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Research article

Preparation and Drug Release Behavior of Diclofenac Sodium Hydrophilic Matrix Tablets

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ABSTRACT: **Objectives:** Diclofenac sodium, an arthritis drug of wide clinic use, shows good solubility, quick absorption and short half life, and is susceptible to generate high blood concentration fluctuation. In order to improve the weakness, hydrophilic matrix tablets of DS were prepared by using hydroxypropylmethyl cellulose (HPMC) as matrix material. The tablets were prepared by direct compression, and the polymer sort and proportion, the amount of microcrystalline cellulose (MCC), and the hardness of tablets were screened to optimize the formulation and process. The results showed that the ratio of matrix material to drug was the chief factor influencing the release behavior of DS from hydrophilic matrix tablets. With the decrease of matrix material, the drug release became faster and more complete. The addition of MCC changed the release of DS to some extent, especially reducing the burst release within 2 h. The influence of pressure was not so much great that distinct difference in drug release was only observed when the pressure was too high to be 11.5 kg. The optimal matrix tablets of DS showed no apparent burst release, and less than 30% of drug was released at 2 h. The drug continuously released slowly to an accumulative release of 94.3% at 12 h. The Higuchi equation and Ritger-Peppas equation fitted the drug release data well, which indicated a typical sustained release of DS controlled by both diffusion and erosion.

KEYWORDS: Diclofenac Sodium; Hydroxypropylmethyl cellulose; Hydrophilic matrix tablet; Sustained release.

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INTRODUCTION

Hydrophilic matrix tablets have an important position in application and development of sustained-release preparations, and it takes high molecular polymer or natural gums as a framework material. When it comes across water or digestive juice, the polymer absorbs water and causes the skeleton expansion to form a gel barrier to control the release of drug[1,2]. The preparing process of hydrophilic matrix tablets is somewhat simple, generally using direct compression. Katzhendle et al.[3] prepared carbamazepine hydrophilic matrix tablets with

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HPMC (100cps, K4M, K100M) of different viscosity. The gel layer of hydrated matrix tablets not only controlled the drug release by zero order kinetics, but also prevented the transformation of carbamazepine to carbamazepine dihydrate during release. Lu Bing et al. used acid-soluble chitosan and alkali-soluble sodium alginate (1:2) as sustained-release matrix to prepare pH independent sustained-release tablets of nefopam hydrochloride[4]. It solved the problem that the drug release rate changed with the different pH value at different position of gastrointestinal tract. Yin Wei prepared nifedipine hydrophilic matrix tablets by using HPMC K100M and PVP K30 as matrix materials and achieved a sustained release behavior following Higuchi equation[5]. The unique physical, chemical and biological properties of hydrophilic gel carrier materials (neutral or ionic polymer) made them widely used in sustained and controlled-release systems.

There are factors affecting the drug release behavior of hydrophilic matrix tablets, including the sort, hydration rate, viscosity of polymers, ratio of polymer to drug and other excipients used[6-9]. Polymers chiefly dominate the drug release behavior from hydrophilic matrix tablets. The commonly used matrix materials include cellulose derivatives, acrylic polymers and natural polymer, such as methyl cellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), carbomer (Carbopol 934p or 974p), polycarbophil, pectin, sodium alginate, guar gum, chitosan and so on[10]. Among so many materials, HPMC was widely used for preparing hydrophilic matrix tablets, which can produce satisfactory sustained release[11-13]. After given orally, the hydrophilic matrix polymers swell and form gel layer to slow down the drug release rate. Moreover, the polymers can contact with adhesive glycoproteins of mucosa or epithelial cells. The chain segments of polymer molecules interpenetrate with adhesive segments or are embedded in the cell gap, producing bioadhesive phenomenon by mechanical interlocking, electrostatic attraction, Van der Waals force, hydrogen bond and so on. This action prolongs the retention time of matrix tablets quite a lot to ensure the complete release of drug in gastrointestinal tract[10].

Diclofenac Sodium (DS) is widely used for treating different kinds of arthritis[14,15]. The immediate preparations of DS likely produce high fluctuation of blood concentration after administration due to its good solubility, quick absorption and short half-life[16,17]. Sustained and controlled release preparations are the common manner to improve the “peak and trough” phenomenon in vivo. In this work, HPMC was used as matrix material to prepare hydrophilic matrix tablets of DS. The influence of polymer materials, drug-carrier ratio, the amount of filler and the hardness of tablets on drug release behavior was well investigated.

