

Enhanced bioavailability of apigenin via preparation of a carbon nanopowder solid dispersion

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Abstract: In this study, a novel carbon nanopowder (CNP) drug carrier was developed to improve the oral bioavailability of apigenin (AP). Solid dispersions (SDs) of AP with CNP were prepared, and their in vitro drug release and in vivo performance were evaluated. The physico-chemical properties of the formulations were examined by differential scanning calorimetry, X-ray diffraction, and scanning electron microscopy. Drug release profiles showed that AP dissolution from the CNP-AP system (weight ratio, 6:1) after 60 minutes improved by 275% compared with that of pure AP. Moreover, the pharmacokinetic analysis of SD formulations in rats showed that the AP area under the curve_{0-t} value was 1.83 times higher for the CNP-AP system than for pure AP, indicating that its bioavailability was significantly improved. In addition, compared with pure AP, SDs had a significantly higher peak and shorter time to peak. Preliminary intestinal toxicity tests indicated that there was no significant difference in the tissues of the rats treated with the CNP-AP system, rats treated with the CNP alone, and controls. In conclusion, CNP-based SDs could be used for enhancing the bioavailability of poorly water-soluble drugs while also improving drug safety.

Keywords: apigenin, carbon nanopowder, solid dispersions, dissolution, oral bioavailability

Introduction

Apigenin (AP), a common bioactive flavonoid, is found in a wide variety of fruits, plants, and vegetables. It has an antiproliferative activity against pancreatic, colorectal, skin, neuroblastoma, and breast cancer cell lines.¹⁻⁵ However, the oral bioavailability of AP is relatively low because of its low lipid (0.001–1.63 mg/mL in nonpolar solvents)⁶ and water (2.16 µg/mL in water)⁷ solubility, which has severely limited its clinical development. Therefore, it is necessary to develop new technologies or formulations to improve AP bioavailability.

According to the Biopharmaceutics Classification System, AP is a class II drug with high intestinal membrane permeability and poor solubility,⁷ which can be improved by increasing the dissolution rate of the drug. Numerous studies have shown that solid dispersion (SD) is a successful and widely used approach to enhancing the dissolution rate of poorly water-soluble drugs.⁸⁻¹¹ In this system, the solubility and dissolution rate of poorly water-soluble drugs can be improved by reducing particle size, enhancing wettability and porosity, and changing the drug state from crystalline to amorphous.¹²⁻¹⁴ At this time, different novel carriers, such as silica nanopowder, are used in SDs.¹⁵ It also has been shown that the dissolution profile can be improved using nanograde SD carriers.

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Carbon nanopowders (CNPs) are carbon nanomaterials with a one-dimensional diameter of less than 100 nm. They are small and have many unique features, including inherent chemical inertness, high dispersibility, and a large specific surface area,^{16–20} which help reduce drug particle size to molecular levels and improve drug dispersion. Carbon nanomaterials have been widely used as drug delivery agents, particularly in targeted therapy.^{21–24} Because nanomaterials have been successfully applied in SDs, the application of CNP as a carrier for an SD preparation is expected to enhance drug solubility.¹⁵ However, there are few reports describing the development of SD, using CNP as the dispersing carrier. The aim of this study was to prepare a novel CNP-AP SD to improve the dissolution rate and oral bioavailability of poorly water-soluble drugs.

Materials and methods

Materials

AP (98%) was purchased from Nanjing Zelang Science and Technology Co, Ltd (Nanjing, People's Republic of China). Luteolin (purity, >99%) was purchased from National Institute for the Control of Pharmaceutical and Biological Products (Chongwen, Beijing, People's Republic of China). CNP (average diameter, 40 nm; purity, >99%; color, black; morphology, almost spherical; true density, 0.43 g/cm³; powerful specific surface area, >1,400 m²/g; electrical conductivity, 0.2 $\Omega \cdot \text{cm}$) was purchased from Beijing Deco Daojin Ltd (Beijing, People's Republic of China). All reagents were of analytical grade except methanol, which was of chromatographic grade. Double-distilled water prepared in our laboratory was used.

Animals

Male Sprague-Dawley rats (body weight, 220 \pm 10 g) were obtained from Experimental Animal Center of the Jiangsu Provincial Academy of Chinese Medicine (Nanjing, People's Republic of China). Before the experiments, the rats were housed in a temperature- and humidity-controlled room (23°C; air humidity, 55%) with free access to water. All animal experiments were reviewed and approved by the Institutional Animal Care and Use Committee of the Jiangsu Provincial Academy of Chinese Medicine.

