Optimization of Preparation Process and Pharmacokinetics of APAP Double-Release Pellet Capsules

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Abstract: In order to develop a kind of APAP double-release pellet capsules, which was prepared with the manual filling method, the immediate and sustained release pellets of a certain proportion were prepared by the fluidized bed coating and the extrusion spheroidization process, respectively. It was founded that both the prepared immediate-release pellets and sustained-release pellets had smooth and round surfaces. The particle size distribution ranged evenly from 16 to 35 mesh. Response surface plots showed that the optimal preparation prescription for immediate-release pellets were that ethanol concentration (X_1) 70%, APAP 20%, MCC (X_2) 40%, PVP K30 (X_3) 20%, and sucrose pellet core 20%; and the optimal preparation prescription for sustained-release pellets were that HPMC concentration (X^*_3) 6.5%, APAP 30%, EC (X^*_1) 20%, MCC (X^*_2) 40%, PVP K30 4%, and lactose 6%. The results of pharmacokinetic analysis revealed that, after the APAP double-release pellet was orally administered, compared with that of conventional tablets, the plasma APAP levels in the blood circulation dramatically rose to significant peaks as a result of the quick and slow release of APAP from the capsules, which significantly prolonged the effective time of drugs in blood. Finally, immediate and sustained antipyretic-analgesic effects were obtained.

1. INTRODUTION

Acetaminophen (N-acetyl-P-aminophenol abbreviation, APAP), also known as paracetamol, is a non-opioid and non-steroidal analgesic agents (Mizogami 2022). It is widely used to treat fever and pain caused by colds, headaches and other diseases in adults and children (Vanova 2022). Currently, it is the most commonly used antipyretic and analgesic drug in the world. However, its efficacy is not long-lasting, the long-term and repeated medication will lead to "peak and valley" phenomenon, and if it is not taken appropriately, hydroxyl compounds which is harmful to people health and even deteriorate the liver is brought into being by the metabolism in vivo (Alchin 2022, Patterson 2021). Thereby, the research and development of new APAP preparations with high efficiency and low toxicity is one of the research hotspots in the medical field.

The multi-unit drug delivery system (MUDDS) had unique advantages over the single pellet system in the treatment of some diseases (Cnota 2005). Studies had shown that the double-release pellets MUDDS made by the mixture of immediate-release and sustained-release pellets according to a certain proportion not only could ensure the initial effect of the drug in vivo, but also make the stable release of MUDDS in vivo so that the efficacy and safety of the drug were significantly improved (Dong 2018, Shan 2022). Therefore, double-release pellets MUDDS has become one of the hotspots in the research of new drug dosage forms.

In this study, the theory of MUDDS was adopted to prepare APAP double-release pellet capsules by mixing the immediate-release pellets prepared by the fluidized bed coating approach with the sustained-release pellets prepared by the preparation procedure of the extrusion spheronization. With the benefit of rapid release composition which were quickly released after oral administration to achieve an effective blood concentration (Hamed 2020), and the sustained release part which released slowly to maintain the blood concentration, there were a number of purposes the present study means to achieve, including the elimination of the peak and valley phenomenon, the improvement in bioavailability, reduction of liver and kidney damage, Finally, further advance of the drug efficacy of APAP (Dyatlov 2018, Singla 2014).

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2. Experimental SECTION

2.1 Materials

N-acetyl-P-aminophenol (APAP, 99%, China) was purchased from Henan Juliang Biotechnology Co., Ltd. (China). Hydroxypropyl methylcellulose (HPMC) Zhengzhou Hongrui Food Additive Co., Ltd. (China). Polyvinylpyrrolidone (PVP K30) and Microcrystalline cellulose (MCC) Shandong Yusuo Huagong Technology Co., Ltd. (China). Ethyl cellulose (EC) Shanghai Yaguo Chemical Co., Ltd. (China). Lactose was purchased from Henan Wanbang Chemical Technology Co., Ltd. and sucrose core was purchased from Anhui Shanhe Pharmaceutical Excipients Co., Ltd. (China). Other reagents such as absolute ethanol and methanol were of analytical grade.