MATERIALS AND METHODS

MATERIALS

Diclofenac sodium (DS) was produced by Anyang Jiuzhou Pharmaceutical Co., Ltd. (Lot 200909026). Diclofenac sodium sustained-release tablets were from Sandoz (China) Pharmaceutical Co., Ltd. (Lot MM023). Diclofenac sodium enteric tablets were manufactured by Beijing Novartis pharmaceutical Co., Ltd. (Lot X0619). Hydroxypropylmethyl cellulose (HPMC) K4M (Lot PD350457) and K15M (Lot PD309252A) were provided by Shanghai Colorcon coating technology Co., Ltd. Other reagents were analytical grade.

PREPARATION OF HYDROPHILIC MATRIX TABLETS OF DS

The DS, HPMC and other excipients were sized through 80 mesh sieve and mixed well. The powder was directly compressed into hydrophilic matrix tablets with 8-mm shallow concave punches. HPMC K4M and HPMC K15M were used as matrix materials and MCC was used as filler. The influence of factors on drug release behavior was investigated to optimize formulation and process, including polymer sort, drug-polymer ratio, the amount of filler and the hardness of tablets

DETERMINATION OF DS

UV spectrophotometric method (UV-2450 UV-Vis spectrophotometer, Shimadzu International Trading Co., Ltd., Japan) was developed to measure the content of DS. DS showed a maximum absorption at 276 nm in phosphate buffer saline (PBS) of pH 6.8, while HPMC and MCC had no absorption at the wavelength. A Calibration curve of DS in PBS (pH 6.8) was established with a good linear relationship within 3-30μg • mL-1. The regression equation was A=0.0297C +0.0125 (r=0.9999). The intra-day and inter-day precision was 0.05%, 0.11%, 0.26% and 0.48%, 0.74%, 0.87% at high, middle, low concentration, respectively. The solution of DS was stable under ambient temperature within 24 h, with RSD of 0.42%, 0.80% and 2.01% for high, middle and low concentration, respectively.

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DRUG RELEASE TEST

According to Method 1 described in Appendix X D of People's Republic of China Pharmacopoeia (Division II, Edition 2010), the drug release behavior of DS from hydrophilic matrix tablets was investigated by using basket device. 1000 ml PBS (pH 6.8) was used as release medium. The test was carried out at 37 ± 0.5 oC and 100 r/min. The samples were taken at 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 4.0 h, 5.0 h, 6.0 h, 8.0 h, 10.0 h and 12.0 h, respectively. After filtered through 0.45 μm microporous membrane, the successive filtrate (diluted when necessary) was tested for absorbance at a wavelength of 276 nm by using UV spectrophotometry. The concentration was calculated by the calibration curve describe in 2.3. The accumulative release amount was then calculated as percentage (Q%). Also, the drug release behavior of the prepared hydrophilic matrix tablets was compared with that of commercially available sustained release and enteric preparations of DS.

STATISTICAL ANALYSIS

Data were expressed as mean ± standard deviation ($\bar{x} \pm SD$), and one-way ANOVA test was used for statistical analysis with SPSS 17.0 software. The results are considered to have a significant difference when $P < 0.05$ and an extremely significant difference when $P < 0.01$.

RESULTS

THE INFLUENCE OF THE SORT AND AMOUNT OF HPMC ON RELEASE BEHAVIOR

Figure 1 showed the influence of DS/HPMC ratio and HPMC sort on release behavior of DS from the hydrophilic gel matrix tablets. With the HPMC amount increased, the drug release lowered in both rate and extent and there were extremely significant difference ($P < 0.01$) between different formulations. The results showed that DS in HPMC K4M matrix tablets released faster when HPMC accounted for a high proportion in formulation. However, DS in HPMC K15M matrix tablets released faster when HPMC amount was low.

