

## Original Research Article

# Evaluation of azithromycin–resin suspension designed for taste-masking and sustained-release

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### Abstract

**Purpose:** To prepare azithromycin (AZI) sustained-release suspension containing AZI-coated microcapsules (AZI-CM) impregnated with AZI-drug resin complex (AZI-DRC), in order to mask the bitter taste of AZI and improve the oral compliance of patients.

**Methods:** The AZI-DRC was prepared using the bath method, with cation exchanger resin Amberlite®IRP64 as a drug carrier, and it was characterized using scanning electron microscopy (SEM), x-ray diffraction (XRD) and Fourier transform infrared (FTIR) spectroscopy. Pretreated AZI-DRC was coated using emulsification-solvent evaporation method to achieve sustained-release effect. The effect of coating on in vitro drug release of the microcapsules was investigated to obtain the optimal AZI-CM through single-factor investigation. The optimized AZI-CM formulation was further dispersed in the optimized suspension matrix to obtain AZI sustained-release suspension. Then, the pharmacokinetics of AZI sustained release from the suspension was studied in rats and compared with commercially available AZI dry suspension.

**Results:** Taste evaluation by volunteers showed that AZI-DRC had a good taste-masking effect on AZI. Results from SEM, XRD and FTIR demonstrated that AZI was present in AZI-DRC solely in amorphous form. Three batches of AZI-CM prepared after optimization produced a significant sustained release effect ( $p < 0.05$ ). The AZI sustained-release suspension did not change significantly after 10 days and 3 months, indicating good stability ( $F > 0.9$ ; drug release:  $f_2 > 50$ ; drug leakage  $< 0.5\%$ ). In vivo results showed that AZI sustained-release suspension had a lower  $C_{max}$ , a higher  $T_{max}$  and a better bioequivalence than AZI dry suspension available in the market.

**Conclusion:** These findings depict a newly developed AZI sustained-release suspension with improved bioavailability, sustained-release effect, masked bitterness, and good therapeutic effect.

**Keywords:** Azithromycin, Ion exchange resin, Emulsified-solvent evaporation method, Sustained-release suspension

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## INTRODUCTION

Azithromycin with broad-spectrum pharmacological properties has been shown to be useful in the treatment of COVID-19 [1]. Azithromycin (AZI) is superior to other antibiotics due to its unique pharmacokinetics, high sustained tissue permeability and wide spectrum of activity [2]. In 2019, the World Health Organization (WHO) listed AZI as one of the safest drugs for any national health system [3].

At present, AZI products in the market are mainly tablets, capsules, granules, dry suspensions, powders for injection, and ophthalmic preparations. Due to the intense bitterness of AZI, it is important to develop an oral liquid preparation for effective masking of the intense bitterness in order to meet the needs of patients through enhancement of its acceptability.

Ion-exchange resin (IER) is a cross-linked, insoluble, polymer-carrying and ionizable functional group [4]. It acts through adsorption or ion exchange with ionized substances, and it has extremely high stability in acid-base solutions. The IER may be used as a drug carrier in studies of oral liquid sustained-release preparations. Moreover, previous studies demonstrated that sustained-release suspension prepared using IER as drug carrier had good sustained-release effects [5-8]. Ion-exchange resins (IERs) bind to the drug ions through an ion-exchange process that masks the bitterness or odor of the drug. Drug-loaded resin remains intact at human saliva pH of 6.8 and does not act on the taste buds. This method has been used in the preparation of dextromethorphan syrup, Seroxal oral liquid and Paxil suspension. Therefore, IER is useful for solving the problem of bitterness of AZI. This study therefore, aimed to prepare AZI sustained-release suspension containing AZI-coated microcapsules (AZI-CM) impregnated with AZI-drug resin complex (AZI-DRC), in order to mask the bitter taste of AZI and optimize drug release.

## EXPERIMENTAL

### Materials

Azithromycin (AZI) was product of Jiuzhou Kangda Biology Co. Ltd, China. Amberlite®IRP64, a cation exchanger resin, was purchased from Rohm & Hass, USA. Eudragit®RS100 was supplied by Shanghai Changwei Pharmaceutical Accessories Technology Co. Ltd, China. Span 80, PEG 400 and PEG 4000 were sourced from Sinopharm Chemical Reagent Group, China, while

Roxithromycin (ROX) was purchased from Central Inspection Institute, China.

### Animals

Twelve male Sprague-Dawley (SD) rats weighing 200 - 220 g were obtained from the Experimental Animal Center of Jiangsu University. This study received ethical approval from Jiangsu University, Zhenjiang, China, *vide* ethical approval reference number UJS-IACUC-202211360. All the conditions of animal handling during the study were strictly in accordance with the standard scheme approved by the Animal Center of Jiangsu University, China and followed international guidelines [9].

### Preparation of AZI-DRC

Azithromycin (2 g) was slowly added to 100 mL of ethanol: citric acid mixture to obtain a 20 mg/mL solution. Amberlite®IRP64 resin (2 g) was added to the solution and evenly dispersed using magnetic stirring, and the temperature was kept at 298 K for 4 h. Then, AZI-drug resin complex (AZI-DRC) formed was washed with deionized water, filtered, and dried in an oven at 45 °C. After vacuum drying, AZI-DRC was passed through an 80-mesh screen prior to further treatment.

