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Formulation, Evaluation and Bioavailability Studies of Azapropazone Albumin Microspheres

Ahmed Ismail

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University at Assiut, Assiut, Egypt

ABSTRACT

Azapropazone loaded microspheres were prepared using bovine albumin as a controlling matrix. The cross-linking of bovine albumin was achieved using glutaraldehyde at three different concentrations. Drug incorporating eficiency of around 81% could be achieved through using this technique of preparation. *In-vitro* release of the drug was examined in simulated intestinal fluid, pH 7.4 at 37°C for microspheres having different glutaraldehyde concentrations, varying particle sizes and different drug loadings. It was observed that the release was diffusion controlled and followed the Higuchi model. Release characteristics were influenced by glutaraldehyde concentration, particle size and drug loading. The bioavailability of azapropazone released from the microspheres of different corss-linking concentrations was studied in rabbits following single oral administration. Microspheres with higher glutaraldehyde concentration was found to control azapropazone release even up to 12 hours. The peak serum concentration of such microspheres were well within the therapeutic level. The study demonstrated the potential of cross-linked bovine albumin as a matrix for controlled release oral preparations.2

INTRODUCTION

Albumin microspheres have attracted considerable attention for several years as a matrix for controlled and sustained delivery of many drugs. Most of the work reported concentrated on albumin microcapsules and microspheres as carriers for such drugs. These protein microspheres provide a potentially useful vehicle for drug delivery to endocytic cells since they are physically and chemically stable, rapidly removed from the vascular system by phagocytosis, amenable to large-scale preparation, readily metabolized and capable for accomodating a broad variety of drug molecules in a relatively nonspecific fashin[1-8]. Zoll *et al.*[9] were the first who prepared microspheres, 12-44 μm in diameter which can be entrapped in the lung capillary bed, and have therefore been used for studies concerning lung scanning and the pulmonary circulation. Sugibayashi *et al.*[8] studied the drug carrier properties of albumin microspheres containing the anti-cancer drug 5,fluorouracial,and their potential chemotherapeutic applications in mice model system. Kramer[10] prepared human abumin microsphers containing either mercaptopurine or daunorubicin hydrochloride. Widder *et al.*[11] prepared magnetic albumin microspheres containing water-soluble drugs such as doxorubicin hydrochloride. Farhadieh[12] entrapped erythromycin in egg albumin microspheres to protect the active drug from digestion in the acid environment of the stomach and to mask its unpleasant taste.

Glutaraldehyde cross-linked and denatured albumin is relatively non-immunogenic in nature, and studies have shown that albumin microspheres biodegrade in the muscle in about two months without causing any adverse tissue reactions[13]. Compared to many synthetic polymers that are employed for effecting sustained delivery of drugs by the oral route, natural polymers have better biocompatibility and non-toxicity. This is particularly true with the albumin protein as it is abundant and inexpensive. Suspension crosslinking of albumin can be accomplished either by direct reaction between functional groups on the polypeptide side chains (self-crosslinking), or by the use of a crosslinking agent. For the purpose of producing albumin microspheres, most workers employ heat treatment for self-crosslinking. Among chemical crosslinking agents, glutaraldehyde and 2,3-butadione are most frequently used. The use of a number of other crosslinking agents has also been reported(14,15,16)Drug release from albumin microspheres can take place via various routes, such as total microspheres disintegration, microsphere hydration, sufrace erosion, particle diffusion and leahcing[17]. Most of the *in-vitro* studies on release of drugs incorporated into microspheres focused on biophasic characterization, which describes an initial fast release (burst effect) followed by slower first order release[18-20]. Yapel[21] described a biphasic release profile for epinephrine entrapped in albumin microspheres. However, at drug contents of over 30% w/w the profile was found to be monophasic.

In in-vitro experiments, Lee et al.(13) found that diffusion over an increasing pathlength is the rate limiting step for drug release after an initial lag period due to microsphere hydration. Sezaki et al.(22) showed that release of mitomycin-C from gelatin microspheres is goverened by carrier diameter. Conjugation of these microspheres with dextran gives rise to monophasic release, which is independnet of carrier diameter. Widder et al.(23) suggested that release of drug from microspheres is primarily a function of matrix hydration rather than matrix degradation, which may explain why denser microspheres obtained by raising the temperature at the denturation stage exhibit slower drug release rates.Many variables have been reported to influence drug release from microspheres. These include the location of the drug in the microspheres, denaturation conditions, diameter of microspheres, physicochemical properties of the drug, amount and type of matrix, physicochemical interactions between the drug and the matrix at various stages of preparation and, finally, the nature of the release medium used(17,24).In this study, the preparation of microspheres of albumin containing azapropazone and in-vitro release profiles of the drug from such microspheres was described. This paper also reports on the bioavailability of azapropazone from gluaraldehyde cross-linked albumin microspheres in rabbits.