2.2 Experimental Process

2.2.1Preparation of Immediate-Release Pellets

APAP, PVP K30, and MCC were added to the ethanol solution and stirred evenly, and the organic solvent was removed to prepare the solid dispersion. The liquid bed coating method was used with ethanol as a wetting agent and sucrose ball core as blank ball core. At an atomization pressure of 0.4 bar, the material temperature was approximately 40℃, the injection speed was 10 r/min, and the fan frequency was 18 Hz. After the coating was completed, it was cured in a constant temperature drying oven at 60℃ for 12 hours.

2.2.2Preparation of Sustained-Release Pellets

APAP, PVP K30, EC were added to the ethanol solution and stirred, followed by MCC, lactose and other excipient to make the mixture homogeneous. The organic solvent was volatilized in a water bath to prepare solid dispersions, and HPMC was used as a binder to prepare soft materials, and the sustained release pellets were prepared by the extrusion and rounding method.

2.2.3Preparation of Double-Release Pellet Capsules

The drug contents of APAP immediate-release pellets and sustained-release pellets were determined according to the method of drug content detection. Acetaminophen double-release pellet capsules were prepared by the manual filling method according to the ratios of immediate-release pellets and sustained-release pellets at 1:2, 1:3, and 1:4.

2.3 Characterization

2.3.1Morphological Observation and Particle Size

The surface morphology of the sustained-release and immediate-release pellets was evaluated by scanning electron microscopy (SEM), and the particle size was distinguished by a screen. The particle size distribution at different screen intervals was counted.

2.3.2Prescription Screening and Optimization

Three factors and three levels of the Box-Behnken experiment design were used to evaluate the effect of different parameters on drug release based on the investigation of each factor. Thus, the formulations of immediate-release pellets and sustained-release pellets were optimized. Table 1 and Table 2 list the levels of influenced and restricted factors for in vitro drug release based on preliminary pharmacokinetic studies. The design of sustained-release pellets and immediate-release pellets required 17 experimental formulations, respectively. The test results in Table 3 and Table 4 were analyzed using Design-Expert 12 software, and according to the generated response surface, the best formulation was selected.

Table 1. Factors and responses of the Box-Behnken design for immediate-release pellets.

Independent variables	Levels used		
	-1	0	1
X_1 = Ethanol concentration (%	60	70	80
X_2 = MCC (%)	30	40	50
X_3 = PVP K30 (%)	15	20	25
Responses	constraints		
Y_1 = the drug release within 3 min	> 70%		
Y_2 = the drug release within 15 min	> 85%		

Table 2. Factors and responses of the Box-Behnken design for sustained-release pellets.

Independent variables	Levels used		
	-1	0	1
X^*_1 = EC (%)	0	20	40
X^*_2 = MCC (%)	30	40	50
X^*_3 = HPMC (%)	3	6.5	10
Responses	constraints		
Y^*_1 = the drug release within 2 h	< 30%		
Y^*_2 = the drug release within 6 h	50%–70%		
Y^*_3 = the drug release within 12 h	> 90%		

Table 3. Independent variables and observed responses of immediate-release pellets Box-Benhnken design.

Formulation	Factors (%)			Responses (%)	
	X_1	X_2	X_3	Y_1	Y_2
1	70	40	20	72.16	89.63
2	80	40	25	64.39	84.88
3	80	30	20	69.51	89.79
4	60	40	25	63.99	84.7
5	70	40	20	71.45	89
6	70	40	20	71.33	90.21
7	60	40	15	71.1	89.18
8	70	40	20	70.62	87.45
9	70	50	25	61.75	79.8
10	70	30	25	66.63	86.49
11	80	40	15	70.08	88.68
12	70	50	15	68.69	88.02

13	70	40	20	71.3	88.95
14	60	30	20	71.71	92.07
15	70	30	15	71.91	92.16
16	60	50	20	69.88	87.87
17	80	50	20	66.63	87.33

Table 4. Independent variables and observed responses of sustained-release pellets Box-Benhnken design.

