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Chitosan cocrystals embedded alginate beads for enhancing the solubility and bioavailability of aceclofenac

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ABSTRACT

Enhanced oral bioavailability of aceclofenac has been achieved using chitosan cocrystals of aceclofenac and its entrapment into alginate matrix a super saturated drug delivery system (SDDS). Prepared SDDS were evaluated by various physiochemical and pharmacological methods. The result revealed that the primary cocrystals enhanced the solubility of the drug and the thick gelled polymer matrix that formed from swelling of calcium alginate beads makes it to release the drug in continuous and sustained manner by supersaturated drug diffusion. The C_{max}, T_{max} and relative bioavailability for aceclofenac cocrystal and aceclofenac SDDS were 2.06 ± 0.42 μg/ml, 1 h, 159.72 ± 10.84 and 2.01 μg/ml, 1 h, 352.76 ± 12.91, respectively. Anti-inflammatory activity of aceclofenac was significantly improved with the SDDS. With respect to the results, it revealed that the SDDS described herein might be a promising tool for the oral sustained release of aceclofenac and likely for that of various other poorly soluble drugs.

1. Introduction

In recent years, controlled release formulations containing aceclofenac has received much attention by the researchers in pharmaceutical industry and academic research. The most commercially viable formulation strategy currently employed for aceclofenac controlled release is a biphasic dosage form which consists of immediate release and a sustained release layer [1]. Variable gastric residence time, unpredictable gastric emptying rate and different pH of gastric region may alter the solubility, diffusion and absorption of the aceclofenac. Poor dissolution rate and bioavailability are the major drawbacks of orally administered aceclofenac, these leads to severe gastric ulceration. Techniques such as solid dispersion and micro crystallization have been employed to improve its dissolution in stomach (pH 1.2) and subsequently attain a quick initial plasma concentration [2,3]. Therefore, controlled release of aceclofenac from its oral dosage forms in acidic pH is an important factor to maintain its narrow therapeutic window for longer duration. Recently Sougata et al. have reported a methods to deliver aceclofenac using alginate–locust bean gum based IPN microsphere [4], but that system only deliver the drug in intestinal pH (6.8) not in stomach. In the present study we attempted to produce a system that delivers the drug in acidic environment.

Solid dispersions and spherical agglomerates and complexation techniques are mainly used to improve the solubility and dissolution rate of aceclofenac [5]. Cocrystalization is one among the technique used to improve the oral solubility and dissolution rate of the drugs. In general pharmaceutical cocrystals improve the physical properties such as solubility, hygroscopicity and compaction behaviors of the drug without affecting pharmacological nature of the drug [6]. For this generally synthetic organic molecules were used but they have the demerits of producing severe gastro intestinal (GI) irritation [7]. Cocrystals with biocompatible polymer were reported recently and evidenced their capability to improve the solubility and dissolution rate of the drug. Pharmaceutical cocrystals of aceclofenac dramatically improve the physical properties such as solubility, dissolution rate and pharmacokinetic properties (peak plasma concentration (C_{max}), time to peak concentration (T_{max}) and bioavailability) in acidic condition are well documented. While considering the cocrystals, USFDA recommended, that the co-former used for cocrystalization should be safe to human ingestion [8,9]. Cocrystals can induce supersaturation in the GI lumen and resulting with an improved solubility and dissolution properties without being thermodynamically unstable [10]. Chitosan a well known biocompatible co-former used for the preparation of

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cocrystals which increases the dissolution rate of poorly soluble drug by enhancing their wettability, altering the surface morphology of the drug and by particle size reduction. Mutalik et al. reported that deposition of chitosan polymer over the drug particles was higher and stronger when associated with sodium citrate. The reaction of chitosan with multivalent anion sodium citrate an anion crosses linker that leads to the formation of bridges between the polymeric chains which resulted in efficient deposition of chitosan on drug particles. Hence, these cocrystals can improve the solubility of the drug in GI fluid but the enhancement of bioavailability with less variability is still a challenging task [5].

Yet now, no such commercial pharmaceutical cocrystal based aceclofenac oral controlled release formulation has been developed. Further poorly water-soluble drugs like aceclofenac would require additional release-rate modulation to enhance the duration and/or onset of action to minimizing the drawbacks due to their short half-lives, gastric irritation potential or slow onset of action [11,12]. To the best of our knowledge, no work has been reported on the encapsulation of aceclofenac cocrystals in floating alginate beads for controlled drug release in gastric acidic condition after oral administration.