MATERIALS AND METHODS

Materials:

- Bovine serum albumin and glutaraldehyde were purchased from (Sigma Chemical Co., St. Louis, USA).
- Azapropazone was kindly provided by (Arab Drug Co., Cairo, A.R.E.).
- All other reagents used were commercial reagent-grade.
- Animals: Rabbits weighing 1.3-2.25 kg were used in the bioavailability studies of albumin microspheres.

Methods:

reparation of albumin microspheres: Drug albumin microspheres were prepared using the modified method of Longs *et al.*[25]. Bovine serum albumin, BSA, (600 mg) was dissolved in 4 ml of distilled water and mixed with 2 ml of azapropazone aqueous solution (30 mg/1 ml). Glutaraldehyde (1.2 ml) was then added to the BSA-azapropazone mixture. This mixture was dropped in isooctane : chloroform (2:1, volumetric ratio, 200 ml total volume) containing 1% polysorbate 80 and emulsified with a mechanical stirrer at 1200 rpm for 5 minutes. This emulsion was transformed into a suspension during the stirring. The suspension was heated in an oil bath at 80-85°C for 5 min. After cooling the suspension at room temperature, supernatant was decanted, n-octane (200 ml) was aded to the residue, and the new suspension was heated in an oil bath at 120°C for 20 min. After decanting n-octane, complete removal of residual solvent was achieved by washing the albumin microspheres in diethyl ether (3 times) followed by petroleum ether (once). After drying albumin microspheres under vaccum, they were stored in desiccator.

DSC microspheres analysis:

Samples of about 5 mg (plain drug, placebo albumin microspheres and albumin microspheres loaded with 50% w/w drug) were accurately weighed and encapsulaetd in flat bottomed aluminum pans with crimped on lid and scanned at 10°C/min in nitrogen gas at a flow rate of 40 ml/min. The instrument was calibrated with pure indium.

X-ray diffraction analysis of the microspheres:

Powder x-ray diffractometric analysis (plain drug, placebo albumin microspheres and albumin microspheres loaded with 50% w/w drug) was measured using automated x-ray diffractometer under the following conditions, Target Cu, filter Ni, Chart speed 40 nm/min and counter 1.7 Kv detector voltage. An attached microprocessor operates as a software program to analyze peak position and intensities was utilized. Standard polycrystalline powder was used to calibrate the equipment.

Determination of microspheres particle size distribution:

Determination of particle size distribution was performed through sieving 1 gm of prepared microspheres using standard test sieves and specifying the weight of the fractions that passed through each sieve. Then, the particle size distribution curve was constructed through plotting percentage of weight fraction against microsphere particle size[13].

Determination of loading efficiency of azapropazone in albumin microspheres:

The amount of drug loaded was determined by digesting 100 mg of microspehres in 500 ml of Sorensen's phosphate buffer, pH 7.4 and aliquots were taken and assayed for drug content by UV spectrophotometry. Corrections for albumin contribution to absorbance were made using reference solutions of empty microspheres in the solvent mixture. Standard curves for the drug dissolved in Sorensen's phosphate buffer pH 7.4 were constructed. The absorbance was spectrophotometricly measured at 255 min.

In-vitro drug release from albumin microspheres:

In-vitro release of azapropazone from albumin microspehres was carried out in simulated intestinal fluid (Sorensen's phosphate buffer pH 7.4) at 37°C

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using USP paddle type dissolution tester. Into 500 ml of the dissolution medium was introduced an accurately weighed sampels of albumin microspheres containing drug (50 mg) and stirred at 100 rpm. Aliquots of the dissolution fluid (1 ml) were withdrawn periodically at various time intervals and an equivalent volume of fresh buffer was added to maintain constant volume of the dissolution medium. The amount of drug in the withdrawn sampels was spectrophotometrically determiend for azapropazone at 255 nm. The dissolution vessels were covered to prevent evaporation. Dissolution studies were carried out in duplicate and the mean was taken.

Bioavailabity studies:

Rabbits weighing 1.25-2.00 kg were used for this study. Animals were fasted for 24 h prior to the administration of the drug. Each rabbit was given a dose of 10 mg/kg body weight of azapropazone powder or an equivalent dose in microspheres form with 10 ml water orally. Venous blood samples (1 ml each) were collected at 1, 2, 3, 4, 6, 9, 12 and 24 h from the ear vein after administration. Samples were incubated at 37°C till clotted. It was then centrifuged at 1500 rpm for 20 min and the serum was separated. Azapropazone in the serum was extracted and analysed in the following way:

Analysis of azapropazone in serum:

Azapropazone was determined in blood by mixing one ml of the serum with 10 ml of pure methanol or ethanol in test tube. The mixture was shaken in a suitabel spilling shaker for 10 minutes, heated at 80°C for two minutes, cooled and centrifuged for 15 minutes. Aliquot from the clear supernatant was taken, and the absorbance was measured at 255 nm[31].