Formulation	Factors (%)			Responses (%)		
	X^*_1	X^*_2	X^*_3	Y^*_1	Y^*_2	Y^*_3
1	40	40	3	26.13	47.18	88.13
2	40	30	6.5	17.13	32.76	81.56
3	20	40	6.5	24.63	61.27	92.43
4	20	30	3	25.65	54.56	85.87
5	20	40	6.5	24.89	56.36	90.09
6	40	50	6.5	21.51	41.9	88.05
7	20	50	10	32.05	60.35	86.74
8	40	40	10	20.29	38.55	83.45
9	20	40	6.5	27.97	60.48	91.27
10	0	40	10	94.24	97.36	98.91
11	0	40	3	96.43	98.42	99.46
12	0	50	6.5	92.78	97.27	99.36
13	20	40	6.5	28.11	56.38	90.93
14	20	40	6.5	27.72	59.34	91.28
15	20	50	3	36.87	68	97.7
16	0	30	6.5	93.45	98.23	99.32
17	20	30	10	20.06	42.38	84.63

2.3.3Study on in Vitro Release of Double-Release Pellet Capsules

The performance of the in vitro release of APAP pellets was assessed using the dissolution device (RC-6, Tianjin, China), in accordance with the Chinese Pharmacopoeia. The APAP dissolution test was performed at 37 ± 1°C with 900 mL of PBS (pH = 6.8) buffer. First, a certain proportion of immediate-release pellets and sustained-release pellets were weighed, and then they were tested in 6 dissolution cups. Keep the rotation speed at 100 rpm and the temperature at 37°C. The temperature and speed were kept at 100 rpm, and 3 mL samples were taken at predetermined time intervals of 0.083, 0.16, 0.25, 0.5 1, 2, 4, 6, 8, 10, and 12 h,, and the sample solution was replaced by the same volume of fresh blank solution. Finally, the samples were analyzed by an UV-vis spectrum.

2.3.4Pharmacokinetic Study Design

All animals were handled in strict accordance with the Regulations on the Management of Laboratory Animals. Before the experiment, all rats must be fasted for 12 h and drink water freely. The rats were divided into two groups. One group was gavaged with two kinds of pellets in a certain proportion, and the other group was gavaged with 1/3 volume of APAP tablets. 0.5 mL of blood was collected at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 h after administration. All blood samples were then placed in a heparin condensate collection vessel. Plasma was obtained by centrifugation at 5000 rpm for 15 min and then frozen at -20°C for analysis.

2.3.5High Performance Liquid Chromatography Analysis Conditions

Chromatographic column: SHIMADZU Supersil AQ-C18 (4.6 mm × 250 mm I.D.), mobile phase: water : methanol (80:20), flow rate: 300 μL/min; UV detection wavelength: 248 nm; column temperature: 25°C, injection volume: 20 μL.

3. Results and discussion

3.1 Characterization of the Pellets

Figure 1 shows SEM images of immediate-release pellets and sustained-release pellets measured under the optimal prescription. It could be seen from Figure 1a–c that the smooth surface of the sustained-release pellets was without cracks, presenting rounds and ovals. As shown in Figure 1d–f, the smooth surface of the immediate-release pellets was without cracks, presented in rounds and ovals. From the profile of the pellet, it could be seen that the sucrose pellet core was fully wrapped inside. The results showed that the immediate-release pellets and sustained-release pellets prepared by the fluidized bed coating method and extrusion spheroiding methods met the preparation requirements.

As could be seen from Figure 2a,b, the particle size distribution of immediate-release pellets and sustained-release pellets. Figure 2a and 2b show the screening results of three different batches of immediate-release and sustained-release pellets, respectively. It can be seen that the particle size of the pellets was mainly distributed between 16 and 35 meshes, and the particle size range was mainly between 0.5 and 1.18 mm. Therefore, the preparation of immediate-release pellets by the fluidized bed coating method and the preparation of sustained-release pellets by the extrusion spheronization method meet the requirements for particle size.

