with a magnetic stirrer. Following that, the microcapsules' that floated on the medium's top were pipetted and separated by filtration, while the particles that gathered at the beaker's bottom were also separated by this manner. Each part of microcapsule was weighed after drying, and the following equation was used to determine buoyancy percent¹⁶:

$$\text{Buoyancy\%} = \frac{\text{Weight of floated microcapsules}}{\text{Total weight of floated and settled microspheres}} \times 100$$

The results were represented as mean \pm SD.

Characterization of the best achieved microcapsules

Scanning electron microscopy (SEM)

Scanning Electron Microscope (JSM 6301F, JEOL, Japan) was used to examine the best achieved microcapsules' surface morphology. The microcapsules were added over double adhesive tape that was adhered to an aluminum stub to create the samples. Gold was then sputtered onto the gold to a thickness of 150 Å. Following that, samples were held in the vacuum chamber while being scanned and photographed with a 15 KV electron beam¹⁷.

Differential scanning calorimetry (DSC)

DSC model DTG-60H, Shimadzu (Tokyo, Japan) was used to examine the thermal behavior of AT, EC, physical mixture, and the best achieved formula (dry microcapsules). The samples of (5 mg) were sealed using aluminum pans and heated to between 50 and 300°C while being exposed to a stream of nitrogen. Indium was used as the reference material to calibrate the DSC temperature and enthalpy scale¹⁸.

Fourier Transform Infra-Red spectroscopy (FTIR)

Utilizing FT-IR (model:NICOLET5700), the potential for drug-polymer interaction was examined. The best achieved formula, AT, EC, and physical mixture FT-IR spectra were captured. Each sample (2 mg) was combined with 100 mg of dry potassium bromide and ground into a fine powder before being compacted into KBr discs using a hydrostatic press. At room temperature, each KBr disc was scanned with a resolution of 4 cm^{-1} throughout a wave number range of $400\text{--}4000\text{ cm}^{-1}$ ¹⁹.

Powder X-ray diffraction

Using an X-ray diffractometer (model:Xpert pro XRD MPD Panalytical), the physical states (crystallinities) of AT, EC, physical mixture and the optimized formula were assessed. The sample was crushed, then packed and organized into an aluminum rotating sample container after being pulverized. 40 mA and 40 kV were employed as the current and voltage, respectively, with Cu K radiation (1.542 \AA) as the radiation source. From 3 to 500 samples were scanned (2 θ)¹⁹.

Statistical Analysis

The range of obtained data is displayed as a mean SD. One-way analysis of variance (ANOVA) was used to compare data from various groups, followed by the Tukey-Kramer multiple comparison test, and data from two groups were compared using a one-tailed student t-test with a 0.05 significance level. Graph Pad prism-7 software (Graph Pad software Inc., San Diego, CA, USA) was used for all statistical calculations.

RESULTS AND DISCUSSION

Result

Preparation of microcapsules

AT-loaded microcapsules were successfully prepared using the emulsion-

solvent evaporation process. Due to the fact that AT and EC were very slightly soluble in light liquid paraffin, it was chosen as the outer phase. Because solvents with dielectric constants ranging from 10 to 40 exhibit poor compatibility with liquid paraffin and the solvents/liquid paraffin system was claimed to be applicable to the microencapsulation process, acetone with a dielectric constant of 20.7 was chosen as the disperse phase. In this investigation, span 80, a non-ionic emulsifying agent, was utilized to lower the interfacial tension and prevent flocculation during the preparation of the microcapsules. The external phase of the emulsion benefited from the 1.5% (w/v) concentration of span 80 added to it²⁰.