Preparation of SDs and physical mixture systems

SDs of AP and CNP were prepared by solvent evaporation. Briefly, AP and CNP (weight ratios, 1:2, 1:4, 1:6, and 1:8) were dissolved in ethanol to a concentration of 0.4 mg \cdot mL⁻¹

and evaporated in a rotary evaporator over a water bath maintained at 40°C until a clear mixture was formed. The physical mixture (PM) of AP and CNP was prepared by mixing AP with CNP at a ratio of 1:6 (weight:weight) and then grinding them thoroughly, using a mortar and pestle, until a homogeneous mixture was obtained.

In vitro dissolution study

Ultrapformance liquid chromatography analysis of AP

The concentration of AP in the dissolution medium was determined by ultrapformance liquid chromatography (UPLC; Waters Acquity, Milford, MA, USA), using a BEH C18 column (50 mm \times 2.1 mm, 1.7 μm) with a mobile phase of acetonitrile and 0.1% formic acid (30:70, volume:volume) at a flow rate of 0.3 mL \cdot minute⁻¹ and ultraviolet detection at 330 nm. All samples were filtered through membrane filters (0.22 μm ; Millipore Corp, Billerica, MA, USA) before use, and the injection volume was 4 μL . The linear calibration curve was obtained in the concentration range of 0.22–21.60 $\mu\text{g/mL}$, with a correlation coefficient of 0.9996.

In vitro dissolution test

The pharmaceutical performance of pure AP and its SDs was assessed by performing an in vitro dissolution test. The test was performed according to the US Pharmacopeia apparatus 2 (paddle) method, using a Beiyang SR8 plus dissolution apparatus (D-800LS dissolution apparatus; Tianjin University exact apparatus Co., Ltd., Tianjin, People's Republic of China) at 37°C, with constant stirring at 100 rpm.

Each powder sample (equivalent to 5 mg AP) was added to the dissolution medium (900 mL distilled water containing 0.4% sodium dodecyl sulfate), and then 5 mL samples were collected and replaced with a temperature-equilibrated dissolution medium at fixed time intervals. The samples were filtered through a 0.22 μm membrane, and the AP content was analyzed by performing UPLC, as described earlier. Data are expressed as mean \pm standard deviation. Statistical comparisons were made using the analysis of variance test and SPSS 18.0 software (IBM, Armonk, NY, USA) for groups at each time.

Characterization of AP SDs

Differential scanning calorimetry

Differential scanning calorimetry (DSC) curves of AP, CNP, PM, and SD were obtained using a DSC 204A/G Phoenix[®] instrument (Netzsch, Selb, Germany) in a nitrogen atmosphere with a flow rate of 100 mL \cdot minute⁻¹. Solid samples

were dried at 40°C before analysis to remove residual water. During the test, each sample was heated from 10°C to 500°C at increasing increments of 10°C/minute.

Scanning electron microscopy

The shape and surface morphology of the powder samples were examined using a scanning electron microscope (S-3000N; Hitachi, Tokyo, Japan).

X-ray diffraction

Powder X-ray diffraction (XRD) patterns were assessed using an XRD system (D8-Advance; Bruker, Karlsruhe, Germany), and the diffraction pattern was recorded with primary monochromated radiation over a 2θ range of 0°–70°. The step size used was 0.04, at a rate of 10 seconds per step.

Bioavailability study

Animal experiment

Eighteen male Sprague-Dawley rats (weight, 280±20 g) randomly divided into three groups were fasted for 12 hours with free access to water before the experiments. They received oral formulations (AP, AP-PM, and AP-SD with an AP/CNP ratio of 1:6) at a dose equivalent to 60 mg/kg of AP. Plasma samples (0.4 mL) were collected from the eye vein at 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after treatment. Then, the plasma samples were separated by centrifugation at 3,000 rpm for 10 minutes and stored at –40°C until analysis.

Sample preparation and UPLC analysis

The AP concentration in blood samples was determined by performing UPLC, as described earlier, except that luteolin was used as an internal standard. The linear calibration curve was obtained between 0.1 and 11.4 µg/mL, with a correlation coefficient of 0.9995. The results obtained from the relative recoveries of high, middle, and low concentrations were 108.21%±17.39%, 104.23%±14.64%, and 93.15%±7.22%, respectively. All of the absolute recoveries were above 80%, with all relative standard deviation values being less than 15%, which was within the acceptable limits to fulfill the guidelines for bioanalytical methods.