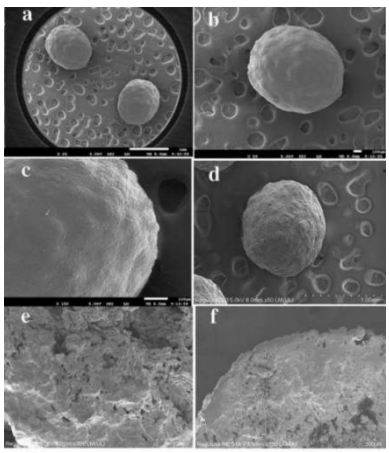

Figure 1. (a–c) and (d–f) were SEM images of sustained-release pellets and immediate-release pellets from different viewing angles, respectively.

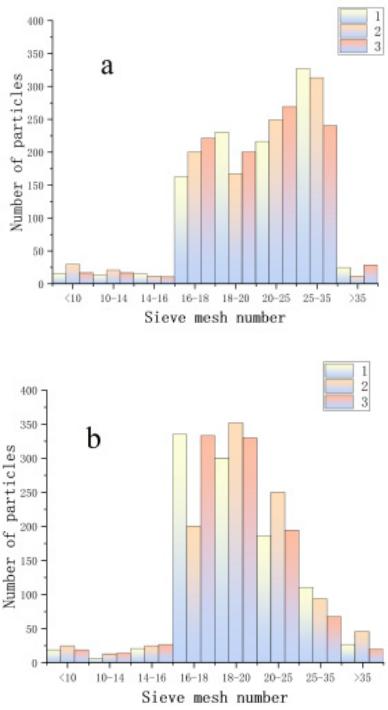

Figure 2. Particle size of immediate-release pellets and sustained-release pellets.

3.2 Optimization of Prescription

3.2.1 Regression Equations

Based on the experimental data, the coefficients and p-values of the fitted quadratic equation calculated by Expert-Design 12.0 were listed in Table 5 and 6, and the last equation contained only statistically significant coefficients. The results that the model had high significance, fitted the real data well, and had practical guiding significance. Therefore, it could be used to analyze and predict the optimal formulation of pellets..

3.2.2 Response Surface Plots

The relationship between independent variables and dependent variables was further elucidated by the 3D response surface graph, which could reflect the influence of the other two factors on the response when one factor remained unchanged. It could be seen from Figure 3 that the influence of the ethanol concentration (X_1) was weaker than that of MCC (X_2) and PVP K30 (X_3) compared with the release amount Y_1. When X_2 and X_3 were kept at the same level, an increase in X_1 from 60% to 80% had little effect on Y_1. However, the change in X_2 and X_3 amplitudes had a great influence on Y_1. When X_2 increased from 30% to 50%, the release of Y_1 decreased significantly. Considering other factors, Y_1 also had obvious changes with the change of X3 content. According to its constraint conditions, $Y_1 > 70\%$ and $Y_2 > 85\%$, as shown in Figure 3, the optimal prescription after response surface optimization was as follows: The concentration of ethanol (X_1) 70%, MCC (X_2) 40%, PVP K30 (X_3) 20%, APAP 20% and sucrose core 20%.

As shown in Figure 4, the drug release amounts Y^*_3 were higher than the constraint range when the X^*_1 content was 0, regardless of the contents of X^*_2 and X^*_3, indicating that the X^*_1 content played an important role in drug release. Therefore, compared with X^*_1, the two factors X^*_2 and X^*_3 had a weak influence on the dissolution of sustained-release pellets. As could be seen from Figure 4a,b, when X^*_1 remains unchanged compared with Y^*_3, the release amount decreases with the increase in X^*_3 concentration, while the release amount increases with the increase in X^*_2 concentration. According to its constraints, $Y_1 < 30\%$, $50\% < Y_2 < 70\%$, $Y_3 > 90\%$ of the Figure 4 showed that the optimal prescription after response surface optimization as follows: The concentration of HPMC (X^*_3) 6.5%, APAP 30%, EC (X^*_1) 20%, MCC (X^*_2) 40%, PVP K30 4%, and lactose 6%.

