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Short Communication

Preparation of highly stable diclofenac potassium pellet with microcrystalline cellulose by extrusion–spheronization

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ABSTRACT

The main purpose of this study is to prepare highly stable diclofenac potassium (DP) pellet with microcrystalline cellulose (MCC) by extrusion–spheronization. Using MCC, DP pellets were prepared and the stability was investigated. Related compounds of DP pellets were analyzed by High Pressure Liquid Chromatography (HPLC). After stability test of 60 °C/75% RH for 10 d, the values of two main related compounds were 0.94% and 2.17%, respectively. Compatibility tests show that instability of DP was mainly caused by MCC. To improve the stability of DP in presence of MCC, different kinds of stabilizers were investigated. Upon addition of 1.5% (w/w) sodium hydroxide, the primary related compound of pellets was reduced to be 0.159% after stability test of 60 °C/75% RH for 50 d. This study demonstrated that MCC induced decomposition of DP upon exposure to moisture could be prohibited by addition of sodium hydroxide. The mechanisms were discussed and residual hydroxyl free radicals in excipients were responsible for decomposition of DP. Finally, this formulation of DP is highly stable with sustained-release behavior.

1. Introduction

Diclofenac potassium (DP), a nonsteroidal anti-inflammatory drug, is a derivative of phenylacetic acid. It has excellent antipyretic, analgesic, and anti-inflammatory properties [1]. DP can be made into matrix sustained-release pellets via extrusion–spheronisation in consideration of the needs of daily treatment and the nature of the drug itself [2]. It has been found that matrix pellets were bioequivalent to the commercially available tablet (Voltaren®) and it's better for DP to make it into matrix pellets than double membrane-controlled type by comparison of performance of coated pellets and matrix tablets in vivo [3].

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Table 1 – Formations of pellets.

Formation no.	DP (g)	MCC (g)	Carbomer 974P (g)	$CaCl_2$ (g)	Tween-80 (g)	$NaCO_3$ (g)	Cysteine hydrochloride (g)	L-Cysteine (g)	Na_2SO_3 (g)	L-Cystine (g)	NaOH (g)
1	25	64	4	1	5	1	–	–	–	–	–
2	25	64	–	–	–	–	5	–	–	–	–
3	25	64	–	–	–	–	–	5	–	–	–
4	25	64	–	–	–	–	–	–	5	–	–
5	25	59	4	1	5	1	–	–	5	–	–
6	25	57	4	1	5	1	–	–	–	5	2
7	25	59	4	1	5	1	–	–	–	5	–
8	25	62	4	1	5	1	–	–	–	–	2
9	25	62.5	4	1	5	1	–	–	–	–	1.5
10	25	63.5	4	1	5	1	–	–	–	–	0.5

–: Not added.

To prepare matrix pellets, microcrystalline cellulose has been considered as a crucial excipient by extrusion–-spheronization. MCC is called as molecular sponge because of its strong ability to maintain moisture due to its large surface area and high internal porosity [4]. Moreover it prevents phase separation during extrusion or spheronization by controlling the movement of water through the plastic mass [5]. Although wetted microcrystalline cellulose has excellent characteristics for process of extrusion–spheronization, there are some reports exhibiting the chemical incompatibility of MCC with a number of drugs, such as ranitidine, thiamine and ketorolac [6–8]. The possible reason for this incompatibility was acid, alkali and bleach used when MCC was prepared. Therefore, it is necessary to examine the compatibility of MCC and drugs before pellets preparation using extrusion–spheronisation method.

In response to incompatibility of MCC with drugs, other excipients such as powdered cellulose and starch were used instead of MCC [9]. However, MCC is irreplaceable as a promoting agents contributing to formation of matrix pellets when pellets were prepared using HPMC or Carbomer due to their high viscosity.

In this study DP pellets with microcrystalline cellulose were previously prepared with poor stability. For this, compatibility tests were carried out and different stabilizers were evaluated. It was found degradation of DP during preparation of pellets was caused by MCC and there were two kinds of primary products of degradation of DP. With the addition of 1.5% (w/w) sodium hydroxide, MCC-based DP matrix pellets were successfully prepared with high stability and sustained-release pattern.