Pharmacokinetic analysis:

The elimination rate constant K_{el} was determiend from the slope of the terminal linear portion of the semi-logarithmic curve of serum concentration against time using linear regression analysis as reported by Maruyama *et al.*[26]. The author determined also the elimination half-life values $t_{½}$ by dividing 0.693 by the elimination rate constant K_{el}. The area under the curve AUC is calculated from the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + C_t / K_{el}$$

where AUC_{0-t} is the area under the curve from time 0 to t calculated using trapezoidal rule. C_t is the concentration at time t.

RESULTS AND DISCUSSION

Characterization of microspheres:

a) Particle size distribution of albumin microspheres:

The particle size distribution of albumin microspheres containing different azapropazone loadings (30, 40 and 50% w/w) cross-linked with 6 ml glutaraldehyde and prepared at stirring speed of 1200 rpm was graphically represented by Figure (5). The obtained results proved that the percentage of weight for microspheres having particle size less than 400 µm was less than 7% for all microspheres having different drug loadigns. Also, it was noticed that upon increasing drug loading, there was a corresponding increase in the percentage of weight of fraction.

b) Loading efficiency of drug in microspheres:

The obtained data regarding loading efficiency of azapropazone within albumin microspheres at different actual drug loading were depicted in Table (1). Results of differential scanning calorimetry and X-ray diffractometry proved that no evidence of any chemical interaction has occurred between azapropazone and albumin, so the drug loading was simply achieved through physical encapsulation. It was obvious that upon increasing azapropazone concentration in n-octane durign microsphere preparation, there was a remarkable increase in loading efficiency.

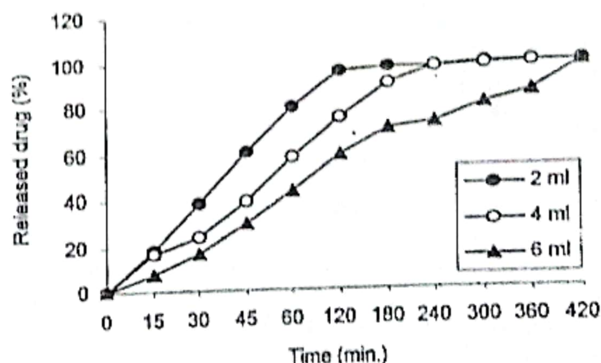

Figure (1): In-vitro release profiles of azapropazone from albumin microspheres of 200-160 µm size containing 30% w/w drug and cross-linked with different concentrations of glutaraldehyde.

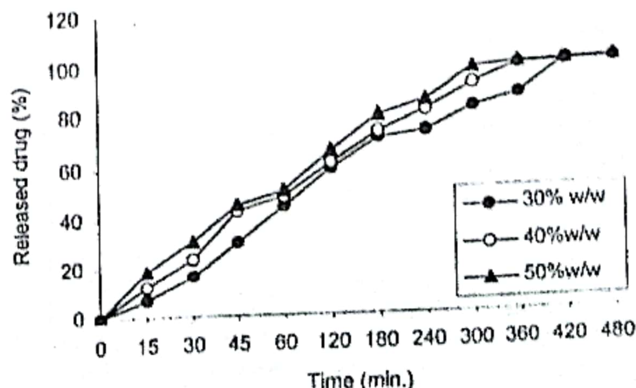

Figure (2): In-vitro release profiles of azapropazone from albumin microspheres of 400-200 µm size cross-linked with 6 ml glutaraldehyde at different drug loadings.

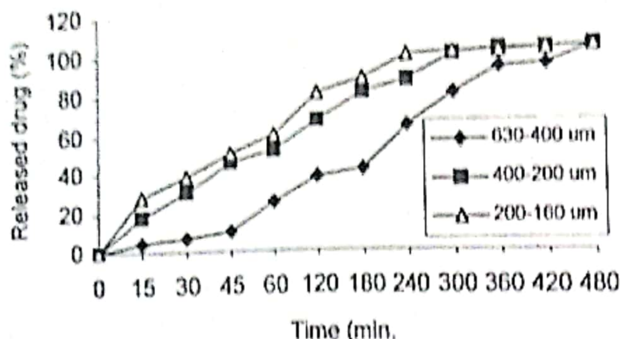

Figure (3): In-vitro release profiles of azapropazone from albumin microspheres containing 50% w/w drug and cross-linked with 6 ml glutaraldehyde at various particle sizes.