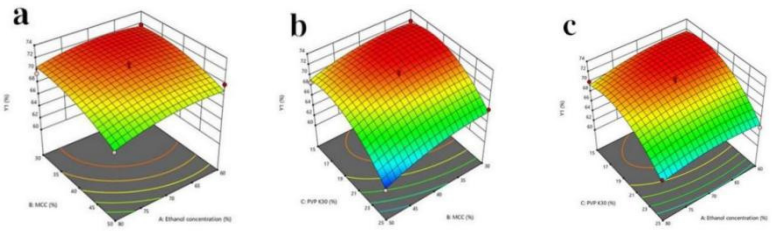

Figure 3. Contour plots showing the effects of (a) X1 and X2, (b) X2 and X3, and (c) X1 and X3 on the response Y1.

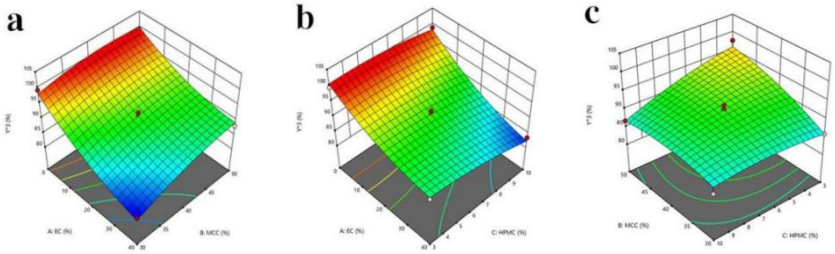

Figure 4. Contour plots showing the effects of (a) X*1 and X*2, (b) X*1 and X*3, (c) X*2 and X*3 on the response Y*3.

Table 5. Regression coefficients and associated P values of the fitted model for the immediate-release pellets.

Term	Drug Release Within3min (Y_1)		Drug Release Within15min (Y_2)	
	Coefficient	*P*-Value	Coefficient	*P*-Value
Constant	71.37	<0.0001*	89.05	0.0043*
X_1	-0.7587	0.0474*	-0.3925	0.4081
X_2	-1.60	0.0015*	-2.19	0.0018*
X_3	-3.13	<0.0001*	-2.77	0.0004*
$X_1 \cdot X_2$	-0.2625	0.5755	0.4350	0.5127
$X_2 \cdot X_3$	-0.4150	0.3841	-0.6375	0.3459
$X_1 \cdot X_3$	3550	0.4531	0.1700	0.7953
$X_1 \cdot X_1$	-0.8973	0.0784	0.2298	0.7197
$X_2 \cdot X_2$	-1.04	0.0480*	-0.0128	0.9840
$X_3 \cdot X_3$	-3.08	<0.0002*	-2.42	0.0057*
Regression Equation	$Y_1 = 71.37 - 0.7587X_1 - 1.60X_2 - 3.13X_3 - 1.04X_2^2 - 3.08X_3^2$		$Y_2 = 89.05 - 2.19X_2 - 2.77X_3 - 2.42X_3^2$	
R-Squared	0.9655		0.9200	

Table 6. Regression coefficients and associated P values of the fitted model for sustained-release pellets.