### Quantification of AZI

An aliquot of 25 mL of NaCl solution (0.5 mol/L) was added to a 50-mL volumetric flask containing AZI-DRC (equivalent to about 300 mg of AZI). The flask was covered with a sealing film, and the temperature was kept at 37 °C while the contents were stirred for 2 h. Then, the sample was allowed to stand for a while to settle. Thereafter, the sample was filtered, and AZI content was determined using HPLC.

The HPLC was done in a C<sub>18</sub> column (150 mm, 4.6 mm, 5 μm) at wavelength of 210 nm, column temperature of 40 °C, sample volume of 20 μL, and flow rate of 1.0 mL/min. The mobile phase consisted of a 60: 40 (v:v) mixture of acetonitrile (A) and 2 mol/L K<sub>2</sub>HPO<sub>4</sub>, pH = 8.0.

### Taste masking of AZI-DRC

Bitterness was evaluated by 10 volunteers. The test sample was AZI-DRC with a drug content of 10 mg. A control sample powder with a drug content of 10 mg was obtained by grinding conventional AZI tablets. The bitterness was scored on a 1-10 scale, with 1 as *bitter* and 10 as *not bitter*.

## Characterization of AZI-DRC

The morphology of AZI-DRC was examined under a scanning electron microscope (SEM, Carl Zeiss of Germany). The mechanism of binding involved in the formation of AZI-DRC was studied using X-ray diffraction (XRD, BRUKER of Germany) and infrared spectrum (IR, SHIMADZU of Japan). This was done to identify the structural differences amongst the cation exchange resin, drug, physical mixture of drug-resin, and AZI-DRC complex.

## Pretreatment of AZI-DRC

During storage, the resin easily swelled after absorbing water in the suspension medium because Amberlite®IRP64 is a gel resin. Therefore, before preparing AZI-CM, it was necessary to carry out impregnation pretreatment to ensure the integrity of the coating film and the stability of drug release. Thus, AZI-DRC was impregnated with Polyethylene Glycol 4000 (PEG 4000), prior to coating. The specific procedure and conditions used were as follows: at 40°C, aqueous solution of PEG 4000 (20%, w/v) was used as the material for impregnation. Under magnetic stirring, AZI-DRC was slowly added to the aqueous solution of PEG 4000. The mixture was stirred for 1 h, filtered, and dried in an oven at 40 °C for 3 h, prior to later use.

## Preparation of AZI-CM

AZI-DRC prepared using ion exchange technology had some sustained release effects, but it needed modification of the sustained release. Therefore, it became necessary to use a suitable coating technology to wrap the coating capsule on the surface of AZI-DRC in order to further delay the release rate of AZI. AZI-coated microcapsules (AZI-CMs) were prepared using emulsification-solvent evaporation method. Eudragit® RS100 (3%) was used as the coating material, and 5 % of PEG 400 was solubilized in 10 mL of acetone to form the dispersed phase. Then, AZI-impregnating resin was slowly added to the sample to make it a suspension. A continuous phase was prepared by thoroughly mixing Span 80 with liquid paraffin. Then, the

dispersed phase was slowly added to the continuous phase and stirred for 2 h, with temperature kept at 30 °C. The acetone layer was allowed to evaporate completely, and the sample was cooled to room temperature. During filtration, the liquid paraffin on the surface of the coating resin was dissolved using petroleum ether, and the product was finally dried at 40 °C to obtain AZI-CM.

## Optimization of the coating process and prescription of AZI-CM

Changes in the coating process and composition tend to affect drug release. Therefore, coating parameters such as type and concentration of coating capsule material, curing temperature and curing time, and the amount of plasticizer, were optimized in this study. The specific operations are shown in Table 1.

## Quality of AZI-CM

The quality of AZI-CM prepared using the optimal conditions was investigated. The morphology of AZI-CM was examined under a scanning electron microscope (SEM). In addition, the particle sizes of three batches of dried AZI-CM were determined using laser particle size analyzer (Mastersizer 3000, England). The reproducibility of the best AZI-CM was studied using *in vitro* drug release assay.

## *In vitro* drug release studies

The USP paddle (device II) method was used for *in vitro* release study. AZI-coated microcapsule (AZI-CM) was added to 900 mL of 0.2 mol/L Na<sub>2</sub>HPO<sub>4</sub> solution (phosphate buffer, pH 7.2) using RC806D intelligent dissolution instrument at paddle rotation speed of 50 rpm and temperature of 37 °C. At different times, 5 mL samples were taken from the dissolution cup and replaced with 5 mL of dissolution medium at the same temperature. After sample filtration, the peak area was measured at 210 nm using HPLC to obtain the amount of AZI drug released. The degree of drug release was then calculated. All *in vitro* release studies were conducted in triplicate.

**Table 1:** Factors that influence AZI-CM coating process and drug release

Type of coating capsule material	Concentration of coating material (mg/mL)	Curing temperature (°C)	Curing time (h)	Amount of plasticizer (%)
Eudragit® RS100	5	20	2	5
Eudragit® RS100	10	30	4	
Eudragit® RL100	15	40	8	10

The similarity factor [10] was used to determine the differences in drug release of AZI-CM under different experimental conditions. The calculation was done as shown in Equation 1:

$$f_2 = 50 \lg \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum W_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

..... (1)

where,  $n$  represents the total number of samples, and  $R_t$  and  $T_t$  represent the cumulative dissolution data at time  $t$  under different experimental conditions.