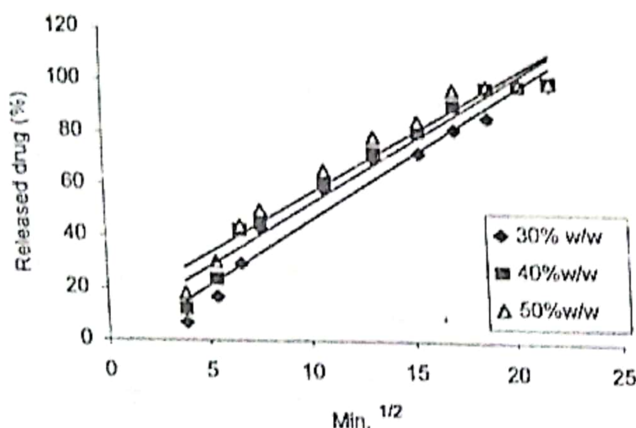

Figure (4): Plots of azapropazone released versus square root of time from microspheres crosslinked with 6 ml glutaraldehyde having particle size of 630 400-μm at different drug loadings.

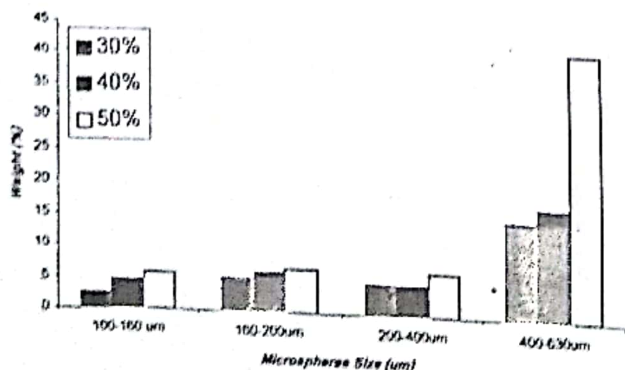

Fig (5): Particle size distribution of albumin microspheres containing different azapropazone loadings cross-linked with 6 ml glutaraldehyde and prepared at stirring speed of 1200 rpm.

c) Differential scanning colorimetry of drug loaded microspheres:

The DSC data plots of plain drug, un-loaded microspheres (placebo) and drug loaded microspheres (50% w/w) were represented by Figure (7) and Table (3). Regarding plain drug endotherm, it was noticed that the endothermic peak appeared at 248°C which was identical with the melting point of drug crystals. The endotherm of drug loaded microspheres showed a slight shift to the left (237.7°C) indicating that the drug was entrapped inside microspheres in the crystaline form. Wendland[27] have pionted that this slight shift in the endothermic peak may be mainly due to the difference in particle size between free drug and drug incorporated in the microspheres.

d) X-ray diffractometry of drug-loaded microspheres:

X-ray diffractometric plots of plain drug, placebo microspheres and albumin microspheres loaded with 50% w/w azapropazone were graphically represented by Figure (8). Due to the appearance of distinguished peaks corresponding to the drug in the drug-loaded microspheres plot, the recorded x-ray plot proved that the drug when incorporated in the microspheres was still in the crystalline form.

Release study of azapropazone from albumin microspheres:

a) Effect of glutaraldehyde concentration on release profile:

Regarding the effect of glutaraldehyde concentration on the release profile, it was obvious from the obtained data graphically represented by Figure (1) that glutaraldehyde apparently affected the release rate of azapropazone from microspheres. As the glutaraldehyde concentration or cross-linking density increased, the release profile was markedy decreased. Regarding microspheres cross-linked with 2 ml glutaraldehyde, nearly 95% drug release was attained after 2 hours, while for microspheres cross-linked with 6 ml glutaraldehyde, nearly 99% release was observed after 7 hours. So, the modulation of azapropazone release may be attaiend through changing glutaraldehyde concentration during microsphere preparation.

b) Effect of microsphere particle size on release profile:

The effect of microsphere particle size on azapropazone release profile was graphically represented by Figure (3). It was evident that the smaller microspheres proved a pronounced high release profile as compared with larger one. This may be interpreted on the basis that the smaller microspheres provide a larger surface area contact with the dissolution medium thereby enhancing the release profile as compared with larger ones. So, there is a possibility for modulating the release profile

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through mixing several batches of microspheres having various particle sizes.

c) Effect of drug loading on release profile:

The effect of drug loading on azapropazone release profile from microspheres was graphically illustrated by Figure (4). The obtained results proved that increasing drug loading from 30-50% w/w resulted in an obvious increase in the release profile. Upon decreasing drug loading, the albumin weight in the microspheres would be increased resulting in an apparent delay in drug diffusion, hence minimizing the release profile.

d) Kinetic of drug release:

Plotting the cumulative percentage of release for 3 batches of microspheres containing 30, 40 and 50% w/w azapropazoen against square root of time proved a considerable linearity with correlation coefficients of 0.983, 0.980 and 0.981 respectively. Accordingly, the obtained data confirmed that the release of azapropazone from albumin microspheres is a diffusion controlled pattern. The obtained data were graphically represented by Figure (4).