Term	Drug release within 2 h (Y^*_1)		Drug release within 6 h (Y^*_2)		Drug release within 12 h (Y^*_3)	
	Coefficient	*P*-Value	Coefficient	*P*-Value	Coefficient	*P*-Value
Constant	26.66	0.000	58.77	0.000	91.20	0.000
X^*_1	-36.48	<0.0001*	-28.86	<0.0001*	-6.98	<0.0001*
X^*_2	3.37	0.0150*	4.95	0.0108*	2.56	0.0021*
X^*_3	-2.31	0.0643	-3.69	0.0373*	-2.18	0.0050*
$X^*_1 \cdot X^*_2$	1.26	0.4237	2.52	0.2545	1.61	0.0732
$X^*_2 \cdot X^*_3$	0.1925	0.9006	1.13	0.5951	-2.43	0.0156*
$X^*_1 \cdot X^*_3$	-0.9125	0.5586	-1.89	0.3832	-1.03	0.2195
$X^*_1 \cdot X^*_1$	30.08	<0.0001*	11.41	0.0007*	2.31	0.0174*
$X^*_2 \cdot X^*_2$	-0.538	0.7249	-2.64	0.2247	-1.44	0.0950
$X^*_3 \cdot X^*_3$	2.52	0.1249	0.1970	0.9236	-1.02	0.2120
Regression Equation	$Y^*_1 = 26.66 - 36.48X^*_1 + 3.37X^*_2 + 30.08X^{*2}_1$		$Y^*_2 = 58.77 - 28.86X^*_1 + 4.95X^*_2 - 3.69X^*_3 + 11.41X^{*2}_1$		$Y^*_3 = 91.20 - 6.98X^*_1 + 2.56X^*_2 - 2.18X^*_3 - 2.43X^*_2X^*_3 + 2.31X^{*2}_1$	
R-Squared	0.9958		0.9849		0.9712	

3.3 In Vitro Release of Double-Release Pellet Capsules

The sustained-release pellets and immediate-release pellets prepared by the best prescription and process were mixed at a ratio of 1:2, 1:3, and 1:4, respectively. APAP double-release pellet capsules were prepared by the manual filling method and then released in vitro in a PBS (pH = 6.8) buffer. Figure 5a–c analyzed the double-release capsules prepared by using immediate-release pellets and sustained-release pellets in different proportions. According to the constraint conditions of double release drugs, the drug release was 15%–35% in 0.5 h, 65%–85% in 6 h, and > 80% in 10 h. The experimental results showed that the cumulative release of Figure 5a at 0.5 h exceeded 35% and did not met the requirements of the double release drug release curve and cumulative release degree, while Figure 5b and 5c met the design requirements. As compared with Figure 5b, the drug release rate in Figure 5c was 65.233% in 6 h. Although it met the drug release requirements, the drug release effect was low. Therefore, we chose the ratio of immediate-release pellets to sustained-release pellets of 1:3 to prepare double-release pellet capsules.

As shown in Figure 5, the slope of 0–1 h was greater than that of 1–12 h. It could be seen that 0–1 h was mainly the release of immediate-release pellets, and 1–12 h was mainly the release of sustained-release pellets. Immediate-release pellets mainly released the drug quickly to reach the therapeutic concentration and had a quick-acting effect; sustained-release pellets maintained the drug concentration and had a long-term therapeutic effect. The mechanism studies in Table 7 and Table 8 showed that the Higuchi equation could best represent the release process and release kinetics of double-release pellets in the 0–1 h period or the 1–12 h period.

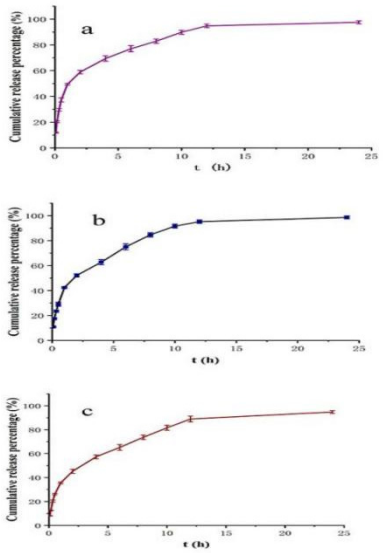

Figure 5. Immediate-release pellets and sustained-release pellets, respectively, by a ratio of 1:2 (a) or 1:3 (b), a ratio of 1:4 (c), preparation of a double interpretation of the graph of micropill capsule in vitro release.

Table 7. A 0–1 h period of release degree fitting.

Model name	R^2
Zero-order model	0.95943
First-order model	0.94954
Higuchi diffusion model	0.99741
Ritger-Peppas model	0.99729

Table 8. A 1–12 h period of release degree fitting.