Evaluation of the prepared microcapsules Determination of entrapment efficiency (EE%), drug loading (%) and yield (%)

Table (2) displays the values for all formulae's entrapment efficiency (EE%) and percent yield (% yield). The values of EE% ranged from 64.12 ± 1.28 to $90.41 \pm 1.23\%$ and the values of yield% ranged from 72.24 ± 2.98 to $84.63 \pm 0.27\%$. According to the data, the ratio of drug to polymer had a significant impact on how well the produced microcapsules trapped the drug, with an increase in polymer ratio causing a drop in drug entrapment efficiency. The previous findings might be related to at high polymer concentration the hydrophobic center of EC may be saturated and may not seize more drug inside its structure²¹. Regarding drug loading percentage (Table 2) it ranged from 3.21 ± 0.90 to $31.45 \pm 2.17\%$. The drug loading decreased by increasing polymer ratio due to the slower hardening of microcapsules that resulted in rapid diffusion to the external environment⁴.

Table 2: Properties of the prepared AT-loaded microcapsules .

Formula code	EE%	% Yield	Drug loading	PS (μm)	Buoyancy %
M1	90.41 ± 1.23	84.63 ± 0.27	31.45 ± 2.17	817.23 ± 19.17	78.32 ± 3.24
M2	86.74 ± 0.22	87.21 ± 0.39	27.28 ± 0.99	652.24 ± 20.04	87.31 ± 2.35
M3	83.11 ± 1.47	76.89 ± 1.34	21.37 ± 1.25	565.32 ± 30.92	83.75 ± 6.35
M4	77.22 ± 0.84	72.24 ± 2.98	12.94 ± 1.95	161.24 ± 9.45	85.63 ± 4.13
M5	64.12 ± 1.28	84.15 ± 2.18	3.21 ± 0.90	140.24 ± 9.32	86.25 ± 4.12

Abbreviation: EE% represents entrapment efficiency percent; AT; Atenolol.

Each value is expressed as mean \pm SD (n=3).

Determination of particle size (PS)

According to **Table (2)**, the mean PS of the prepared microcapsules ranged from 140.24 ± 9.32 to $817.23 \pm 19.17\mu\text{m}$. From the previously illustrated results it was found that at higher EC (polymer) amount the PS of the formed microcapsules decreased this came in accordance with previous literature²². Further, previous investigation correlated the EE% values with PS as they hypothesized that higher EE% values might produce larger carriers, and vice versa²³. This previously assumed hypothesis supported the findings of the present study.

In-vitro release study of the prepared microcapsules

The release properties of AT from various microcapsule formulations are described in **Fig. (1)**. After 12 hrs, the drug was released in the following amounts for all microcapsule formulations (M1-M5): 91.23 ± 3.21 , 85.91 ± 2.63 , 81.63 ± 2.34 , 75.05 ± 1.95 and $75.93 \pm 1.59\%$. As the concentration of EC rose from 1:1 to 1:5, the rate of drug release decreased, with M1 formulation showing the maximum drug release ($91.23 \pm 3.21\%$). It shows that a key component in regulating the drug release profile is the polymer

concentration. The drug release significantly decreased with the increase in the amount of polymer in the microcapsule's matrix because more concentrations of the polymer give rise to an increased diffusional pathlength. This may lead to decrease in overall drug release from the polymer matrix²⁴.

In-vitro buoyancy behavior

Table (2) displays the buoyancy percent for all equations, with values ranging from 78.32 ± 3.24 to $87.31 \pm 2.35\%$. These findings showed that when the drug: polymer ratio increased, the produced microcapsules' ability to float increased over a period of 12 hrs without clearly gelling. This is in agreement with earlier research, which used an emulsion solvent evaporation approach to create floating EC microspheres that were then loaded with ranitidine HCl¹⁶.

The difference in the percentage buoyancy of different microcapsules containing different amounts EC was significant, EC being insoluble and un-swellable remains floated hence by increasing EC content microcapsule predominately increases the buoyancy compared to microcapsules with lower content EC²⁵.