Bioavailability studies:

Azapropazone was orally administered either in the form of pure powder or microspheres prepared through albumin cross-linking using 2,4 or 6 ml glutaraldehyde (30% w/w drug loading and 160-200 µm particle size) and serum concentration curves were depicted in Figure (7), figure(6) A, B, C and D).

Regarding oral administration of azapropazone powder, the serum concentration curve proved that the maximum serum concentration was obtained at 4½ hours after administration. It was also noticed that the elimination was fast and a complete removal of the drug was attained at less than 24 hours. These data were graphically represented by curve (A).

On contrast, the serum concentration curves of the three types of administered microspheres proved a remarkable controlling action. The serum concentration curve of microspheres crosss-linked with 2 ml glutaraldehyde also showed a maximum serum concentration of nearly 4½ hours but the rate of elimination was slow as compared with azapropazone

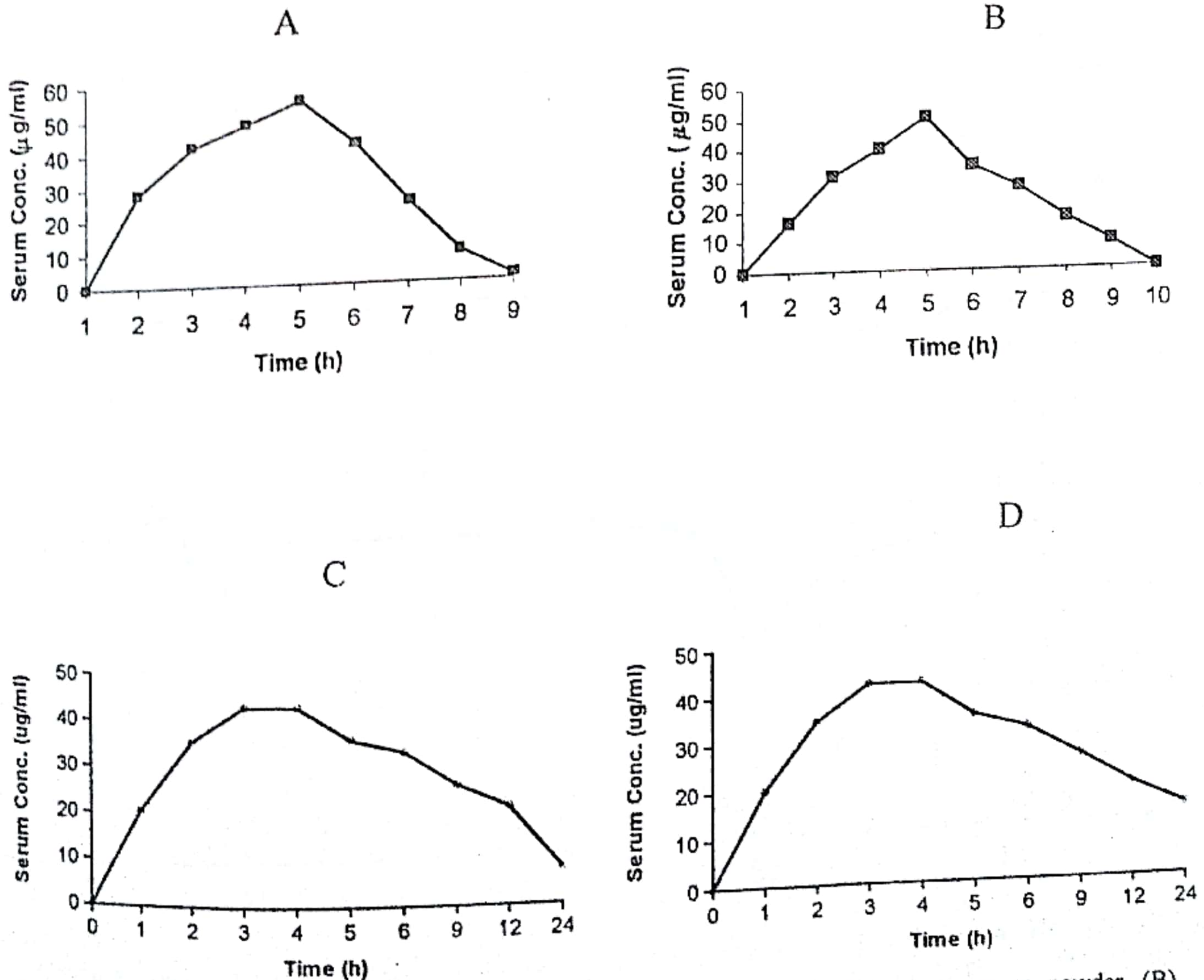

Fig (6): Azapropazon serum concentations after oral administartion of (A) azapropazone powder, (B) azapropazone-loaded albumin microsphers cross-linked with 2 ml, (C) 4 ml and (D) 6 ml glutaraldhyde.