Usually, the calculated range of  $f_2$  should be 0 - 100, and the larger the value, the smaller the difference. Greater values mean smaller differences, and when  $f_2$  is greater than or equal to 50, it shows that the release behaviors of the two drugs are similar under the same dissolution conditions. The experimental conditions have greater influence on drug release when the calculated  $f_2$  is lower than 50 or even smaller [11].

### Preparation of AZI sustained-release suspension

The composition of the suspension matrix was optimized using sedimentation volume ratio ( $F$ ) and re-dispersibility ( $RI$ ) based on previous research [5-8]. In this suspension system, sucrose was used as filler, high fructose corn syrup and tragacanth gum were used as suspending agents, propylene glycol served as the regulator, while methyl p-hydroxybenzoate and propyl p-hydroxybenzoate were used as preservatives [12]. Strawberry flavor essence was used to adjust the taste, and FD & C served as toner (Table 2).

The prescribed composition of AZI slow-release suspension was determined as follows: sucrose and high fructose corn syrup were added to pure water and stirred to dissolve, resulting in solution 1. Propylene glycol was heated in a water bath at 60 °C, and then methyl p-hydroxybenzoate,

propyl p-hydroxybenzoate and spin fish gum were added to solution 1 and dissolved completely to obtain solution 2. The two solutions were mixed and stirred evenly, with the sequential addition of FD&C, strawberry essence, EDTA (chelating agent), and AZI-CM (containing about 600 mg AZI) during the mixing process, to ensure even dispersal. Finally, a drop of polysorbate 80 was added, and the solution was stirred continuously for 20 min.

The stability of AZI slow-release suspension was evaluated using the influencing factor test and accelerated test. Three batches of AZI sustained-release suspensions were put in clean containers without sealing, and placed at 60°C and 4500 ± 500 Lx for 10 days. Samples were removed at 0, 5 and 10 days for the determination of  $F$ ,  $RI$ , drug content, release rate and drug leakage. Again, three batches of AZI sustained-release suspensions were put in clean containers without sealing, placed in a stability test box for 3 months, and the temperature was set at 40 °C ± 0.2 °C. Samples taken at 1, 2 and 3 months were evaluated for  $F$ ,  $RI$ , drug content, release rate and drug leakage.

### In vivo pharmacokinetics study

The *in vivo* pharmacokinetics of AZI slow-release suspension and commercial AZI dry suspension were studied in 12 male SD rats weighing 180 – 220 g. In this study, commercial AZI dry suspension (Xishumei, Pfizer) was used as the control. Six SD rats (group A) were randomly fed with the prepared AZI slow-release suspension. The remaining six SD rats (group B) were fed with AZI dry suspension made by shaking an appropriate amount of dry suspension in purified water. In essence, after fasting for 12 h, the SD rats in both groups were administered the appropriate AZI at a dose of 30 mg/kg body weight via gavage. About 0.5 mL of orbital blood was taken from each SD rat after 0.25, 0.5, 1, 2.5, 4, 6, 12, 24 and 48 h, and the samples were subjected to AZI analysis.

**Table 2:** Composition of AZI sustained-release suspension

AZI-CM	Equivalent to 600 mg of AZI (in 40 mL suspension medium)
Sucrose	6 g
Propylene glycol	2 g
Tragacanth gum	0.2 g
HFCS	12 g
EDTA	0.00224 g
Propyl p-hydroxybenzoate	0.012 g
Methyl p-hydroxybenzoate	0.072 g
Strawberry Flavor	0.0402 g

### Analysis of AZI in plasma samples

Rat plasma obtained from each orbital blood sample (100  $\mu$ L) was centrifuged at 15000 rpm for 7 min and the supernatant was dried with nitrogen in a water bath at 40  $^{\circ}$ C. The supernatant was dissolved in 300  $\mu$ L of mobile phase and injected into HPLC for the determination of the drug content, and the internal standard Roxithromycin (ROX) was used for quantification of peak area ratio. The HPLC system was verified with respect to precision, accuracy, specificity, standard curve and recovery rate indicators.

## RESULTS

### Taste masking effect of AZI-DRC

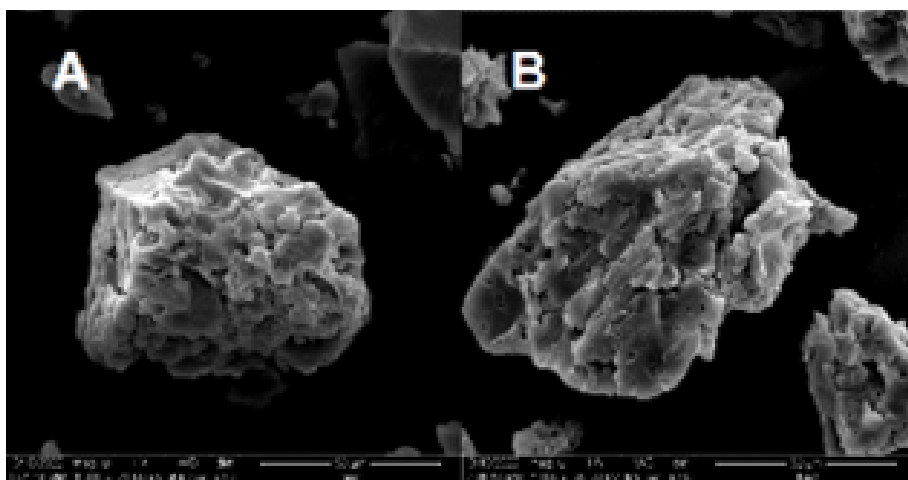
The score of AZI-DRC ranged from 8 to 10. Indeed, 50 % of the ten volunteers gave AZI-DRC a score of 10. In contrast, the range of scores for ordinary tablet powder of AZI was 1 - 2, with 70 % of the ten volunteers giving a score of 1. The results showed that AZI-DRC prepared using an ion exchanger produced a good

