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Formulation of Etodolac as micro sponge drug delivery system

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ABSTRACT: Etodolac (ED) is a drug which belongs to NSAIDs and is classified as class II by Biopharmaceutical classification system (BCS) with low solubility and high permeability. The aim of present study was to formulate Etodolac (ED) as a micro sponge technology. This enhances the release of drug from the system. ED is a drug belongs to NSAID groups that classified as class II by BCS with low solubility and high permeability. This technology is a patented delivery system in which the drug loaded in pores of cross-linked polymers. In this technique, ED was mixed with two phases. In phase I and phase II, the polyvinyl alcohol (PVA) and Eudragit E100 were used, respectively, with a different doses of ED. The micro sponge yield, entrapment efficacy, FTIR, particle size, and dissolution test were all studied. Preparation of ED loaded micro sponge using Eudagit E100 in ratio of (500 Drug: 100 Polymer) succeed to enhance the drug dissolution rate with accepted entrapment efficiency and percentage yield.

Keywords: Micro sponges, Etodolac, solubility.

INTRODUCTION

Etodolac (ED) has a wide range of use due to its pharmacological action as analgesic, antipyretic, and anti-inflammatory. Beside these actions the ED is one of the potent platelet aggregation inhibitors. ED is a poorly water soluble drug that classified as class II by biopharmaceutical classification system BCS with low solubility and good permeability.(1) The low solubility of ED results in low bioavailability.(2) Solubility enhancement of drug with low aqueous solubility is required to improve its dissolution and then bioavailability. For these purpose many carriers such as micro carriers have been used such as micro sponge as a patent technology. (3, 4, 5) Micro sponge technology is a porous system like a sponge that can be loaded with a different amount of drugs. This system composed of cross- linked polymers as interconnected void in each particle.(6) This system will be lost after releasing its content in controlled manner and different doses.(7) The drug particles release from the surface of micro sponge system related to the pore size.(8) Micro sponge entrapment of drugs has many advantages besides the controlling of release and efficient drug loading, including the side effect decreasing, increasing stability, elegancy of final formula and flexibility in formulation.(6, 9) Micro sponge system is stable in a very wide range of pH from highly acidic (pH=1) to highly basic (pH= 11) and in a high temperature up to 130 °C. The pore size of this system is too small (0.25 µm) for bacteria to grow in; therefore, there is no need for sterilization of system. Such a system can be overloaded with about 50-60% of drug that is freely flow.(10) Loading of drug particles in a small pores provide a high surface area for drugs due to small particle size (micro size) that will improve the solubility, absorbance and bioavailability.(11) Micro sponge system can be prepared by two techniques, the liquid-liquid suspension polymerization and the quasi-emulsion solvent diffusion. The procedure of preparation is depending on the physicochemical properties of drug to be formulated. The aim of this study is to formulate ED as micro sponge drug delivery system to improve its dissolution rate then its bioavailability.

MATERIALS AND METHODS

Materials:

Etodolac was bought form FDC limited India. PVA was from Sigma chemical co. USA. Eudragit E100 was received from Evionk Rohm GmbH, Germany (brand name). Sodium Hydroxide was bought from Himedia India. Hydrochloric acid

was from Riedel-De-Haen AG seelze, Germany. Methanol was from BDH, England. Potassium di- hydrogen ortho-phosphate was bought from Merck Germany.

METHODS

Preparation of ED micro sponge

Quasi-emulsion diffusion method was used for preparation of ED micro sponge. The method consists of preparing two phases, phase I (external phase) and phase II (internal phase). Phase I is a mixture of 100 mg PVA in 100 ml distilled water. While, the phase II is a mixture of 100 mg Eudragit E100 in 5 ml DCM, after that ED was added with continuous stirring. Mixing of the two phase was performed by the addition of phase II drop by drop to phase I with continuous stirring for about 60 minutes. The mixture was filtered and the filtrate was dried in oven at 40 °C temperature for 24 hours. As shown in Table (1), different formulas was prepared with different ED doses.(12)

Table 1: ED micro sponge formulas.

Formula number	Etodolac (mg)	Eudragit E100 (mg)	PVA (mg)	DCM (ml)	Distilled water (ml)
F1	250	100 mg	5	5	5
F2	500	100 mg	5	5	5
F3	750	100 mg	5	5	5
F4	1000	100 mg	5	5	5
F5	1250	100 mg	5	5	5
F6	1500	100 mg	5	5	5

Evaluation of micro sponge

Production yield and entrapment efficacy

The entrapment and yield of the micro sponge system was calculated using the following equations (13):

$$yield\% = \frac{weight\ of\ formula}{theoretical\ weight\ of\ formula} 100$$

$$entrapment\ efficacy\% = \frac{actual\ drug\ content}{theoretical\ drug\ content} 100$$

Particle size evaluation

The microscopic counting method was used to determine the particle size of the micro sponge.

Differential scanning colorimetry (DSC)

The DSC for pure ED and ED loaded micro sponge was studied. Samples were placed in aluminum pans and heat elevated from 50 to 300 °C at a rate of 20°C/min and nitrogen atmosphere.(14)

In vitro dissolution test

Dissolution test was performed by using USP paddle dissolution apparatus in 900 ml HCl (pH 1.2) as dissolution media. Media temperature was 37 °C with continuous stirring at 100 rpm. A sample of 5ml was drowning according to a scheduled time, then replenished with 5 ml pure acidic media. The absorbance was measured in UV visible spectrophotometer to determine the concentration using the ED calibration curve in the same medium at the drug lambda max of 247 nm.(15) Fourier transformer infrared spectroscopy (FTIR) FTIR was used to determine any physicochemical interaction between ED and other excipients. Accordingly, the FTIR of pure ED and ED mixed with other excipient was studied.(15)

RESULTS AND DISCUSSION

Evaluation of the formulated micro sponge Production yield % and entrapment efficacy%

The production yield and entrapment efficacy percent were determined as shown in Table (2). Formula (1) failed to produce micro sponge and a solid sticky mass is produced, therefore it was neglected.