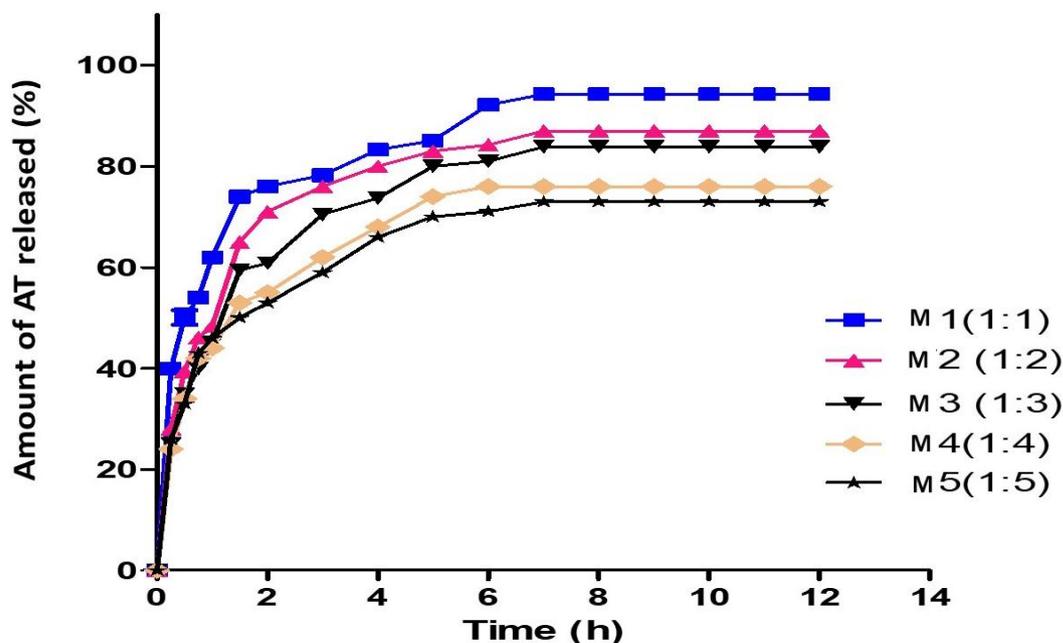


Fig. 1: In-vitro drug release profiles of the prepared microcapsules in 0.1 N HCl (pH 1.2).

Characterization of the best achieved microcapsules

Scanning electron microscopy (SEM)

The SEM microphotographs of the prepared microcapsules (M1) were displayed in **Fig. 2**. SEM analysis was used to examine the surface morphology and form of microcapsules. The manufactured microcapsules (M1) with a drug-polymer ratio of 1:1 clearly showed a spherical shape, had walls free of drug crystals, and some of them had prominent pores visible on the surface. This outcome is consistent with previous literature²⁶.

Differential scanning calorimetry (DSC)

The assessment of potential incompatibilities between the drug and various additives represents a significant element of the pre-formulation stage during the development

of solid dosage forms. **Fig. (3a)** displayed the DSC thermogram of pure AT, which displayed a significant intense endothermic peak at 153.21 °C, corresponding to the drug's melting point²⁷. **Fig. e (3b)** illustrated the thermogram of EC that did not showed any thermal effect in the temperature range studied²⁸. Moreover, **Fig. (3c)** showed the thermogram of physical mixture of the best microcapsule components that showed the characteristic peak of AT this came in accordance with previous literature²⁹. Further, **Fig. (3d)** represented the DSC thermogram for the prepared microcapsules (M1), it was found that the peak that are characteristics of AT disappeared due transformation of AT from crystalline to amorphous form that confirmed the successive entrapping of AT inside microcapsules³⁰.