Frozen plasma samples were thawed at room temperature and prepared for analysis. Briefly, 0.2 mL methanol containing luteolin (1.1 µg/mL) was added to 0.2 mL of a plasma sample as an internal standard. Then, 600 µL methanol was added and the mixture was vortex-mixed for 5 minutes to extract AP and luteolin. After centrifugation at 13,000 rpm for 10 minutes, the precipitate containing proteins and carbon nanomaterial was

discarded. The supernatant was collected and evaporated to dryness under a gentle stream of nitrogen. Finally, the residue obtained was resuspended in 200 µL methanol and centrifuged at 13,000 rpm for 10 minutes. Four microliters of supernatant was injected into the UPLC system for analysis.

Data presentation and analysis

The main pharmacokinetic parameters, including peak concentration (C_{max}), time to maximum, and area under the curve (AUC_{0-t} and $AUC_{0-\infty}$), were determined by a compartmental analysis using the software program DAS version 1.0 (Chinese Pharmacology Society, Beijing, People's Republic of China). Data are expressed as mean ± standard deviation. Statistical comparisons were made using the analysis of variance test and the SPSS 18.0 software for groups at each time. A *P*-value less than 0.05 was considered to be statistically significant.

Intestinal toxicity evaluation of carbon nanopowder

Twenty-four male Sprague-Dawley rats (weight, 280±20 g) were used to study the effect of CNP treatment on the intestine. The rats were randomly divided into four groups (six rats each). CNP, PM, and SD (AP/CNP ratio of 1:6) at a dose equivalent to 60 mg/kg of AP were orally administered to three groups, and one group received the same volume of saline solution. After 2 weeks, the rats were killed and the jejunum was excised. Samples were fixed with 10% formalin, followed by paraffin embedding and hematoxylin-eosin staining. Finally, the mucosal structure of the samples was observed under a light microscope (Olympus DX45; Olympus Corporation, Tokyo, Japan).

Results and discussion

In vitro dissolution study

The in vitro dissolution profiles of AP and different SD formulations are shown in Figure 1. Compared with AP alone, SDs showed higher dissolution of AP at different AP/CNP ratios. Only approximately 38% of AP was dissolved from the AP powder during the 180-minute study period under the experimental conditions (900 mL distilled water containing 0.4% sodium dodecyl sulfate). However, approximately 92% of AP was dissolved from the SD with an AP/CNP ratio of 1:6 within 60 minutes, which suggested that the carrier greatly improved the dissolution behavior of AP. Dissolution might have been enhanced because of the disordered structure of amorphous SDs.²⁵ The dissolution rates of poorly water-soluble drugs fenofibrate and celecoxib markedly increased with the use of mesoporous carbon.^{26,27} Our results indicated that AP dissolution did not increase significantly when the

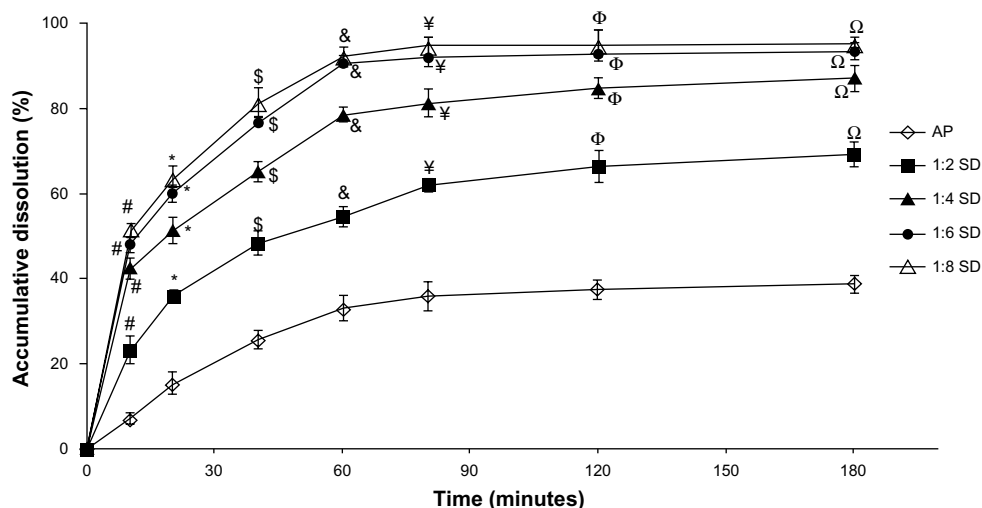


Figure 1 The dissolution profiles of AP and SDs at different AP/CNP ratios of 1:2, 1:4, 1:6, and 1:8.