Model name	R^2
Zero-order model	0.96037
First-order model	0.82167
Higuchi diffusion model	0.99217
Ritger-Peppas model	0.98995

3.4 Pharmacokinetic Study

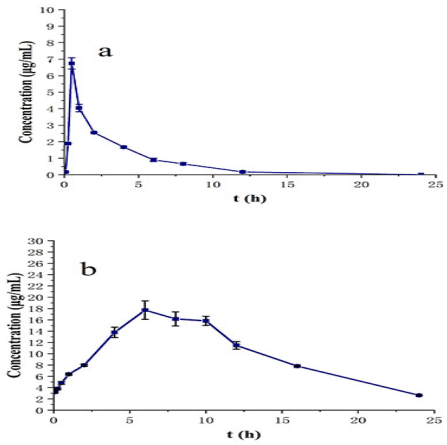

Figure 6. Plasma concentration-time curves of ordinary tablets (a) and double-release pellet capsules (b) in rats.

Table 9. The pharmacokinetic parameters of APAP double-release pellet capsules and ordinary tablet in rats (n=6).

parameter	Tablet (10.29 mg/kg)	Double release pellet capsules (30.86 mg/kg)
C_{max} (μg/mL)	6.743 ± 0.342	17.719 ± 1.643
T_{max} (h)	0.5	6
$T_{1/2}$ (h)	2.47 ± 0.32	5.53 ± 0.56
AUC_{0-24} (h·μg/mL)	18.36641903 ± 0.364	238.605551 ± 12.743
$AUC_{0-\infty}$ (h·μg/mL)	18.38732128 ± 0.423	260.14142193 ± 14.072
MRT (h)	3.79 ± 0.263	9.828 ± 0.679

A pharmacokinetic study was carried out on APAP double-release pellet capsules and ordinary tablets. The average blood concentration curve with time was shown in Figure 6, and the main pharmacokinetic parameters calculated by Phoenix 8.1.0 software were shown in Table 9. According to Figure 6a, the blood concentration of ordinary tablets increased rapidly and reached its peak after 0.5 h of administration, with a blood concentration C_{max} of 6.743 ± 0.342 μg/mL. APAP had a shorter half-life $T_{1/2}$ of 2.47 ± 0.32 h, which enables rapid elimination of the drug in vivo. It could be seen from Figure 6b that, compared with ordinary tablets, the blood concentration of APAP double-release pellet capsules increased slowly in rats, the fluctuation of blood concentration C_{max} was small, and the peak value was reached 6 h after administration, with a long half-life $T_{1/2}$ of 5.53 ± 0.56 h. The drug elimination process was gentle, which was in line with the characteristics of double-release preparations and could well maintain the drug effect. The results of the pharmacokinetic parameters were in line with the characteristics of this preparation.

4. ConclusionS

In conclusion, based on the theory of MUDDS， APAP double-release pellet capsules was prepared by mixing immediate-release pellets and sustained-release pellets according to a certain proportion with the manual filling process. The results showed that the surfaces of immediate-release pellets and sustained-release pellets were smooth and round, and the particle size distribution was between 16 and 35 mesh. The in vitro release pattern of double-release pellets showed that the release of immediate-release pellets occurred mainly in 0–1 h and that of sustained-release pellets was in 1–12 h. Furthermore, the pharmacokinetic parameters were AUC, $T_{1/2}$, and C_{max} of 238.605551 ± 12.743 h·μg/mL, 6 h, and 17.719 ± 1.643 μg/mL, respectively. And the half-life of APAP double-release pellets was longer than that of APAP tablets, which was helpful to avoid the peak and valley phenomenon, reduce the frequency of administration, and reduce the side effects of the drug. More importantly, compared with hospital commonly used preparations, it was not only to achieve the effective

concentration in the blood so quickly, but also maintaine it for a long time in vivo after APAP double-release pellet capsules was taken. The above-mentioned results laid foundation for the deep development and the practical application of the APAP double-release pellet capsules.

Acknowledgements

The authors acknowledge the financial support of the People's Livelihood Science and Technology Project of Qingdao.

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