2. Materials and methods

2.1. Materials

Diclofenac potassium (DP) was provided by Kangenbei Pharmaceutical Company (Jinhua, Zhejiang, China). Microcrystalline cellulose (MCC, Avicel PH101) was offered by Huzhou Zhanwang Chemical Company (Huzhou, China). Calcium chloride anhydrous ($CaCl_2$), sodium carbonate anhydrous (Na_2CO_3), sodium sulfite anhydrous (Na_2SO_3), sodium hydroxide (NaOH), polysorbate 80 (Tween-80), L-cysteine, cysteine hydrochloride, L-cystine, sodium dihydrogen phosphate (NaH_2PO_3), and potassium dihydrogen phosphate (KH_2PO_3) were obtained from Bodi Chemical Company (Tianjin, China). Carbomer 974P (Carbopol®974P NF) was supplied by Noveon (China) Inc. Phosphoric acid (H_3PO_4) was obtained from Shenyang Economic and Technological Development Zone Reagent Factory (Shenyang, China). Methanol of chromatographic grade was purchased from Concord Technology Co., Ltd (Tianjin, China). All the other reagents were of analytical grade.

2.2. Methods

2.2.1. Compatibility tests

MCC, Na_2CO_3, $CaCl_2$, Carbomer 974P and Tween-80 were used in the previous formulation of DP pellets and water was used as a wetting agent in the process of pellets preparation. According to Table 2, the wet granulation was prepared by mixing DP with the individual excipients using water, respectively. The obtained granules were dried at 40 °C for 12 h. To evaluate the stability of DP in presence of different excipients, the dried particles were placed at 60 °C in a calorstat oven for 10 d. In parallel, stability of DP in physical mixture of DP and MCC was also examined in the same manner.

2.2.2. Preparation of pellets

All the pellets were made via the extrusion–spheronization according to formations in Table 1. The solid powders of DP, MCC, Carbomer 974P were accurately weighed and blended completely. Tween-80, $CaCl_2$, Na_2SO_3 or Na_2CO_3 were dissolved in water. Then the solutions were added to the powder mixture to prepare damp mass, which was then passed through a single screw extruder (WL350, Wenzhou Pharmaceutical Equipment Factory, China) with a 1.0 mm screen at 150 rpm. The extrudates were processed in a spheronizer (WL350, Wenzhou Pharmaceutical Equipment Factory, China) furnished with a cross-hatched plate rotated at 300 rpm for about 30 min. The obtained pellets were dried at 40 °C for 12 h.

2.2.3. Stability test

All the pellets prepared in 2.2.2 and the corresponding physical mixtures were placed in 60 °C/75% RH for 10 d. Separately, pellets of F_9 were placed for 50 d. Then the related substances were assayed.

Table 2 – Stability of DP in compatibility tests.

Excipients in particles	Ratio of excipients to drug (w/w)	Percentage of the related substances	
		Related substance C (%)	Related substance B (%)
$CaCl_2$	1:25	0.05	0.04
Carbomer 974P	4:25	0.06	0.06
Tween-80	5:25	0.05	0.04
Na_2CO_3	1:25	0.06	0.03
MCC[1]	64:25	0.94	2.17

2.2.4. *Dissolution test*

Dissolution testing of the pellets of F_9 and Voltaren® were performed according to USP31-NF26 Apparatus II (paddle) at 100 rpm in 900 ml PBS buffer solution (pH 6.2) at 37 ± 0.5 °C. At different time intervals (0.25,0.5,1, 2, 3, 4, 6, 8, 10 and 12 h), 4 ml samples were withdrawn and replaced by fresh medium. The drug content was determined at 276 nm (UV-7504, UV/Vis spectrophotometer, Xin Mao Instrument Company, Shanghai, China).

2.2.5. *Analyzing method of related substance*

Related substance was measured by High Pressure Liquid Chromatography (HPLC) according to British Pharmacopoeia (2010). An HPLC system (HITACHI L-2000, Hitachi Limited, Japan) equipped with an auto sampler and a UV detector set at 254 nm was used for the analysis of the related substance of DP according to British Pharmacopoeia (2010). The method used an Agilent® spherisorb C_8 column (250 × 4.6 mm, 5 μm) with a mobile phase consisting of methanol:phosphoric acid buffer salt (pH = 2.5) (66:34). The flow rate was 1.0 ml/min.

