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Dual release and molecular mechanism of bilayered aceclofenac tablet using polymer mixture

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ABSTRACT

The objectives of the present study were to develop a controlled-release bilayered tablet of aceclofenac (AFN) 200 mg with dual release and to gain a mechanistic understanding of the enhanced sustained release capability achieved by utilizing a binary mixture of the sustained release materials. Different formulations of the sustained-release layer were formulated by employing hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) as the major retarding polymers. The *in vitro* dissolution studies of AFN bilayered tablets were carried out in intestinal fluid (pH 6.8 buffer). The mechanism of the synergistic rate-retarding effect of the polymer mixture containing HPC and carbomer was elucidated by the rate of swelling and erosion in intestinal fluid and the molecular interactions in the polymer network. The optimized bilayered tablets had similar *in vitro* dissolution profiles to the marketed tablet *Clanza® CR* based on the similarity factor (f2) in combination with their satisfactory micromeritic, physicochemical properties, and stability profiles. Drug release from HPMC-based matrix was controlled by non-Fickian transport, while drug release from HPC-based matrix was solely governed by drug diffusion. The swelling and erosion data exhibited a dramatic increase of water uptake and a reduction of weight loss in the polymer mixture-loaded tablet. Fourier transform infrared (FTIR) spectra revealed strong hydrogen bonding between HPC and carbomer in the polymer mixture. Regarding spatial distribution of polymers in the polymer mixture-loaded tablet, carbomer was found to be the main component of the gel layer during the first 2 h of the hydration process, which was responsible for retarding drug release at initial stage. This process was then followed by a gradual transition of HPC from the glassy core to the gel layer for further increasing gel strength.

1. Introduction

Controlled release oral dosage forms are widely used for numerous therapies and offer better patient compliance, maintain uniform dose levels, and reduce dose frequency as well as side effects (Morita et al., 2000; Vergote et al., 2001). In certain disease conditions, an immediate disposition of the dose needs to be released in the shortest time possible to provide a rapid onset of action, followed by extended drug release to maintain the therapeutic effect (Streubel et al., 2000). In order to obtain this dual drug release concept, many approaches, such as multilayer tablet (Dey et al., 2012; Patra et al., 2007), multi-particulate system (Lopes et al., 2006; Roy and Shahiwala, 2009), and dual release-providing monolithic matrix tablet (Cao et al., 2005) have been applied. Particularly, the bilayered tablet technology has been attracting extensive attention from manufacturers for drug formulation development. Bilayered tablets exhibit some key benefits compared to conventional monolayer tablets. For instance, this technology prevents chemical incompatibilities between the formulation components, including drug-drug and drug-excipient interactions, by physical separation. In addition, bilayered tablets provide pre-determined release profiles by combining layers with various release patterns (Abebe et al., 2014; Vaithiyalingam and Sayeed, 2010).

Aceclofenac (AFN) is an anti-inflammatory pain relief drug that is a derivative of phenylacetic acid. AFN shows excellent effects on toothaches, pain after surgery or childbirth, and chronic articular diseases such as rheumatic arthritis, osteoarthropathy, and ankylosing spondylitis (Brogden and Wiseman, 1996; Noh et al., 2015). Regarding its physicochemical properties, AFN is readily dissolved in an organic solvent but is relatively less soluble in water

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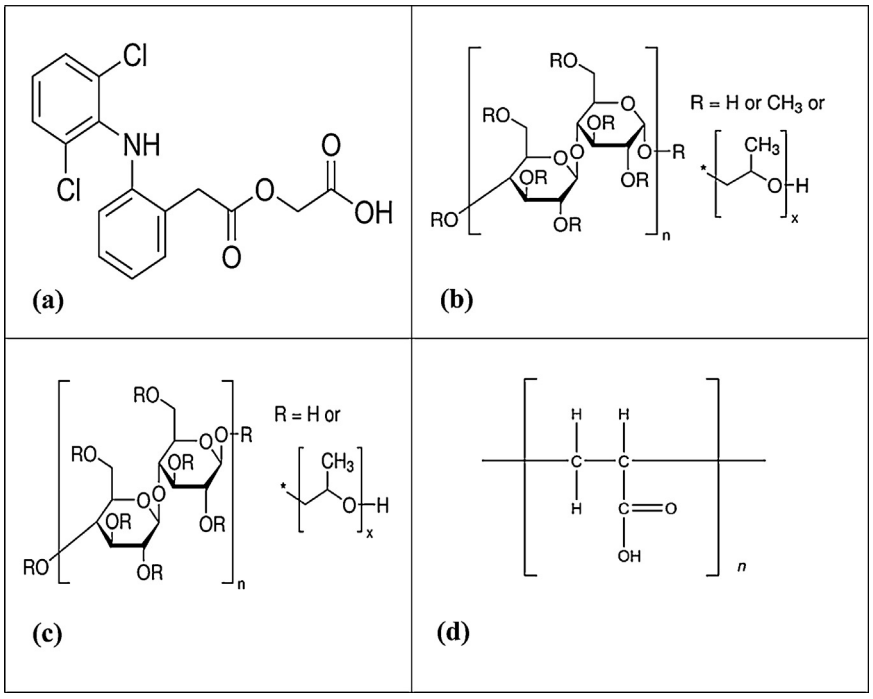