Table 2: Results of ED micro sponge yield% and entrapment%.

Formula No.	ED	Eudragit E100	Yield (%)	Entrapment efficacy (%)
F1	250mg	100 mg	-	-
F2	500mg	100 mg	80%	74%
F3	750mg	100 mg	81%	76%
F4	1000mg	100 mg	87%	83%
F5	1250mg	100 mg	88%	72%
F6	1500mg	100 mg	87%	78%

Particle size evaluation Particle size determination of all formulas was within acceptable range for micro sponge. As shown in Table (3).

Table 3: Results of ED micro sponge particle size.

Formula Code	P.S
F1	-
F2	89 µ
F3	90 µ
F4	95.5 µ
F5	93 µ
F6	90 µ

Differential scanning colorimetry (DSC)

Thermal analysis using DSC had been used to study the physical stability of ED in presence of Eudragit E100. As shown in Figure (2a) the melting point peaks of ED at 115°C was appeared. While in Figure (2b), the shifting in peak was small due to change in crystallinity. This change is not a chemical interaction related change.(16) In vitro dissolution test the results of the dissolution test were as shown in Figure (3). According to the results of dissolution tests, the ED release from the micro sponge system in different manner with maximum release from F2 that was loaded with 500 mg of ED with 91% release of ED, as shown in Figures (3). In general, the release was decreased as the loading was increased to reach About 25% and 35% only in formulas F5 and F6, respectively. ED is an acidic drug, so the solubility in acidic solution of pH 1.2 is low. As a results as the dose was increased the solubility was decreased and finally the percent of drug release was affected. Accordingly, the formula F2 with maximum release percent of 91% is the best formula.

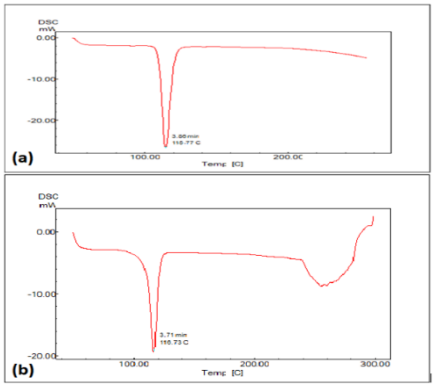

Fig.1: DSC of ED and ED loaded micro sponge.

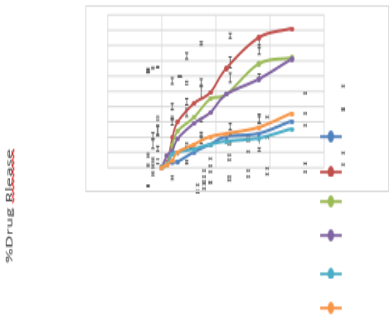

Fig.2: Percent of ED release from micro sponge system from six formulas in acidic buffer (pH 1.2), all the results represent mean percent release ± SD, n=3.

Fourier transformer infrared (FTIR) spectroscopy: FTIR spectrum of ED have a characteristic peak at 1694 nm that is specific for (C=O) group. At 1215.6 nm the peak of (C-F) group was appeared. ED carboxylate peak was appeared in the range of (2500-3300) nm which is due to the hydrogen bonding. The spectrum of combination showed no interaction between ED and other excipients as shown in Figure (1). All the characteristic peaks of ED are present in the micro sponge formula which indicates no chemical interaction occurred between the drug and the excipients during preparation.

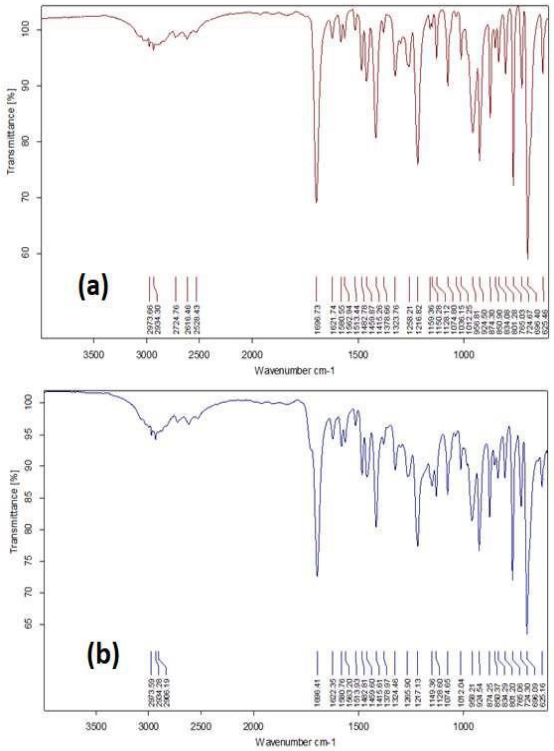

Fig.3: FTIR spectra of pure ED (a) and the combination of ED and excipients (b)

CONCLUSION

The micro sponge of the ED was formulated successfully. The F2 formula that contained 500 mg of the drug, 100 mg of eudragit E100 and 5 mg PVA is the optimized formula which had better drug loading and release. Therefore, micros pong can improve ED solubility, dissolution rate and bioavailability.

Ethical Clearance

No ethical issues were encountered.

SOURCE OF FUNDING

Self-funded.

CONFLICT OF INTEREST

No conflict of interest.

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