Gastro retentive floating drug delivery systems will be useful to overcome the above said drawbacks and improve the oral absorption of the drug by making the drug available in gastric region for longer time [13]. Alginate, is a natural, hydrophilic, high molecular weight, linear anionic heteropolysaccharide extracted from marine brown algae, tangle weed, agar-agar, etc. Among the various floatable multiple-unit dosage forms, calcium alginate gel beads have proved as a unique vehicle for multiple-unit drug delivery systems due to its biocompatibility, biodegradability, ease of preparation, abundant sources and low cost [14]. Alginic acid from sodium alginate forms the gel matrix rapidly in the presence of calcium ion, hence it is easier to incorporate drugs or protein during gelation. The hydrogel properties of calcium alginate beads were taken into account to control the release of drugs and floating ability of such beads increases the gastric retention significantly [15,16].

It is an objective of the present invention to provide a controlled-release formulation of aceclofenac which comprise both functions such as solubility enhancement and modulated drug release. The main target of such formulation is to keep the drug in supersaturated conditions for an extended period of time and achieving maintenance of the drug concentrations in high levels. Such formulation, releases the drug at a concentration effective for pain alleviation at an initial stage, and then releases the drug in a sustained manner over a long period of time. Also, the formulation maintains the active drug concentration at a constant level to increase the therapeutic effect of the drug and thus increasing patient's compliance [17].

The main objective of this work is to develop once daily aceclofenac controlled drug release formulations by the incorporation of aceclofenac cocrystals in alginate beads (modified release supersaturated drug delivery system). To achieve this goal, aceclofenac cocrystals were prepared using chitosan as a co-former. Characterization of cocrystal was carried out by FT-IR, SEM and XRD analysis. Enhancement of dissolution rate was assessed in simulated gastric fluid (pH 1.2).

2. Experimental

2.1. Materials

Aceclofenac, chitosan (low molecular weight, >85% deacetylated, poly(D-glucosamine) from Sigma–Aldrich, GmbH, sodium alginate (alginic acid sodium salt from brown algae, medium viscosity) purchased from Sigma–Aldrich, Carrageenan was obtained from Sigma–Aldrich, USA, glacial acetic acid and calcium chloride were purchased from Dae Jung Chemicals and Metals, Korea. All other chemical used in the experiments were of commercial grade from Dae Jung Metals and Chemicals, Korea.

Table 1
Different ratio of chitosan used for aceclofenac cocrystals preparation.

S. no.	Ingredients	C1	C2	C3	C4	C5
1.	Aceclofenac (mg)	400	400	400	400	400
2.	Chitosan (%)	0.1	0.2	0.3	0.4	0.5
3.	Acetic acid (1%) (ml)	20	20	20	20	20
4.	Sodium citrate (2%) (ml)	100	100	100	100	100

2.2. Methods

2.2.1. Preparation of cocrystals

Aceclofenac, chitosan cocrystals were prepared by solvent exchange method [18]. An accurately weighed amount of chitosan was dissolved in 1% acetic acid (20 ml). Then an accurately weighed quantity of aceclofenac was added into the above solution and the resulting solution was added drop wise into 1% sodium citrate solution with continuous stirring. Herein, sodium citrate was used as a salting out agent to precipitate chitosan as chitosan citrate on aceclofenac crystals. Aceclofenac chitosan cocrystal was filtered through Whatman filter paper No.1 and crystals were dried at 45 °C for 24 h and passed through sieve no #40. Table 1 depicts the various cocrystals formulation using chitosan at different concentration.

The particle size of the cocrystals was determined by laser light scattering methodology using Malvern particle size analyzer (Malvern Master Sizer 2000, SM, Malvern, United Kingdom). The cocrystals in anhydrous alcohol were added to the sample dispersion unit and stirred to reduce the particle aggregation. The laser obscuration range was maintained between 15% and 20%. The average volume-mean particle size in mean diameter was measured after performing the experiment in triplicate.

2.2.2. Preparation of aceclofenac SDDS

The selected formulation of aceclofenac cocrystals was dispersed in 30 ml sodium alginate solution (0.5–2.5, w/v) containing equivalent amount sodium bicarbonate ($NaHCO_3$) as gas-forming agent. The mixture was then degassed under vacuum and sonicated. The resulting dispersion was dropped through a 33 gauge syringe into stirred solution of 1% (w/v) $CaCl_2$. To improve the mechanical strength of the beads thus formed stirring was continued for another 10 min. The formed beads were collected, washed with distilled water and little alcohol, and subsequently dried at 40 °C overnight. The formulation composition of aceclofenac SDDS was shown in Table 2.

2.3. Characterization of floating beads

2.3.1. FT-IR spectral analysis

The aceclofenac cocrystals and aceclofenac SDDS were characterized by FT-IR spectroscopy. A Thermo scientific Nicolet IR 200 spectrometer was used for this purpose. The spectra were recorded

Table 2
Formulation composition of aceclofenac SDDS.

S. no.	Ingredients	F1	F2	F3	F4	F5
1.	Aceclofenac cocrystals (mg)	400	400	400	400	400
2.	Alginate (%)	0.5	1.0	1.5	2.0	2.5
3.	Calcium chloride (g)	2	2	2	2	2
4.	Acetic acid (10%) (ml)	100	100	100	100	100