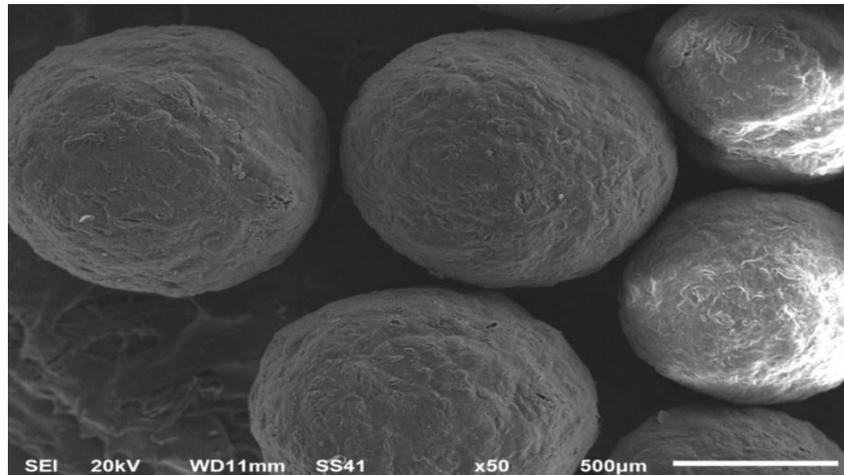


Fig. 2: Scanning electron microphotographs of the microspheres (M1) amplified: a (×50)

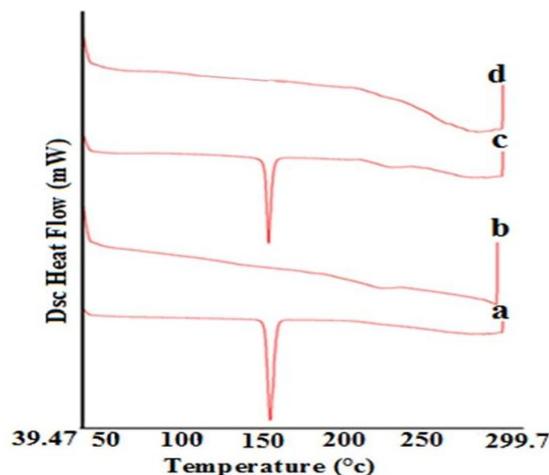


Fig. 3 : Differential scanning calorimetry thermograms of pure AT (a), EC (b), physical mixture of AT and EC (c) and AT-EC microcapsules (formula M1) (d).

Fourier Transform Infra-Red spectroscopy (FT-IR)

In order to clarify the potential for chemical interaction between AT and other excipients, Fourier transform infrared spectroscopy was conducted. **Fig. (4 a)** showed the FT-IR spectra of AT that revealed various distinctive bands, including those at 3175–3357 cm^{-1} (hydroxyl and amine group absorption bands), 2965 cm^{-1} (aliphatic C–H group absorption bands), and 1639 cm^{-1} (C=O amide group absorption bands)³¹. **Fig. (4b)** illustrated IR spectrum of EC shows broad band at 3396 cm^{-1} representing the hydroxyl group. The band at 2929 cm^{-1} corresponds to the CH_2 group of cellulose. The peaks at 1115 cm^{-1} and 1054 cm^{-1} corresponds to C-O-C stretching vibration in EC³². As shown in **Figs (4c, 4d)**, the spectrum of the physical mixture and the optimized microspheres was comparable to that of AT alone, confirming that there was no interaction between the medication and microcapsule component³³.

Powder X-ray diffraction (PXRD)

XRD is the key technique for drug analysis. The XRD analysis of crystalline compounds gives a diffraction pattern consisting of a well-defined, narrow, sharp and significant peak while amorphous materials do not give clear peaks rather the pattern has noise signals, smeared peak or it can have some short order bumps³⁴.

Fig. (5a), AT exhibited sharp and intense peaks at a different diffraction angle (2θ) with their counts at 9.75°, 12.45°, 16.66°, 19.55°, and 25.5°. EC **Fig. (5b)** showed low-intensity peak different diffraction angle (2θ) with their counts at 11.5° and 12.55°³⁵.

Fig. (5c) shows the diffraction pattern for AT in the physical mixture, which is typical of crystalline materials because it has multiple distinct peaks as pure AT. **Fig. (5d)** showed XRD pattern for the optimum formula in which drug's crystallinity was noticeably reduced, due to the development of microcapsules, which resulted in the formation of a new solid state (amorphas state) as seen in the diffractogram of microcapsules (M1)³⁶.