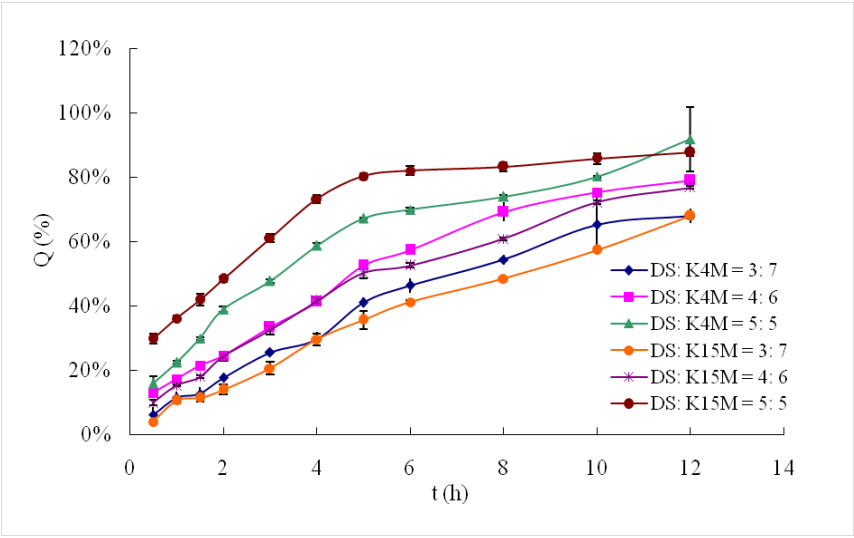

Figure 1. Influence of DS/HPMC ratio and HPMC sort on the release behavior of DS from hydrophilic matrix tablets.(n = 3)

THE INFLUENCE OF THE AMOUNT OF MCC ON RELEASE BEHAVIOR

Addition of MCC improved the shape of hydrophilic matrix tablets and made the process smoothly conducted. No matter how much MCC was used, at a drug-polymer ratio of 1:1, the matrix tablets prepared by HPMC K4M led to less initial burst release and better sustained release when compared with those prepared by HPMC K15M. As shown in Figure 2, although adding MCC in HPMC K4M matrix tablets affected little of the release behavior of DS, the burst release at the beginning was reduced. The release curves of the three matrix tablet formulations made of HPMC K4M showed significant difference with $P < 0.01$ in group. The drug release curves of matrix tablets without MCC showed a similarity factor (f_2) of 72.40 and 54.03 with those containing 1/5 and 1/3 MCC in formulation. The f_2 value between matrix tablets of different MCC amount was 77.54 and no significant difference was observed between their release behavior ($P > 0.05$). When MCC added, the DS release at late stage ascended

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distinctly in HPMC K15M matrix tablets. The three formulations resulted in significantly different drug release curves ($P < 0.01$) in statistics. However, the f_2 value between each other still higher than 50%.

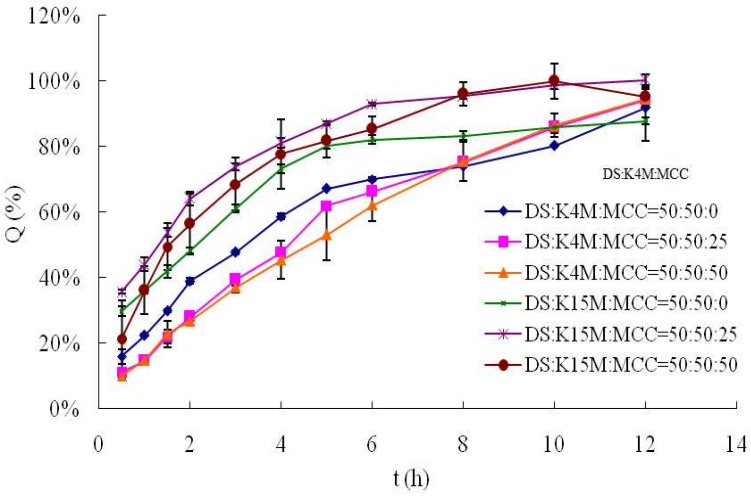

Figure 2. Influence of the amount of MCC on the release behavior of DS from hydrophilic matrix tablets.(n = 3)

THE INFLUENCE OF THE AMOUNT OF HPMC K4M ON RELEASE BEHAVIOR OF MATRIX TABLETS CONTAINING MCC

Fixing the proportion of MCC in formulation, the influence of the amount of HPMC K4M on release behavior of matrix tablets containing MCC was illustrated in Figure 3. The drug release gradually turned fast and complete as the polymer proportion decreased in formulation. A small burst release and a complete sustained release was achieved by formulation of DS:HPMC K4M:MCC at 1:1:0.5.