masking effect on the bitterness of AZI. The acidic cation exchange resin combined with AZI, thereby blocking the contact between drug molecules and bitter receptors. Thus, the AZI-DRC complex produced a good taste-masking effect [13].

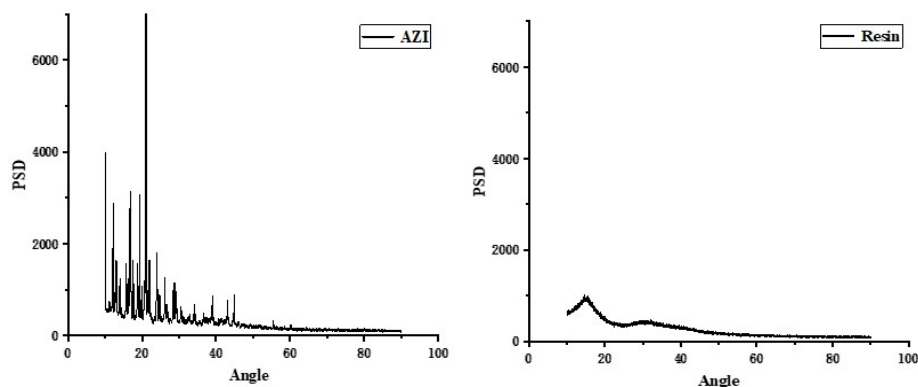
### Morphology of AZI-DRC

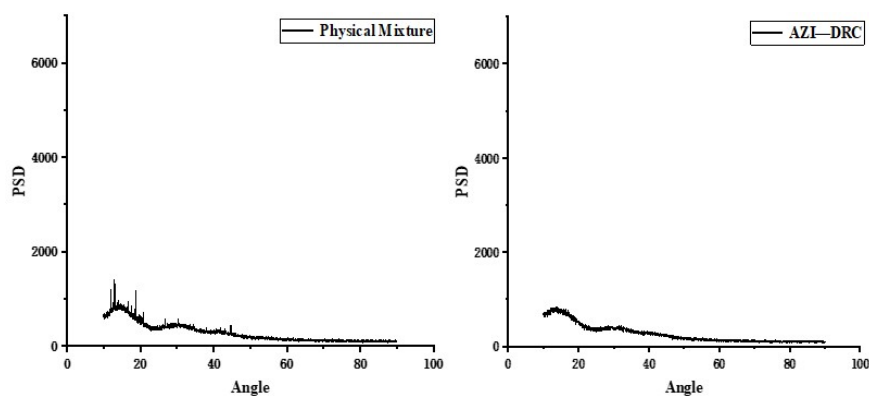
The blank cation exchanger resin and AZI-DRC were examined under SEM. The results showed that there were no obvious changes in the morphologies of the two samples and there was no AZI crystal on the surface of AZI-DRC. These data are shown in Figure 1.

The mechanism of binding involved in the formation of the drug-resin complex was studied using X-ray diffraction (XRD) and infrared spectrum (IR) in order to identify the structural differences amongst the free drug, physical mixture of drug and resin, blank cation exchanger resin, and drug-resin complex. The results are shown in Figure 2 and Figure 3.



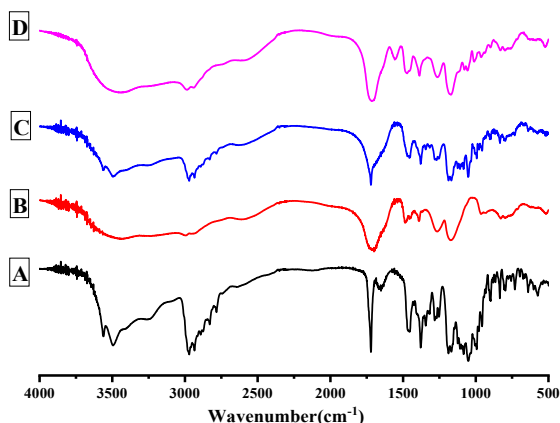
**Figure 1:** SEM images of blank resin (A) and AZI-DRC (B)





**Figure 2:** X-ray diffractograms of AZI drug (A), Amberlite® IRP64 blank resin (B), physical mixture of AZI: blank resin (6:4 ratio) (C), and AZI-DRC (D)

In the X-ray diffractograms, the drug (AZI) and physical mixture had a sharp crystallization peak at 10-45 ( $2^\theta$ ) (Figure 2 A and C), but there was no sharp peak in the blank resin and AZI-DRC (Figure 2 B and D). In the infrared spectra, it was observed that AZI (Figure 3 A) and physical mixture of AZI: blank resin (6:4 ratio) (Figure 3 C) had convex peaks at  $3500\text{ cm}^{-1}$ , which represented -OH expansion, while AZI-DRC (Figure 3 D) and blank Amberlite® IRP64 resin (Figure 3 B) did not have convex sharp peaks. Thus, the results for XRD and IR revealed that AZI existed only in amorphous form in AZI-DRC, instead of being adsorbed on the surface of the resin. This accounted for the chemical combination between the drug and the resin [14].