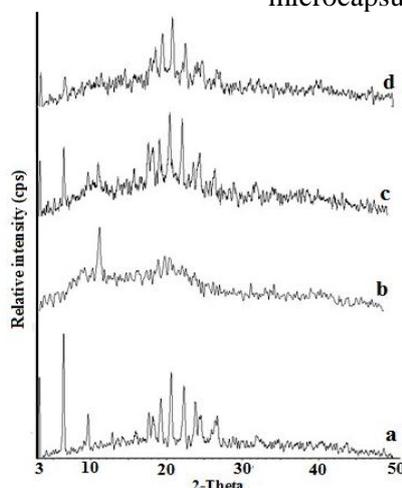


Fig. 4: The Fourier transform infrared (FTIR) spectra of pure AT (a), EC (b), physical mixture of AT and EC (c) and AT-EC microcapsules (M1) (d).

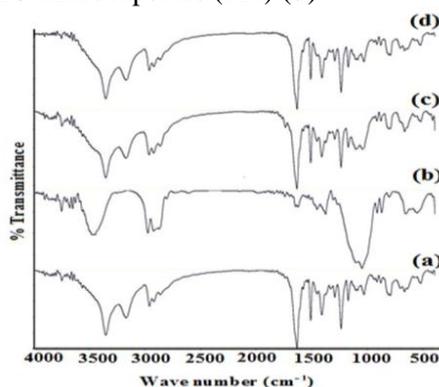


Fig. 5: Powder X-ray diffraction pattern of pure AT (a), EC (b), physical mixture of AT and EC (c) and AT-EC microcapsules M1 (d).

Conclusion

The produced microcapsule's optimized formula, M1, which contained a drug: polymer ratio of 1:1, demonstrated outstanding flow qualities. The respective EE%, yield%, drug loading%, particle size, buoyancy%, values were $90.41 \pm 1.23\%$, $84.63 \pm 0.27\%$, $31.45 \pm 2.17\%$, $817.23 \pm 19.17 \mu\text{m}$, and $78.32 \pm 3.24\%$, respectively. The best formula (M1) demonstrated $91.23 \pm 3.21\%$ amount of drug released after a 12-hr period. There was no chemical interaction between the AT and polymer, according to the FT-IR study. DSC assessment showed the complete entrapment of AT inside microcapsules. Further, XRD analysis showed that the complete transformation of AT from crystalline to amorphous form inside microcapsules. The previous findings demonstrated the good capability of M1 as floating dosage form for AT for sustained and continuous drug delivery of AT.

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تحضير وتوصيف حويصلات دقيقة ممتدة المفعول حاملة لدواء الاتينولول

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محتوي الغرض من دراسة هذا الفصل هو لتحضير الحويصلات الدقيقة الطافية الممتدة المفعول بأستخدام بوليمر أثيل سيليلوز. وتم تقييم الحويصلات الدقيقة المحضرة من حيث نسبة حجز العقار، نسبة تحميل العقار، نسبة الطفو، تحليل حجم الجسيمات، المسح الضوئي المجهرى الإلكتروني، التحليل الطيفي للأشعة تحت الحمراء، المسح الحراري التفاضلي والانطلاق المعمللي للعقار. وقد بينت النتائج الآتي:

اثبتت النتائج مدي قابليه الحويصلات الدقيقة علي تحوصل الدواء بداخلها بطريقة فعالة:-

- بينت دراسة المسح الضوئي المجهرى الإلكتروني ان المصوغات المحضرة كروية الشكل.
- أظهرت نتائج قياسات المسح الحراري التفاضلي، التحليل الطيفي للأشعة تحت الحمراء عدم وجود تفاعل بين العقار والبوليمر المستخدم.
- اثبتت نتائج حيود الأشعة السينية تحول العقار من الشكل المحدد له الي شكل غير محدد بداخل الجسيمات الكرويه
- تم الحصول على الانطلاق الممتد المناسب من المصوغة M1 التي تحتوي على نسبة الدواء الي البوليمر (1:1) والتي اثبتت مدي انطلاق العقار بطريقة ثابتة علي مدار ١٢ ساعه.