Appropriate amount of the tested substances, made into DP solution with the concentration of 500 μg/ml as a sample, was dissolved with methanol. The sample above was diluted with the mixture of methanol and double distilled water (66:34) (v/v) to obtain a final drug concentration of 1 μg/ml as reference solution. The injection volume was 20 μl. The percent values of the related substances were calculated according to the following formula.

$$S = \frac{Ar}{Am} \times 0.2$$

which S was the percent value of the related substance, Ar and Am were the area value of related substance and the main peak of reference solution, respectively.

Table 3 – Stability of DP in MCC-based pellets with different stabilizers.

Formation no.	Time at 60 °C (d)	Percentage of the related substances	
		Related substance C (%)	Related substance B (%)
1	5	0.330	0.576
2	5	0.722	1.283
3	5	0.309	0.699
4	0	0.047	0.029
	5	0.073	0.055
	10	0.067	0.061
5	5	0.477	1.685
	10	0.524	1.788
6	0	0.079	0.065
	5	0.434	1.469
7	0	0.070	0.043
	5	0.041	0.035
	10	0.084	0.074
8	0	0.048	0.026
	5	0.063	0.072
	10	0.123	0.159
9	10	0.087	0.107
	50	0.063	0.099
10	0	0.043	0.022
	5	0.204	0.670

3. Results and discussion

3.1. *Compatibility tests*

Compatibility tests of DP with different excipients were performed and the results were shown in Table 2. It can be seen that the percentage of related substances of particles containing MCC was much higher than other particles consisting of other excipients such as Carbomer 974P, Tween-80. As shown in Table 3, the stability test of F_1 containing MCC was previously carried out and the result indicated high amount of related substances. Therefore it could be concluded that the degradation of drug was resulted from MCC. However, the area percent values of related substances for physical mixture of MCC and DP were only 0.07% and 0.05%, respectively. This lower levels of related substance revealed simple physical mixture could not lead to degradation of drug, whereas MCC would promote the instability of DP in the presence of water.

There were three peaks in Fig. 1a (No. 1–3) in the chromatographs of pellets prepared via extrusion–spheronization containing MCC and DP. According to reference of DP in Fig. 1b, peaks (No. 1 and 3) were of the primary related substances (C and B). The area percent values of related substances (C and B), estimated with respect to the main peak area of reference solution, were recorded in the Table 2. It has been reported that the related substances with similar retention times were diclofenac alcohol and diclofenac aldehyde [10,11]. Based on the results above and with the inspiration of a literature [8] about the effect of antioxidants on the stability of tromethamine salt, this study inferred that there may be a relationship between the instability of the drug and redox reaction.

3.2. *The effect of stabilizers*

Based on the speculation that the instability of the drug may be caused by the oxidation reaction, to improve the stability of DP in presence of MCC, different stabilizers being