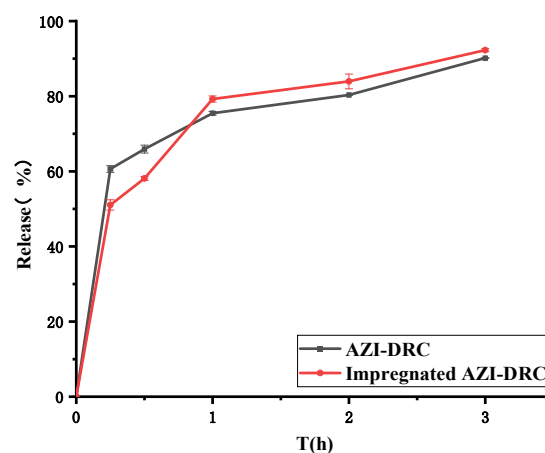
**Figure 3:** Infrared spectra of AZI drug (A), Amberlite® IRP64 blank resin (B), physical mixture of AZI: blank resin (6:4 ratio) (C) and AZI-DRC (D)

#### Prevention of AZI-DRC from swelling in water

In this study, the degrees of swelling of several resins and the effect of impregnation treatment on the *in vitro* release of AZI-DRC were investigated. The degree of swelling ( $R$ ) of blank resin in water was 1.691, while that of AZI-DRC

was decreased to 1.119 (Table 3). The results showed that AZI ions replaced the ions in the resin, and the swelling space became smaller. However, the  $R$  of the impregnated resin was 1.024, which was close to 1. This observation may be considered as no swelling, indicating that the impregnated treatment effectively controlled the water absorption and rate of swelling of AZI-DRC, ensured the integrity of the coating film, kept the resin intact, ensured a more stable drug release, and prevented sudden drug release.

The results showed that the impregnation treatment had no significant effect on the drug release of AZI-DRC (Figure 4). Thus, the two formulations (AZI-DRC and impregnated AZI-DRC) had similar drug release rates before and after impregnation treatment.



**Figure 4:** Dissolution of AZI-DRC before and after impregnation

#### Influence of coating resin on AZI release

Uncoated AZI-D caused sudden drug release due to the high ionic environment in the gastrointestinal tract. Therefore, sustained

release effect was achieved by preparing AZI drug resin microcapsules [15]. The polyacrylic resin was selected as the coating capsule material and the emulsification-solvent evaporation method was selected as the coating technology.

In this study, the influence of coating materials on drug release was investigated. The results showed that the slow-release effect of Eudragit® RS100 was better than that of Eudragit® RL100, as Eudragit® RL100 had greater permeability and swelling properties which released the drug at a faster speed. Therefore, Eudragit® RS100 was selected for the preparation of AZI-CM (Figure 5 A).

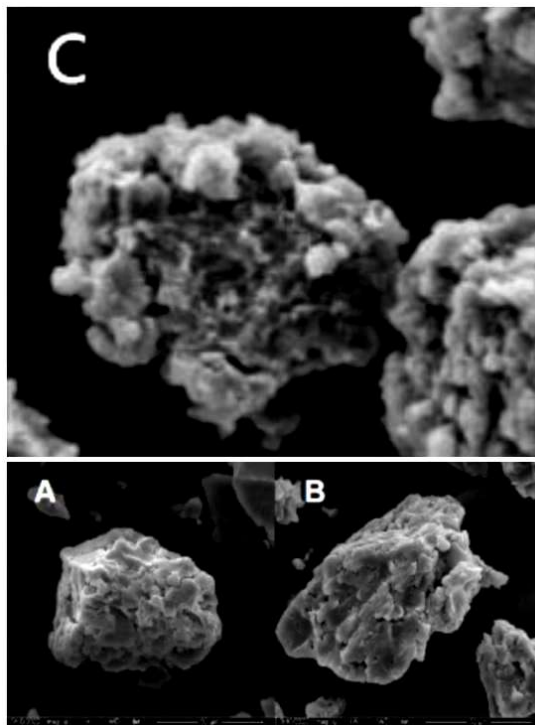
In addition to the types of capsule materials, the concentration of coating capsule material, plasticizer dosage, curing temperature, and curing time affect the release of drugs from microcapsules. The greater the concentration of the coating capsule, the slower the release of AZI from the coating resin. There were more coating capsules in the same volume, with the final AZI-CM being thicker, which made the release of AZI from the resin slower with increase in concentration of coating solution. These results are shown in Figure 5 B.

The higher the temperature, the faster the drug release. At 20°C and 30°C, there was no obvious difference in *in vitro* release behavior of AZI-CM, but at 40°C, the release speed of AZI-CM was faster. The high increase in drug release speed was due to high temperature-induced fast volatilization of acetone and partially completed coating process (Figure 5 C). The release of AZI from AZI-CM was clearly slowed down with increase in curing time. A compact film was formed when the curing time was 8 h, and the drug release rate was significantly reduced. However, the coating process was not completely formed when the curing time was 2 h. The film formed was loose, resulting in a faster release behavior (Figure 5 D). The release curves of the two AZI-CM were very close when the doses of PEG 400 were different. Therefore, a 5% dose of PEG 400 was chosen as plasticizer, based on economic factors (Figure 5 E). Thus, the optimal conditions were as follows: curing temperature of 30 °C, curing time of 2 h, and concentration of retarding material of 10 mg/mL.