powder, curve (B). Regarding microspheres cross-linked with 4 ml glutaraldehyde, the serum concentration curve showed a maximum serum concentration which was attained after 2 hours and was located within the range of azapropazone therapeutic efficacy (20-45 μg/ml). This maximum therapeutic serum concentration was maintained for nearly 12 hours and proved a slow elimination as compared with free drug, thereby, a complete elimination does'nt occur even after 24 hours, indicating a resultant controlled action. The obtained results showed that the serum concentration cruve of microspheres cross-linked with 6 ml glutaraldehyde did'nt largely differ from that of microspheres cross-linked with 4 ml glutaraldehyde.

The pharmacokinetic parameters regarding both azapropazone powder and medicated microspheres were listed in Table (2). It was obvious that upon increasing glutaraldehyde concentration, there was a corresponding decrease in the elimination rate constant, K_{el}. The obtained results showed that there is no considerable difference in K_{el} values for microspheres cross-linked with either 4 ml or 6 ml glutaraldehyde whereas a sharp decrease in this parameter is noticed in microspheres cross-linked with 4 ml and 6 ml glutaraldehyde. The elimination half-life, $t_{½}$, for azapropazone powder is about 4 hours. In the case of microspheres, this parameter increases with the increase in glutaraldehyde concentration. Also, no pronounced difference was observed between $t_{½}$ of both microspheres cross-linked with 4 ml and 6 ml glutaraldehyde.

The concluded results in this study showed the possibility of using glutaraldehyde cross-linked bovine albumin to prepare microspheres capable for controlling the release of azapropazone. Also, these prepared microspheres can release the drug to reach its therapeutic level over a prolonged periods. The microspheres cross-linked with 4 and 6 ml glutaraldehyde proved a peak serum concentration located with the drug therapeutic level. The study proved the possibility of using bovine albumin as a matrtix for controlling azapropazone release when formulated for oral preparations.