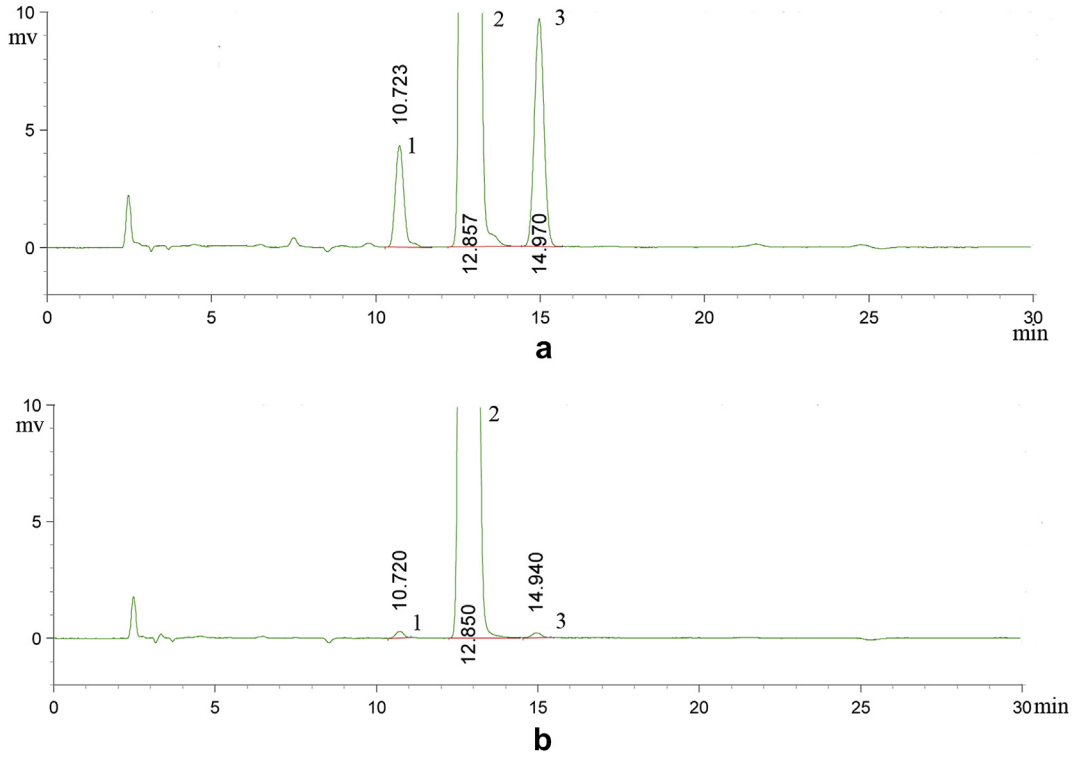

Fig. 1 – The chromatographs of DP pellets and DP. (1,2,3 represent related substance C, DP and related substance B respectively.). a: DP pellets of F1 after 10 d of accelerated stability test. b: DP.

antioxidants, such as sodium sulfite anhydrous, L-cysteine and cysteine hydrochloride were investigated as in Table 2 from F_2 to F_4 and the results were illustrated in Table 3 from F_2 to F_4.

It was obvious that among them only sodium sulfite anhydrous could markedly reduce the degradation of drug from the results of F_2 to F_4. By contrast, L-cysteine and cysteine hydrochloride did not show the effect to enhance the stability of drug. As cysteine was unstable under neutral condition, it was easily changed into cystine due to oxidation reaction at room temperature. Therefore it was speculated that oxidation reaction may occur during the preparation process of pellets so that cysteine could not achieve antioxidative effect. The reducing action of cysteine hydrochloride could inhibit the degradation of drugs theoretically, but aqueous solution of cysteine hydrochloride was acidic. It was inferred that acidic solution may make diclofenac potassium unstable so cysteine hydrochloride could not enhance the stability of DP when it was dissolved with water. Furthermore a strange phenomenon was found in the study: sodium sulfite anhydrous did not inhibit the degradation of drug when the formulation was made into pellets by extrusion–spheronization with other excipients. But this phenomenon could not completely deny the role of sodium sulfite in improving the stability of DP. So it was guessed that there may be reaction between sodium sulfite and other excipients in formulation or sodium sulfite had changes in the process of extrusion–spheronization. Further studies were necessary to verify whether the assumption was correct or not.

L-cystine can promote the function of the cellular redox, so here L-cystine was added intended to stabilize the drug. Although cystine was soluble both in acid and alkali, pellets were made with L-cystine dissolved in sodium hydroxide because that the structure of DP may not stable in acid environment. The results of the stability test of F_6 and F_7 were shown in Table 3. The results of F_6 confirmed that the addition of L-cystine dissolved in NaOH solution could protect DP against degradation. However, in F_7, when grinded cystine was added, stabilization effect did not work. Thus, it was speculated that sodium hydroxide may have profound effect on the stabilization of drug.