#### Quality evaluation of AZI coating resin

The result of SEM for AZI-CM showed obvious encapsulation when compared with that for AZI-

DRC (Figure 6). The particle size of three batches of dried AZI-CM was determined using laser particle size analyzer. The results showed that AZI-CM had a uniform particle size distribution, with particle size mainly within the range of 100 - 127 µm. These results are presented in Figure 7.

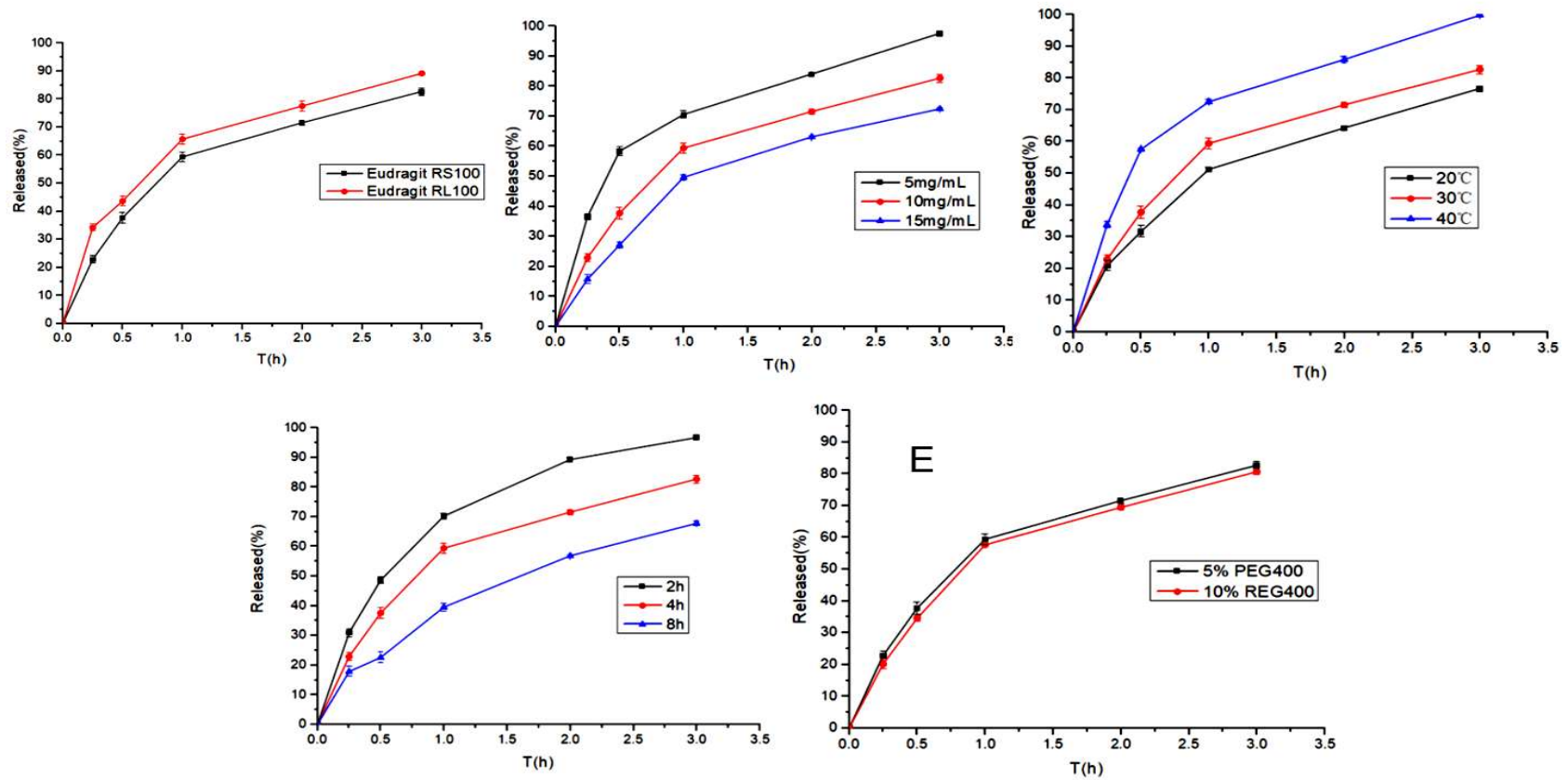


**Figure 6:** Scanning electron microscope images of blank resin (A), AZI-DRC (B), and coating resin (C)

The reproducibility of the best AZI-CM was also studied using *in vitro* drug release. *In vitro* release  $f_2$  values of the three batches of AZI-CM were all higher than 80 (Figure 8), which indicated that *in vitro* release behaviors of the three batches of AZI-CM were highly reproducible.