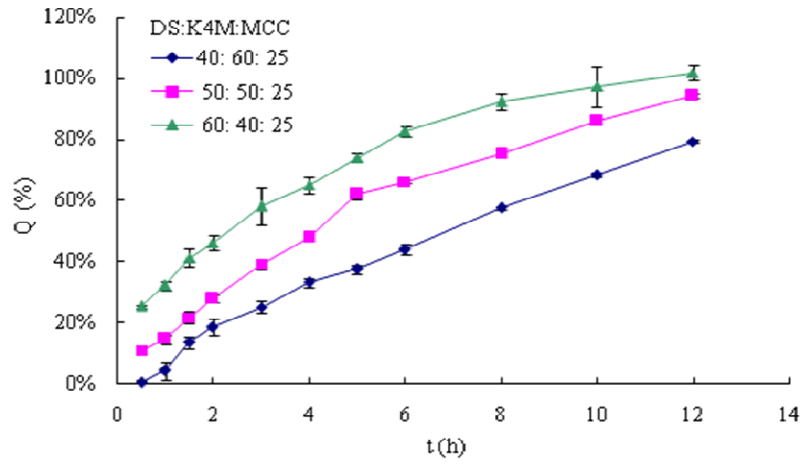

Figure 3. Influence of DS/HPMC K4M ratio on the release behavior of DS from hydrophilic matrix tablets containing MCC.(n = 3)

THE INFULENCE OF HARDNESS ON RELEASE BEHAVIOR

The hardness of hydrophilic matrix tablets had a certain influence on the release of DS (Figure 4). The release of drug tended to decrease with the hardness increased, but the tendency was not absolutely consistent. When the hardness was too high, the rate and extent of drug release dropped distinctly. Statistical results showed that both the matrix tablets of hardness of 3 kg ($P < 0.05$) and 11.5 kg ($P < 0.01$) had significant difference with those of other hardness values tested here. There

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was no significant difference between matrix tablets of hardness of 4 kg and 4.5kg as well as between those of hardness of 6 kg and 8 kg ($P > 0.05$), but the two groups showed significant difference ($P < 0.05$).

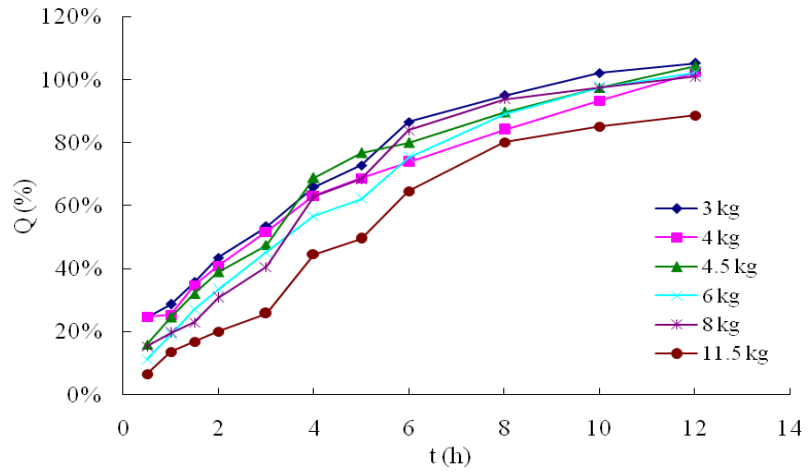

Figure 4. Influence of hardness on the release behavior of DS from hydrophilic matrix tablets.

COMPARISON OF THE RELEASE BEHAVIOR OF DS HYDROPHILIC MATRIX TABLETS WITH COMMERCIAL PREPARATIONS

The release curves of commercial sustained release and enteric tablets and hydrophilic matrix tablets prepared in this work were shown in Figure 5. In PBS (pH 6.8), both hydrophilic matrix tablets and commercial sustained release tablets showed obvious sustained release when compared with commercial enteric tablets. The commercial sustained release tablets exhibited a faster initial release than hydrophilic matrix tablets within 2 hours. After 3 hours, the hydrophilic matrix tablets released DS faster than commercial one and about 94.3% of the drug was released at 12 h, which was almost 20% higher than commercial one. The similarity factor of drug release was 46.83 between them. By using different mathematic equation to fit the drug release data, DS hydrophilic matrix tablets followed Higuchi and Ritger-Peppas equation well, and the commercial sustained release tablets followed first order kinetics best (Table 1).