Notes: Each point represents the mean \pm standard deviation ($n=3$). * $P<0.01$ versus pure AP at 10 minutes; * $P<0.01$ versus pure AP at 20 minutes; * $P<0.01$ versus pure AP at 40 minutes; * $P<0.01$ versus pure AP at 60 minutes; * $P<0.01$ versus pure AP at 80 minutes; * $P<0.01$ versus pure AP at 120 minutes; * $P<0.01$ versus pure AP at 180 minutes.

Abbreviations: AP, apigenin; SD, solid dispersion; CNP, carbon nanopowder.

AP/CNP ratio reached 1:8 ($P>0.5$ versus an AP/CNP ratio of 1:6; Figure 1). Therefore, the SD with an AP/CNP ratio of 1:6 was selected for further study.

Characterization of AP solid dispersion

Differential scanning calorimetry

Figure 2 shows the results of the DSC analysis of AP, CNP, PM, and SD. The DSC curve of AP (Figure 2A) had a sharp endothermic peak at approximately 365°C corresponding to the melting point of AP and indicating its crystalline nature. This is in agreement with the results reported by Zhang et al.²⁸ However, the characteristic AP peak completely disappeared in the SD with an AP/CNP ratio of 1:6

(Figure 2C), suggesting that AP was molecularly dispersed and might have been in an amorphous form, which facilitated dissolution. A broad endothermic peak appeared at approximately 95°C, indicating water loss resulting from the hygroscopic nature of CNP (Figure 2B). Furthermore, both the drug endothermic peak and dehydration peak were observed in the PM with an AP/CNP ratio of 1:6, which indicated there was no interaction between AP and CNP in the PM.

Scanning electron microscopy

The results of the scanning electron microscopy analysis of AP and the SD with an AP/CNP ratio of 1:6 are shown in Figure 3. AP particles exhibited flat broken needles of different size, with a smooth surface (Figure 3A). In contrast, no AP particles were observed in the SD, indicating that AP was well dispersed in CNP (Figure 3B).

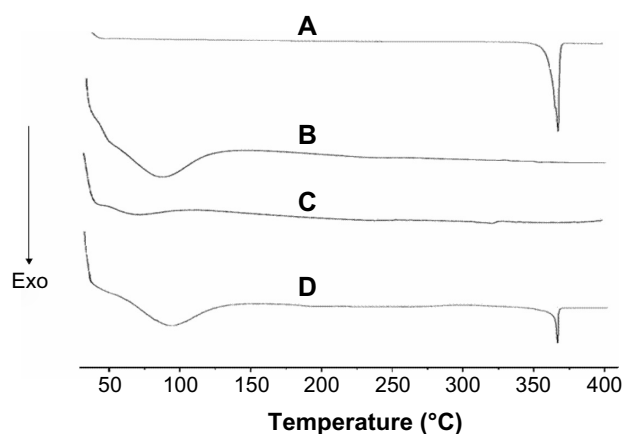


Figure 2 DSC curves of AP (A), CNP (B), SD at AP/CNP ratio of 1:6 (C) and AP/CNP 1:6 PM (D).

Abbreviations: Exo, exothermic direction; DSC, differential scanning calorimetry; AP, apigenin; SD, solid dispersion; CNP, carbon nanopowder; PM, physical mixture.

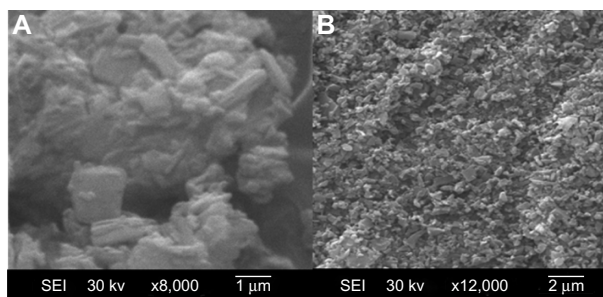


Figure 3 SEM of AP (A) and AP solid dispersion prepared with an AP/CNP ratio of 1:6 (B); magnification, 8,000 \times .

Abbreviations: SEM, scanning electron microscopy; AP, apigenin; CNP, carbon nanopowder; SEI, secondary electrons image.