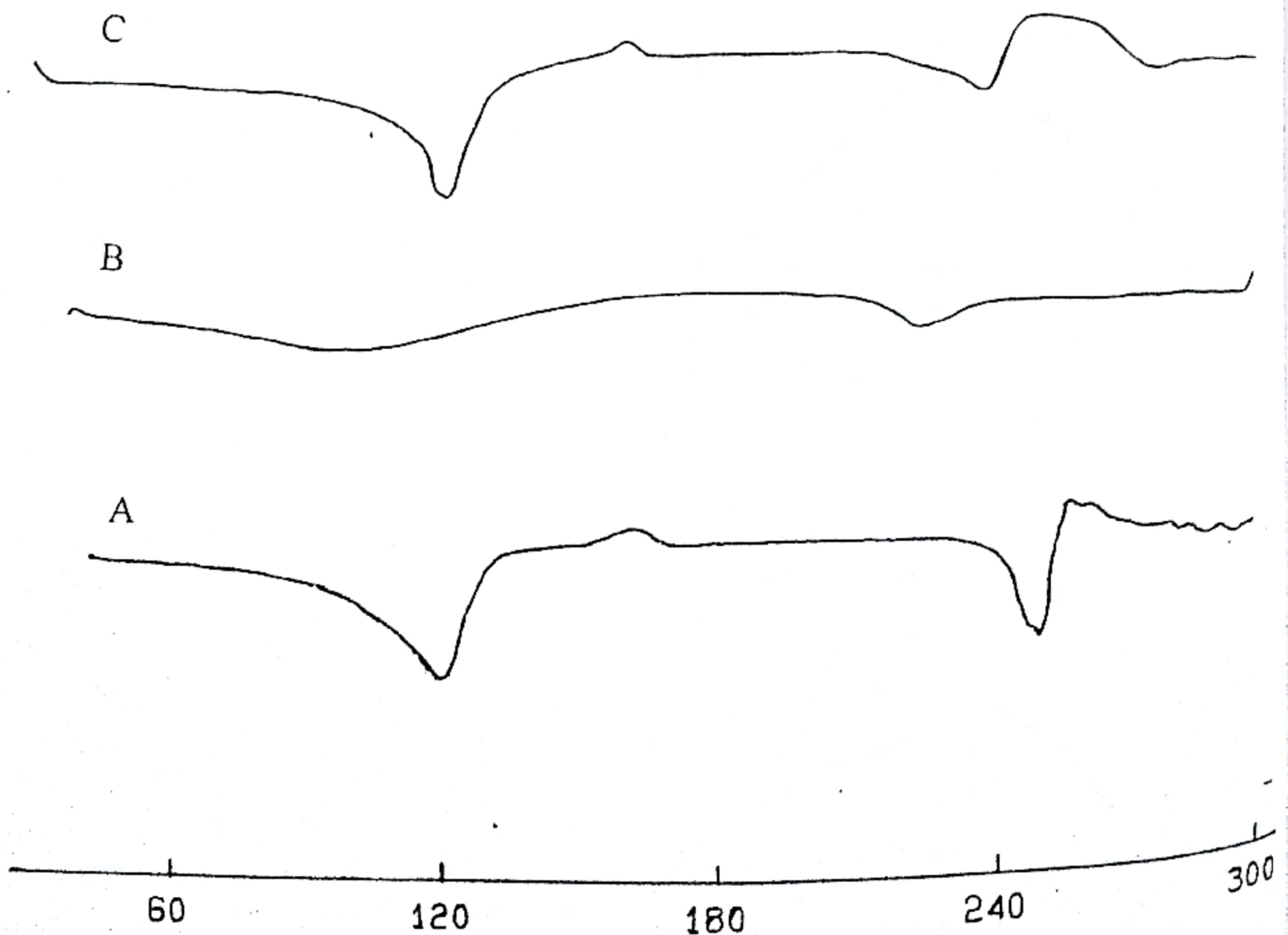

Fig (7): DSC curves of (A) plain azapropazone, (B) placebo albumin microsphers and (C) albumin microsphers loaded with 50% azapropazone.

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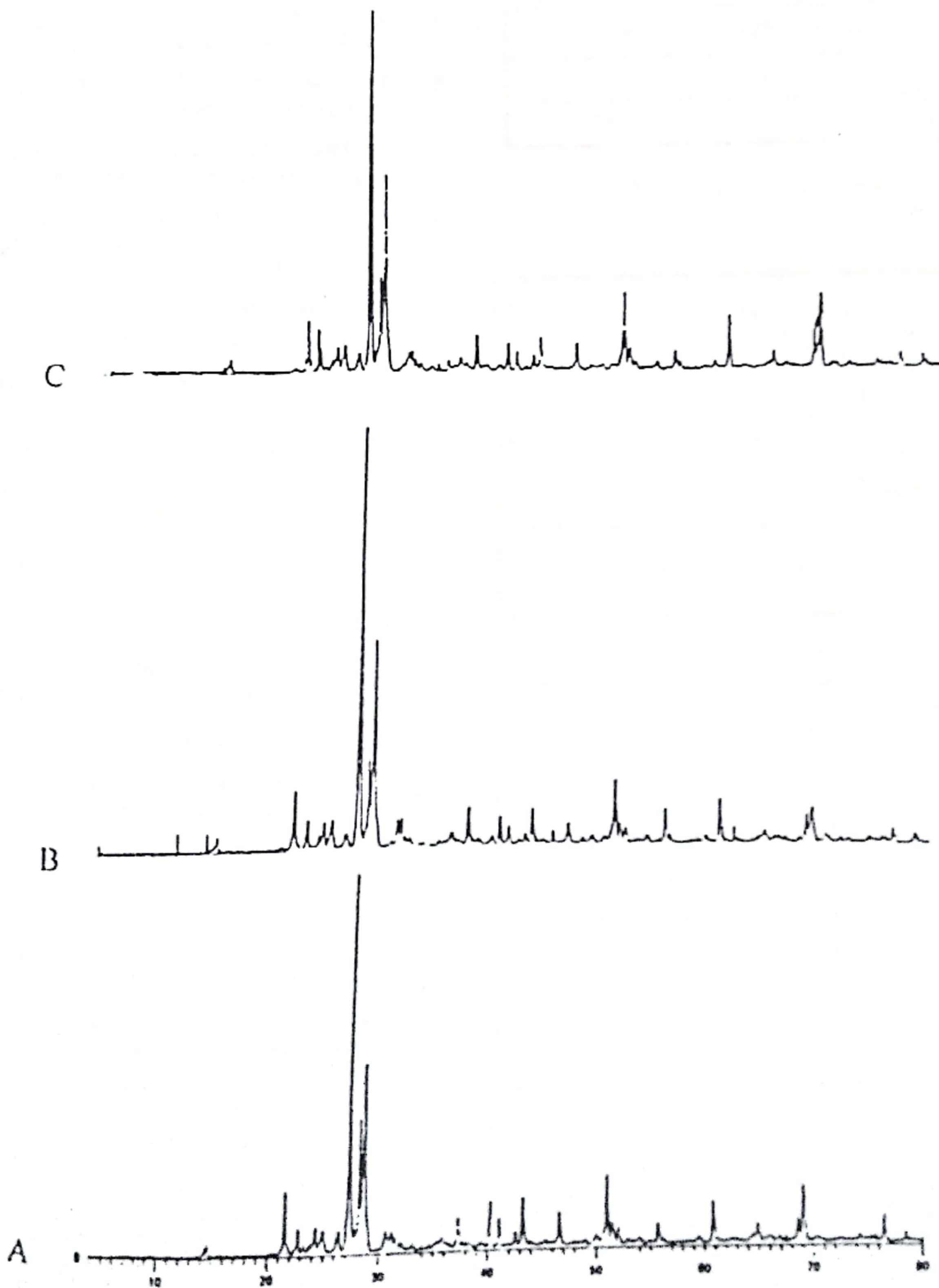