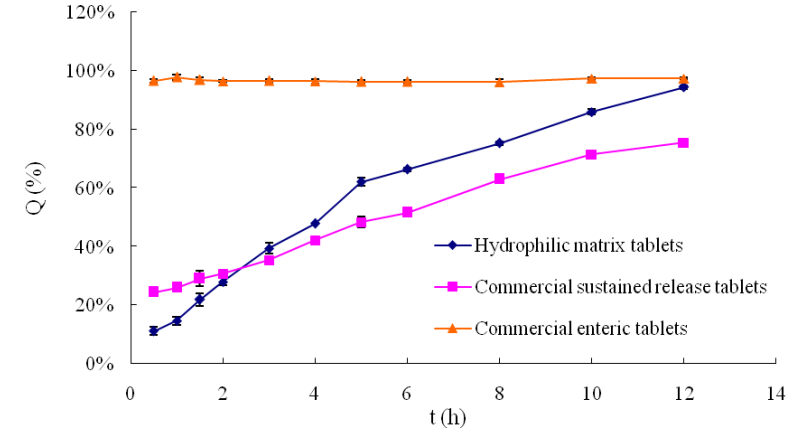

Figure 5. Comparison of the release behavior of DS from hydrophilic matrix tablets with commercial tablets (n = 3)

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Table1. The model fitting of drug release data.

Tablets	Model	Equation	R^2
Hydrophilic Matrix Tablets	Zero order kinetics	Q = 0.1389 + 0.0743t	0.9540
	First order kinetics	Ln(1-Q) = 0.1338 - 0.2219t	0.9664
	Higuchi equation	$Q = -0.1521 + 0.3213t^{1/2}$	0.9916
	Ritger-Peppas equation	$Q=0.1705t^{0.7217}$	0.9881
Commercial Sustained Release Tablets	Zero order kinetics	Q=0.2227＋0.0476t	0.9897
	First order kinetics	Ln(1-Q) = -0.1719 - 0.1021t	0.9902
	Higuchi equation	$Q = 0.0473 + 0.2003t^{1/2}$	0.9753
	Ritger-Peppas equation	$Q=0.2631t^{0.3900}$	0.9395

Note: Q refers to the accumulative release of DS at time t.

DISCUSSION

In this work, DS, a drug of good solubility in water, was prepared into hydrophilic matrix tablets, which generated satisfactory sustained release effect. HPMC is hydrophilic polymer, and it can be hydrated to form gel barrier in water, which hinders the drug release. As the ratio of polymer increased in formulation, the enhanced gel barrier gradually reduced the drug release rate. The hydration rate of low-viscosity HPMC K4M is faster than high-viscosity HPMC K15M. When put into water, HPMC K4M formed gel barrier quickly so that the initial release of its hydrophilic matrix tablets was somewhat slower than that of HPMC K15M. However, due to its low viscosity, the gel layer of HPMC K4M is not so strong as that of HPMC K15M. With the extension of drug release time, HPMC K15M produced better sustained release effect than HPMC K4M at late stage by slowly forming strong gel barrier. Therefore, when the proportion of polymer was relatively low, the advantage of fast hydration of HPMC K4M resulted in a slower DS release compared with HPMC K15M.

In hydrophilic matrix tablets, the drug is released mainly through diffusion and erosion. From the results of model fitting of drug release data, the Higuchi Equation and Ritger-Peppas Equation fitted the data of hydrophilic matrix tablets well. In Ritger-Peppas Equation, n value was 0.7217, which is within 0.45-0.85. It followed that the DS release from hydrophilic matrix tablets was controlled by diffusion and erosion as well.

The addition of MCC showed different influence on DS release from HPMC K15M and HPMC K4M matrix tablets. After coming across release medium, MCC absorbed water and swelled rapidly. The swelling enlarged the gaps in gel layer formed by matrix material so that to make drug release out of the matrix more easily. This influence was even greater in matrix tablets prepared by HPMC K15M of high viscosity, slow hydration and low permeability. With the increase of MCC amount, DS release from HPMC K15M matrix tablets accelerated. However, in matrix tablets of HPMC K4M, the fast hydration weakened the action of MCC so that no distinct influence was observed on drug release.

There is a relationship between drug release and hardness of hydrophilic matrix tablets. The hardness can affect the porosity and tortuosity of matrix tablets[18]. It was shown that drug release rate obviously slowed down at high hardness. The gaps of matrix tablets were squeezed and deformed under strong compression force to obtain high hardness. The porosity decreased and tortuosity increased to form a compact matrix, which had poor permeation to water and retarded release rate of drug.

CONCLUSION

In summary, the hydrophilic matrix tablets of DS were prepared by direct compression simply. The drug released behavior was chiefly dominated by the sort of polymer and the drug-polymer ratio, and influenced by the amount of filler and the hardness of tablets to some extent. Through the comparison of hydrophilic matrix tablets with two different commercial tablets of DS, it was known that the hydrophilic matrix tablets prepared in this work possessed better sustained release behavior than commercial sustained release tablets, which showed low initial burst release and final complete release of DS.

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