XRD

The powder XRD patterns of AP, CNP, PM, and SD are shown in Figure 4. AP showed characteristic peaks at diffraction angles (Figure 4A), but no typical peaks were found in the XRD patterns of CNP (Figure 4B). As shown in Figure 4D, the XRD pattern of the PM was almost identical to that of AP alone. In contrast, the major AP peaks were not observed in the SD (Figure 4C). XRD results suggested that AP existed in an amorphous state in the SD, which was also demonstrated by the DSC analysis.

Oral bioavailability

Pharmacokinetic studies in rats were carried out to evaluate the oral absorption of AP and its SD and PM. The mean plasma concentration–time profiles of AP after oral administration are shown in Figure 5. The main pharmacokinetic parameters are listed in Table 1. Compared with AP alone and PM, the SD system showed a significant improvement in C_{max} and AUC_{0-t} . Oral administration of AP alone resulted in very low AP blood levels, with a C_{max} of $1.33 \pm 0.24 \mu\text{g/mL}$ and AUC_{0-t} of $11.76 \pm 1.52 \mu\text{g} \cdot \text{hour/mL}$. In contrast, the C_{max} and AUC_{0-t} values for the SD system reached $3.26 \pm 0.33 \mu\text{g/mL}$ and $21.48 \pm 2.83 \mu\text{g} \cdot \text{hour/mL}$, respectively (Table 1). These results indicate that the SD enhanced the relative oral bioavailability of AP by approximately 183%. Furthermore, compared with AP alone and PM, SD was associated with a short time to maximum. These results were relatively consistent with the results of the dissolution test, suggesting that the enhanced oral bioavailability of the SD might be partly attributable to the increased drug dissolution and absorption rates in rats. Previous studies have demonstrated that a significant increase in the drug dissolution rate might result in higher drug permeability between the gastrointestinal

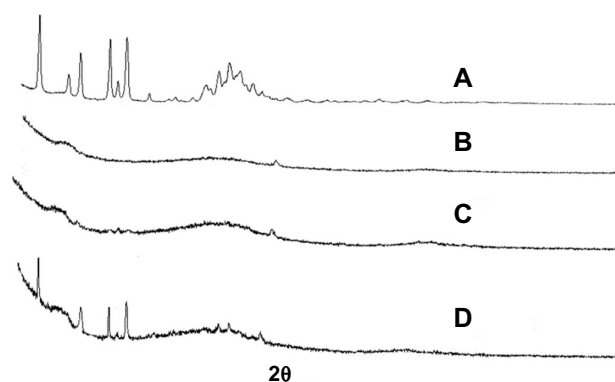


Figure 4 X-ray diffraction.

Notes: (A) AP, (B) CNP, (C) AP/CNP ratio of 1:6 (w/w) SD, and (D) AP/CNP ratio of 1:6 (w/w) PM.

Abbreviations: AP, apigenin; CNP, carbon nanopowder; PM, physical mixture; SD, solid dispersion; w/w, weight/weight.

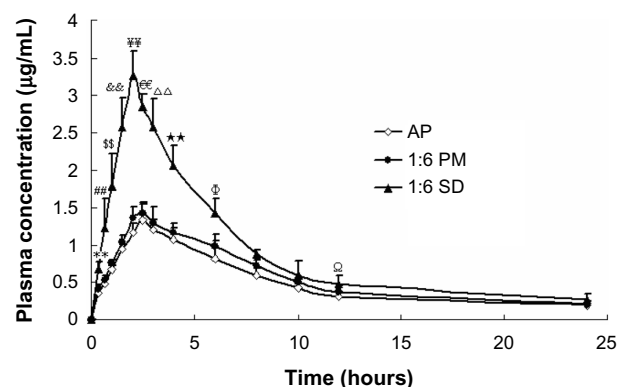


Figure 5 Mean plasma concentration–time curve of AP in rats after oral administration of AP, SD (AP/CNP ratio of 1:6), and PM (AP/CNP ratio of 1:6) equivalent to 60 mg kg^{-1} of AP ($n=6$), respectively.

Notes: Values are mean \pm SD ($n=6/\text{group/time point}$). $**P<0.01$ versus pure AP at 0.33 hours; $***P<0.01$ versus pure AP at 0.67 hours; $^{**}P<0.01$ versus pure AP at 1 hour; $^{**}P<0.01$ versus pure AP at 1.5 hours; $^{**}P<0.01$ versus pure AP at 2 hours; $^{**}P<0.01$ versus pure AP at 2.5 hours; $^{**}P<0.01$ versus pure AP at 3 hours; $^{**}P<0.01$ versus pure AP at 4 hours; $^{*}P<0.05$ versus pure AP at 6 hours; $^{*}P<0.05$ versus pure AP at 12 hours.