#### Stability of AZI sustained-release suspension

The stability of AZI slow-release suspension was evaluated with test for influencing factors and accelerated test [16]. The synthesized AZI slow-release suspension did not change significantly when kept for 10 days and 3 months in the stability test chamber (Tables 3 and 4). Therefore, the suspension met the requirements specified in the China Pharmacopoeia. The results also showed that AZI sustained-release suspension had good stability.



**Figure 5:** Factors that affect *in vitro* drug release from AZI-DRC. (A) Effect of different coating materials on *in vitro* AZI release of AZI-CM; (B) effect of different concentrations of coating capsule on *in vitro* AZI release of AZI-CM; (C) effect of curing temperature on *in vitro* AZI release of AZI-CM; (D) effect of curing time on *in vitro* AZI release of AZI-CM, and (E) effect of plasticizer dosage on *in vitro* AZI release of AZI-CM



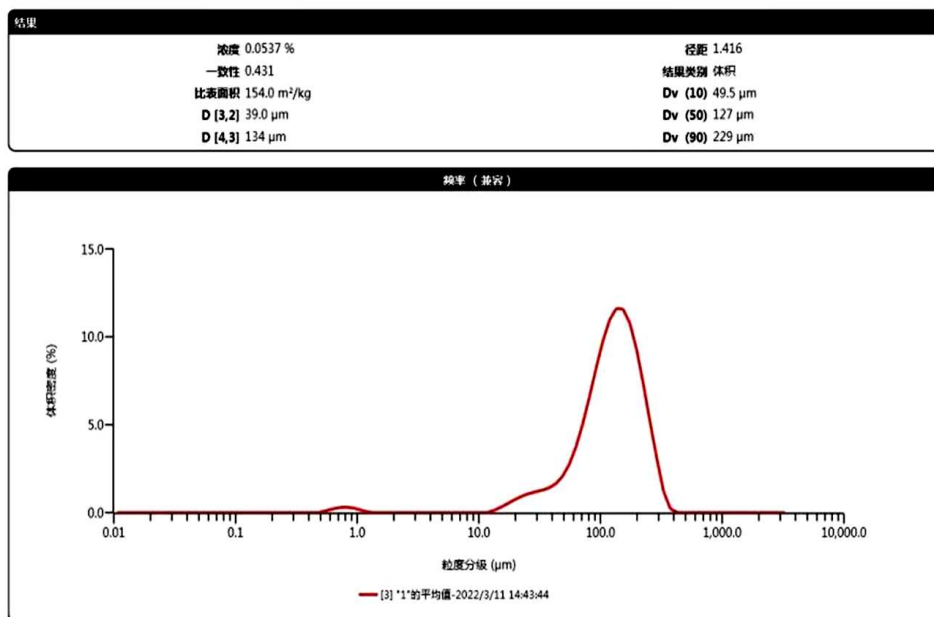


Figure 7: Particle size distribution diagram of AZI-CM

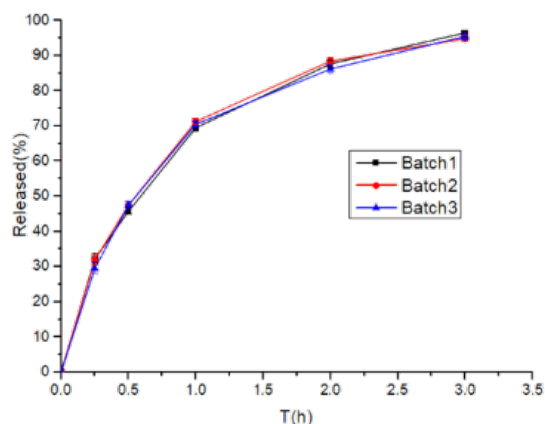


Figure 8: *In vitro* release profile of three batches of AZI-CM

***In vivo* pharmacokinetics**

In this study, the pharmacokinetics parameters [17] of AZI suspension and commercial dry suspension were compared. Quantitative results of pharmacokinetics were obtained by analyzing BAPP2.0. The results showed that the synthesized AZI slow-release suspension had a longer  $T_{max}$  but a smaller  $C_{max}$  than the corresponding values for the commercial dry suspension (Figure 9 and Table 5).

In addition, results from calculations of relative bioavailability indicated that AZI sustained-release suspension had good bioequivalence. The relative bioavailability of the synthesized AZI slow-release suspension was calculated using the formula:

$$F_r = \frac{AUC_{0-24(test)}}{AUC_{0-24(reference)} \dots \dots \dots (3)}$$

where  $AUC_{0-24}$  (reference) is the sum of areas under group B curves, and  $AUC_{0-24}$  (test) is the sum of areas under group A curves.

The results showed that the relative bioavailability of AZI sustained-release suspension was similar to that of the commercially available AZI dry suspension, with a value of 110.23%. This is an indication of good bioequivalence.