Fig 1. Molecular structures of (a) aceclofenac (AFN), (b) hydroxypropyl methylcellulose (HPMC), (c) hydroxypropyl cellulose (HPC), and (d) carbomer.

(Kumar and Gupta, 2014; Tran et al., 2009). When AFN is taken orally, onset time is within 30 min, time to C_{max} (T_{max}) is approximately 1.5–2.5 h, and duration is approximately 12 h. AFN has a short biological half-life (approximately 4 h), which makes it suitable to be formulated in controlled release dosage form (Dooley et al., 2001; Lee et al., 2013).

Several polymers have been employed in the formulation of matrix-based controlled release drug delivery systems. Cellulose ether derivatives, such as methyl cellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and sodium carboxymethyl cellulose (Na CMC), have become increasingly prominent for hydrophilic matrices because they are simple to formulate, cost-effective, and easy to handle with a good *in vitro–in vivo* correlation (Maderuelo et al., 2011; Salsa et al., 1997). In particular, HPMC is the most frequently used material in hydrophilic matrix tablets, mainly due to its hydrophilic and swelling properties, nontoxicity, and its capability to accommodate high levels of drug loading (Maderuelo et al., 2011). However, because of the increased need for finding suitable polymers to achieve desired drug release patterns, a wide range of both synthetic and natural polymers is screened for their ability to retard the release of specific drug substances. Because discovering a new polymeric substance and testing for its safety is expensive, an attractive alternative strategy is to investigate the use of polymer mixtures of pharmaceutically approved polymeric materials. One potent approach is to combine a nonionic polymer with an ionic polymer to provide better capture of water by the matrix. Consequently, the viscosity of the gel layer and the diffusion path length of the matrix tablet, which are critical factors affecting the drug release rate, in turn increase (Nerurkar et al., 2005).

Carbomer is an anionic polymer of acrylic acid cross-linked with polyalkenyl polyether that can readily hydrate, absorb water, and swell. The hydrophilic nature and highly cross-linked structure of this material render it appropriate for controlled release drug delivery systems (Ravi et al., 2008). However, the matrix tablet using carbomer as the retarding polymer typically has highly variable drug release due to its ionic nature and high sensitivity to the pH of the medium. In addition, the carbomer-based matrix tablet shows a high erosion rate, leading to a catastrophic break-up of the polymeric matrix during the dissolution process. For this reason, carbomer is commonly combined with a secondary polymer to minimize fluctuations and maintain matrix integrity (Maderuelo et al., 2011; Sakeer et al., 2010). For instance, combinations of carbomer and a nonionic polymer, such as HPMC (Perez-Marcos et al., 1996; Samani et al., 2003), polyethylene oxide (PEO) (Kapil et al., 2010; Zhang et al., 2016), and polyvinylpyrrolidone (PVP) (Yusif et al., 2016), have been reported to be used for controlled release purposes. In addition, the inter-polymer complex (IPC) consisting of carbomer and a cationic polymer such as chitosan was prepared to resolve the pH dependency problem of carbomer (Park et al., 2008). Due to the rapid swelling property of carbomer, it was hypothesized that carbomer would facilitate the swelling process of a polymeric matrix when it is combined with a polymer having a retarded swelling rate, thereby preventing the burst release at early stages. HPC was reported to have a low liquid penetration rate coupled with a slow rate of erosion (Sinha Roy and

Table 1
Formulation compositions (mg) of the AFN immediate release layer.

Function	Ingredient	mg/tab
Active ingredient	AFN	110.0
Diluent	Lactose monohydrate	80.0
Diluent	Microcrystalline cellulose (Avicel® PH101)	40.0
Binder	HPC-L	5.0
Disintegrant	Crospovidone (Kollidon® CL)	7.5
Solubilizer	Poloxamer 407	5.0
Lubricant	Magnesium stearate	2.5
Total weight (mg)		250.0

AFN, aceclofenac; HPC-L, low-viscosity hydroxypropyl cellulose.