There has been also some studies about the effect of pH value on the stability of the drug in some reports [8,12]. Taking all these considerations into account, sodium hydroxide was examined with respect to the stabilization effect on CP in presence of MCC. The results were illustrated from F_8 to F_{10} in Table 3. As seen in Table 3, degradation of DP was slowed down when NaOH (2%w/w) was added. Therefore, it was concluded that it was NaOH rather than L-cystine had the ability to keep drug stable. To further evaluate the stabilization effect of NaOH, different amount of NaOH as 2% (w/w), 1.5% (w/w) and 0.5% (w/w) were added and the results were presented in Table 3. As shown in Fig. 2, with the increase of NaOH, the stabilization effect was increased. With addition of 1.5% and 2.0% of NaOH, the related substances after stability test were qualified. It was concluded that the drug become more stable with the rising of pH value. Here, the formulation with addition of 1.5% NaOH was selected

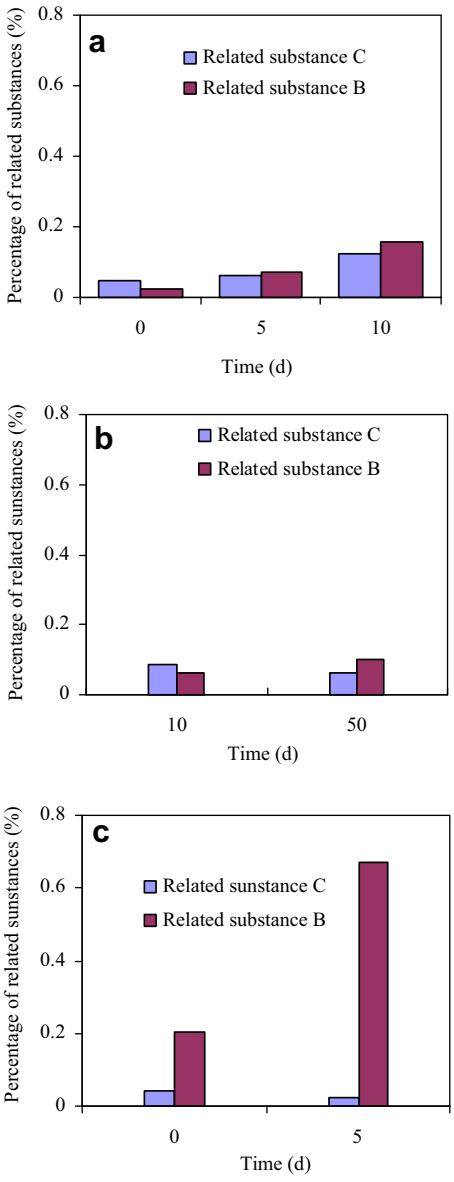

Fig. 2 – Effect of NaOH addition on percentages of primary related substances C and B in DP pellets after accelerated stability test at 60 °C/75% RH. a : 2% (w/w), NaOH, 10 d b: 1.5% (w/w) NaOH, 50 d c: 0.5% (w/w) NaOH, 5 d.

and the stability was verified even after 50 d of accelerated test at 60 °C/75%. RH.

3.3. *Degradation mechanism of DP in presence of MCC*

According to the analysis about impurities, the main degradation products of diclofenac may be diclofenac alcohol and diclofenac aldehyde shown in Fig. 3. The two kinds of specified impurities were also reported in British Pharmacopoeia (2010) about active pharmaceutical ingredients (API) of diclofenac potassium. It was reported that diclofenac aldehyde was found in aqueous degradation of diclofenac by heterogeneous photocatalysis, and the reaction was resulted from hydroxyl free radicals [13–15]. But the mechanism of degradation was not clear.

Dissolved pulps were used to make MCC in the known conventional MCC processes [16–18]. Dissolved pulps may be produced from kraft, soda or sulfite pulp by bleaching and other treatments. Then the repulped material above is then acid hydrolyzed with a mineral acid, such as HCl or H_2SO_4 to dissolve the amorphous cellulose. After neutralization with alkaline, the material is then dried, milled and bagged. It can be seen from the above MCC preparation process that hydrogen peroxide substance was used in the process of to dissolve pulps [18]. Hydrogen peroxide can produce hydroxyl radicals under certain conditions [19], therefore it was suspected that hydroxyl radicals were produced in the processing of bleaching during the preparation of MCC. The hydroxyl radicals in MCC lead to drug oxidation reaction then degradation of drug can happen though decarboxylation. Moreover a research pointed out that the value of pH have an effect on the formation of hydroxyl radicals [15], thus it had an effect on the degradation of diclofenac. When the value of pH was 5, the degradation rate was maximal while with the increasing of pH value degradation rate decreased, especially when it was 10, the degradation rate was minimal. So it was inferred that the addition of NaOH inhibited the degradation though reducing the formation of hydroxyl radicals.

