CHAPTER I

GENERAL BACKGROUND

INTRODUCTION

Diclofenac sodium is a widely used potent nonsteroidal anti-inflammatory drug with pronounced analgesic and antipyretic activity. It is used mainly for the long term symptomatic treatment of rheumatoid arthritis, osteoporosis, ankylosing spondylitis, renal colic, acute gout, and following some surgical procedure (Gohel, 1998). Its half-life is approximately 2 hours. The usual dose by oral is 75-150 mg daily in divided doses.

In general, the conventional diclofenac sodium dosage forms require drug intake every 8 hours that create many problems and limit its use. The major problem is an irregularity of drug plasma level that the occurrence is called peak and valley. Moreover, if the dosage interval is too long, each single dose must be higher. This implies that the upper limit of therapeutic concentration is easily exceeded, increasing the risk of toxic manifestation. Due to the long interval, the rapid elimination of diclofenac sodium leads to low concentration before the next dose is taken and recurrence of symptoms may be the result. With more frequency medications, each dose is smaller, but the interval between dose may be so short as to interfere with normal activities (Jame, 1993). The most important factor in increasing medical awareness of diclofenac sodium is the design and development of sustained release preparations of drug. Indeed, one of the main purposes of the sustained release is to improve safety and minimize side effects of drug by reducing fluctuation in drug levels.

At present, dosage forms with sustained drug release characteristics have various types in the pharmaceutical industry. The encapsulated granules or tablets are widely used as sustained release dosage forms. They are generally prepared with film coating techniques. The coating materials may be soluble materials or insoluble materials and the coating solvent may be organic solvent. However, it is very hazardous to human and environment.

Therefore, organic solvent is replaced by aqueous system. These dosage forms have considerable disadvantages such as, they are elaborate to produce and the lacquer film is mechanically sensitive. The slightest damage to the lacquer film leads to the risk of sudden release of the entire content of active ingredient, which is extremely undesirable (Kolter et al., 1997). Another sustained release dosage form is the matrix type dosage form, such as, the matrix types tablet as well as coated tablets and particles. It can be prepared by several methods. For example, it can be compressed directly from the powder mixture of drug and polymers or solid dispersed particle prepared with polymers (Edith, 1999). The pellets are one kind of matrix type dosage forms used to achieve sustained release. They are particles of 1 - 2.5 mm diameters, which contained various hydrophobic or hydrophilic materials. The release mechanisms for controlling drug release are either diffusion or erosion from hydrophobic system and swelling in water to gel form that drug is liberated primarily by diffusion. (Lee and Robinson, 1978; Kydanieus, 1980) A pelletization process, which using a disk and drum pelletizer, usually produces pellets. The agglomerative granulation is the first step . Then, the obtained wet mass is passed through the extruder and spheronizer for cutting and rounding off the resulting sphere particles respectively. The last step is drying and screening operation. They were filled into hard gelatin capsules or compressed to be tablet (Pich et al., 1989; Edith, 1999).

All of these processes have many disadvantages that they give the undesirable pellets such as, broad particles size distribution, the irregularity of the shape and/or the surface structure. Moreover, the solvent in these processes affects the porous structure of the products. The weight of the individual pellet fluctuates greatly. The undesirable characteristics of pellets are not suitable for producing the effective sustained release dosage forms. However, these disadvantage properties could be overcome by the microtablet (Pich et al., 1989).

Microtablet is the tablet, which has a diameter and height that are preferably approximately equal and, independently of one another, from 1 – 3 mm, preferably 1.5–2.5 mm. Its shape is nearly spherical or cylindrical with a flat or convex upper and lower side. The microtablet according to the invention is produced in conventional techniques, which commonly use to produce the plain tablet. The method can be classified to the following steps: granulation, drying, dry mixing, and tabletting (Banker et al., 1991). The equipment is similar to that produces the plain tablets, except the tooling of the tabletting machine. The

special punches and dies that required precision and mechanical stability must be used. Because the punch station is equipped with a punch holder that contained many small concave punches per punch holder, for example, 19 punches per punch holder. The most awareness factor for producing the microtablets is the flowability of powder because it affects the properties of microtablets (Mielck et al., 1998; Rey et al., 2000).

The characteristics of microtablets are better than those of pellets such as narrow size distribution, the uniformity of the shape and/or the surface structure because of the controlling by punch and die. Moreover, the weight of the individual microtablet is not fluctuated. These advantages are desirable for producing sustained-release dosage form. (Kolter et al., 1997; Pich et al., 1989). The types of additives use to produce microtablets are similar to the plain tablet, such as, diluent, binder, and lubricant (Banker et al., 1991).

The widely used sustained release materials are cellulose derivatives. They can be classified into two types. The first type is the water – soluble cellulose such as high viscosity grades hydroxypropylmethylcellulose. Their release mechanisms are gradual solution and swelling with erosion. Another type is the water – insoluble cellulose such as high viscosity grades ethylcellulose. Their release mechanisms are diffusion and dialysis.

At present, there are many research articles about the microtablets. Kolter et al. (1997) reported techniques for in situ preparation of microtablets by wet granulation with fluidized bed granulator and coating the microtablets with sustained release materials. The effect of additives in the formulation and coating materials were studied. They observed that, the amounts of drug release were more than 70% at 8th hours in all formulations. Therefore, their products could not give a desirable release for a 24 hours sustained release preparation.

Pich et al. (1989) used various methods to prepare microtablets, such as fluidized bed granulator and coating techniques, extraction method, and direct compression. Moreover, each technique has different drug and additive in the formulation. The properties of these microtablets were studied. They observed that microtablets are very uniform particle size with regular shape and high weight uniformity. These are desirable properties for preparing sustained release dosage forms.

For the aim of study, the microtablets containing various types and amount of cellulose derivatives as sustained release materials were investigated. The production techniques of microtablet were similar to those of the plain tablet, which were direct compression and wet granulation techniques. The shape of microtablets was nearly spherical because diameter of the punch and die were equal to height of microtablet. The effects of the cellulose derivatives and ratio of drug to the amount of cellulose derivatives on the properties of the product were studied.

The physical and physicochemical characteristics of the microtablets were also tested. The suitability of production techniques in the manufacture of sustained release microtablet was verified. The drug release patterns of these microtablets were compared to a commercial product (Voltaren SR 75 mg).

Objectives of this study

On the basis of the rational mentioned earlier, the objectives of this research are,

1. To prepare sustained release diclofenac sodium microtablets with cellulose derivatives (hydroxypropylmethylcellulose, ethylcellulose) using direct compression and wet granulation techniques and to evaluate the physicochemical properties of the microtablets.

2. To study the effect of types and amount of cellulose derivatives and preparation techniques on the release of drug from microtablets.

3. To evaluate drug release from the capsules containing the prepared microtablets in composition to that of a commercial product.

4. To investigate the model and mechanism of drug release from the prepared microtablets.