Abbreviations: AP, apigenin; CNP, carbon nanopowder; SD, solid dispersion; PM, physical mixture.

lumen and blood, leading to higher drug bioavailability.²⁹ In addition, the PM had slightly higher bioavailability than pure AP (Table 1), which might have been caused by the absorption-promoting activity of CNP.

Intestinal toxicity evaluation of CNP

The jejunum mucosal structure of rats in the four treatment groups is shown in Figure 6. There were no notable differences in the mucosal structure among the groups (Figure 6A–D). In all groups, the morphology of the jejunum mucosa was normal, and goblet cells were present. There was no degeneration, necrosis, interstitial congestion, edema, or inflammatory cell infiltration in the mucosa, submucosa, muscular, or serosa cells. These preliminary results indicated there were no toxic effects on rat mucosa 2 weeks

Table 1 The main pharmacokinetic parameters of AP after oral administration of AP, PM (AP/CNP ratio of 1:6) or SD (AP/CNP ratio of 1:6) in rats in a dose of 60 mg/kg

Parameters	Pure AP	SD	PM
T_{max} (h)	2.5 ± 0.33	$2.0 \pm 0.28^{**}$	2.5 ± 0.36
C_{max} ($\mu\text{g/mL}$)	1.33 ± 0.24	$3.26 \pm 0.33^{**}$	1.43 ± 0.18
$t_{1/2}$ (h)	4.198 ± 0.29	3.37 ± 0.46	4.337 ± 0.32
AUC_{0-t} ($\text{h} \cdot \mu\text{g/mL}$)	11.763 ± 1.52	$21.483 \pm 2.83^{**}$	13.55 ± 1.44
$AUC_{0-\infty}$ ($\text{h} \cdot \mu\text{g/mL}$)	12.022 ± 2.61	$26.53 \pm 3.84^{**}$	13.897 ± 3.19
Relative bioavailability (%)		183	115

Notes: Data are expressed as the mean \pm standard deviation ($n=6$). $**P<0.01$, versus 60 mg/kg pure AP.

Abbreviations: AUC, area under the curve; C_{max} , peak concentration; CNP, carbon nanopowder; AP, apigenin; SD, solid dispersion; PM, physical mixture; T_{max} , time to C_{max} ; $t_{1/2}$, half life.

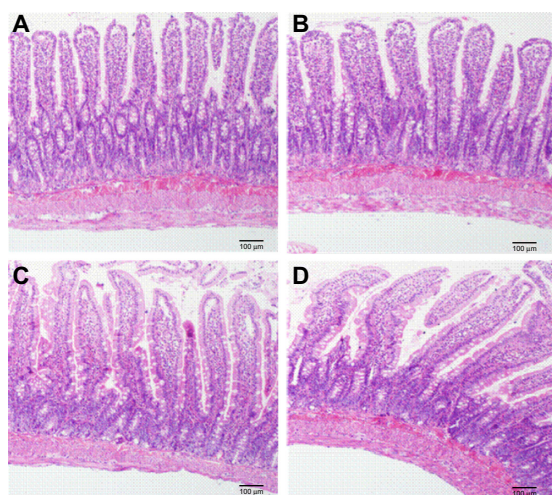


Figure 6 Influences of CNP, SD (AP/CNP ratio of 1:6), and PM (AP/CNP ratio of 1:6) pretreatment on mucosal structures of rats.

Notes: (A) control group, (B) CNP group, (C) SD group, and (D) PM group. Magnification, 100 \times .

Abbreviations: CNP, carbon nanopowder; AP, apigenin; SD, solid dispersion; PM, physical mixture.

after exposure to CNP and SD. However, further research is needed to evaluate CNP toxicity.

Conclusion

In this study, a novel SD formulation of AP for oral administration was prepared using CNP. The results demonstrated that CNP-based SD was a successful strategy to improve the dissolution behavior and oral bioavailability of AP. SDs prepared with water-soluble polymer carriers are usually soft and sticky and have poor flow properties, which hinders their application in large-scale pharmaceutical formulation.^{11,30,31} In this study, SDs prepared with CNPs were not sticky and flowed freely, which may facilitate the downstream processing of solid formulations. Thus, we can conclude that CNP has great potential for clinical application as a novel and promising SD carrier.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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