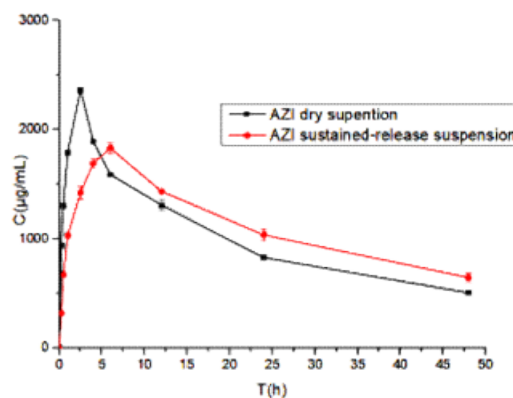


Figure 9: Plasma drug concentration-time curve of AZI slow-release suspension and commercial dry suspension (n = 6)

**Table 3:** Factors that influence the stability of AZI sustained-release suspension (n = 3)

Condition	Time (days)	F	RI	Drug leakage (%)	Content (%)	Drug release (%)
60 °C	0	0.92	***	0.28	93.77	$f_2 > 50$
	5	0.94	**	0.32	92.03	$f_2 > 50$
	10	0.94	**	0.41	91.41	$f_2 > 50$
4500 ± 500 Lx	0	0.92	***	0.28	93.77	$f_2 > 50$
	5	0.96	***	0.35	97.10	$f_2 > 50$
	10	0.94	**	0.44	93.01	$f_2 > 50$

\*Re-dispersibility

**Table 4:** Accelerated stability results of AZI sustained-release suspension (n=3)

Time (months)	F	RI	Drug leakage (%)	Content (%)	Drug release (%)
0	0.92	***	0.28	93.77	$f_2 > 50$
1	0.94	***	0.36	91.10	$f_2 > 50$
2	0.92	***	0.39	93.87	$f_2 > 50$
3	0.91	**	0.47	92.61	$f_2 > 50$

\*re-dispersibility

**Table 5:** Analysis of related pharmacokinetic parameters (n=6)

Parameter	Dry suspension	Sustained-released suspension
$t_{1/2}$ (h)	19.57	29.01
$T_{max}$ (h)	2.5	6
$C_{max}$ (µg/mL)	2367.07	1831.48
$MRT_{0-24}$ (h)	30.99	43.24
$AUC_{0-24}$ (µg/h/mL)	48152.29	53077.5

## DISCUSSION

Azithromycin (AZI), a broad-spectrum antibacterial agent, is used for treating numerous infectious diseases. The available AZI preparations in pharmacies are mostly solid preparations which fundamentally retain the bitter taste of AZI. Even after the ordinary powder preparations are made into suspensions, patients' compliance is still low. This greatly reduces the use of AZI as an antibiotic drug for patients (especially children). In this study, a new type of AZI sustained-release suspension containing IER was successfully prepared. AZI was immobilized on the surface of a cation exchanger using ion exchange. Thereafter, characterization using SEM, XRD and FTIR showed that AZI was bound via ion exchange rather than physical adsorption, and the prepared AZI-DRC changed the original crystalline state of the drug [18]. Therefore, the combination of AZI and IER blocked direct contact between drug molecules and bitter receptors, thereby reducing the capacity of human taste organs to sense the bitterness of the drug.

AZI-DRC prepared using the technique of ion exchange had some slow-release effects. In order to further improve the adaptability of patients, it was necessary to wrap the coating capsule on the surface of AZI-DRC so as to further delay the release rate of AZI *in vivo*. In

this study, pretreated AZI drug-resin complex was coated using emulsification-solvent evaporation and optimized in order to achieve further sustained-release effect. *In vitro* drug release curves of three batches of optimal drug-resin microcapsules showed that AZI drug resin microcapsules had good and highly reproducible sustained release performance.

The use of liquid-controlled drug delivery system prolongs the retention time of AZI in the body and reduces the toxic side effects of common AZI preparations due to excessive dosage. The particle size of AZI coating resin was mainly distributed in the range of 100 - 127 µm (less than 200 µm). This satisfies the condition required for the preparation of sustained-release suspension. Therefore, in this study, AZI-CM was made into sustained-release suspension, and the quality of the suspension was evaluated. The results showed that the synthesized AZI sustained-release suspension had good stability after 3 months. Moreover, the re-dispersibility and drug content of AZI sustained-release suspension were good after 3 months.

The pharmacokinetics of the synthesized AZI sustained-release suspension *in vivo* was also studied. Compared with AZI dry suspension available in the market, the optimized suspension effectively had a lower  $C_{max}$  and a higher  $T_{max}$  which reduced the blood drug concentration and

prolonged the duration of action of the drug. The relative bioavailability of the optimized AZI sustained-release suspension was similar to that of the commercially available AZI dry suspension (110.23 %). This is an indication of good bioequivalence.

### Limitation of the study

This study focused only on the pharmacokinetics of AZI in rats. Subsequent studies should investigate the pharmacodynamics and clinical benefits of the drug.

## CONCLUSION

A new type of AZI sustained-release suspension was prepared using cation exchanger resin Amberlite®IRP64 as a drug carrier. The synthesized AZI sustained-release suspension has good bioavailability, remarkable sustained-release effect, and taste masking capacity. Compared with AZI drugs currently in the market in China, AZI sustained-release suspension has the advantages of reducing the frequency of AZI administration and improving the oral compliance of patients. These findings indicate that the newly developed AZI sustained-release suspension has a good prospect for further investigation as an antibacterial formulation before commercialization.

## DECLARATIONS

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### Ethical approval

None provided.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

This work was done by the authors named in this article, and all liabilities related to claims in the contents of this article will be borne by the authors. Quanzhu Yang and Yongjian Yang designed the study and conducted the experiments. Xin Zhang and Tianxiang Chen analyzed and interpreted the data, while Caleb Kesse Firempong, Hongfei Liu, Jingwei Jin, Haibing He and Yingshu Feng prepared the manuscript, with contributions from all the co-authors.

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