Furthermore, the above preparation process of MCC contains acid hydrolyzed with a mineral acid. From the structure of DP, DP was changed into diclofenac easily under acid condition, and stability of the structure of diclofenac was much lower than diclofenac salts. To protect DP against mineral acid in MCC, the addition of NaOH can stabilize DP as diclofenac salt.

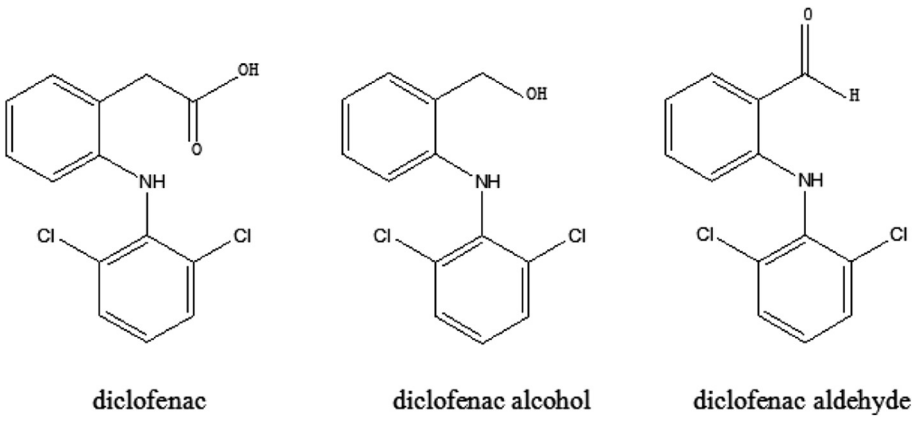

Fig. 3 – Structures of diclofenac and its degradation products.

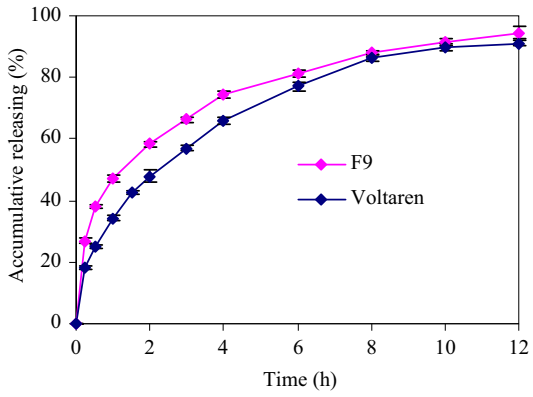

Fig. 4 – The release profile of F_9 and Voltaren® in pH 6.2 phosphate buffered saline ($n = 6$).

3.4. *In vitro release*

With improved stability, the DP MCC-based matrix pellets and commercially available preparation Voltaren® were investigated with respect to in vitro release. As shown in Fig. 4, within 12 h, the release of DP from MCC matrix pellets was continuous and complete and it didn't have obvious difference from Voltaren®.

4. Conclusion

The main related substances of diclofenac potassium sustained-release pellets with MCC after accelerated stability test at 60 °C/75% RH were well-controlled with addition of NaOH. The degradation of DP was speculated to be a free radical oxidation process. Residual free radical in MCC during production process and exposure to moisture are mainly responsible for this decomposition. The stability of DP was effectively increased with addition of 1.5% (w/w) and 2% (w/w) NaOH with maximal amount to be 0.159% of one of the related substances in the accelerated test. The stability of formulation with addition of 1.5% NaOH was verified even after 50 d of accelerated test at 60 °C/75% RH. These formulations of DP loaded MCC-based matrix pellets were stable with well-control release rate.

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