Fig (8): X-ray deffrection patterns of (A) palin azapropazone , (B) placebo albumin microsphers , and (C) albumin microsphers loaded with 50% azapropazone.

Table (1): Loading efficiency of azapropazone in albumin microspheres at different actual drug loadings.

Calculated Loading (%)	Actual loading	Loading efficiency (%)
60	50	83
50	40	80
45	30	67

Table (2): Pharmacokinetic parameters of azapropazone albumin microspheres following oral administration in rabbits

Preparation	$AUC_{0-\infty}$ (µg/ml /h)	K_{el} (h^{-1})	$t_{½}$ (h)	C_{max} (µg/ml)	t_{max} (h)
Azapropazone Powder	420	0.131	5.3	55.2	4.00
Microspheres cross-linked with: 2 ml glutaraldehyde	189.5	0.041	16.7	50.12	4.86
4 ml glutaraldehyde	485	0.029	24.1	42.33	10.8
6 ml glutaraldehyde	510	0.022	42.48	42.54	11.6

Table (3): Thermal analysis data of (A) plain azapropazone, (B) placebo albumin microspheres and (C) albumin microspheres loaded with 50% azapropazone.

Formula	Thaw point (°C)	Peak point (°C)	ΔH(J/g)
Plain drug	73.6 151.4 228	119.1 160.6 248.5	-214.62 11.59 -94.62
Placebo albumin microspheres	199.1	222.7	-35.99
Albumin microspheres loaded with 50% azapropazone	82.1 151.4 214	118.9 159 237.7	-174.56 7.66 -74.54

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صياغة وتقييم ودراسة الإتاحة الحيوية لكريات الزلال الدقيقة المحتوية على عقار الآزابروبازون

أحمد إسماعيل

قسم الصيدلانيات والصيدلة الصناعية - كلية الصيدلة - جامعة الأزهر بأسيوط

تضمنت الدراسة تحضير كريات الآزابروبازون الدقيقة وذلك باستخدام زلال البقر كوسط للتحكم في الانطلاق وقد تم إحداث الربط والتشابك لجزيئات الزلال باستخدام الجلوترالدهيد في ثلاث تركيزات مختلفة. وقد وصلت كفاءة الكريات لاحتواء الدواء إلى حوالي ٨١% وذلك باستخدام هذه التقنية. وقد أجريت دراسات انطلاق العقار وذلك في محاليل محاكية للعصارة المعوية ذات رقم أس أيدروجيني قدره ٧,٤ عند ٣٧°م لكريات دقيقة تحتوى على تركيزات متباينة من الجلوترالدهيد وذات أحجام جزيئية مختلفة وتركيزات متعددة من العقار. وقد لوحظ من الدراسة أن انطلاق العقار يتبع نمط هيجوشي للانتشار وأنه يعتمد على كل من تركيز الجلوترالدهيد والحجم الجزئي للكريات وكمية العقار المتغمس فيها.

وتضمنت الدراسة تجارب الإتاحة البيولوجية لانطلاق العقار من الكريات التي تم تحضيرها باستخدام ثلاث تركيزات من الجلوترالدهيد وذلك عن طريق تعاطي جرعة واحدة بالفم للأرانب المستخدمة في التجارب. وقد أوضحت الدراسة أن الكريات المحضرة باستخدام تركيز عالي من الجلوترالدهيد أظهرت انطلاق دوائي متحكم فيه قد يصل إلى ١٢ ساعة وأن أقصى تركيز للعقار في المصل كان واقعا في حدود التأثيرات الطبيعية المرغوبة للعقار. ويستنتج من الدراسة إمكانية استخدام زلال البقر كوسط للتحكم في انطلاق عقار الآزابروبازون وذلك عند تصميمه في مستحضرات يتم تعاطيها بالفم.