MICROSPHERE AND TABLET IN CAPSULE SYSTEM: A NOVEL CHRONOTHERAPEUTIC SYSTEM OF DICLOFENAC SODIUM FOR SITE AND TIME SPECIFIC DELIVERY

ABSTRACT

The objective of the present study is to develop and evaluate microsphere and tablet in capsule system for the treatment of rheumatoid arthritis as a dual pulse release system. The capsule system contains enteric coated cap filled with microspheres (sustained release) that lock the impermeable capsule body (coated with ethyl cellulose). The capsule body consists of diclofenac sodium loaded core tablet in the bottom (immediate release), which is sealed with swellable hydrogel plug tablet. Formulations selected for capsule system were MP1 due to least particle size (90.44±0.20 µm) and maximum cumulative release (91.49±0.20 %), T3 for least disintegration time (4±0.040 min) and maximum cumulative release (85.50±0.09 %) and HP2 for maintenance of lag phase that was 6 h and *in vitro* study was Performed. This formulation included two pulses in one system for reduction of dose frequency and better treatment of night pain and morning stiffness in rheumatoid arthritis patients.

Keywords: Chronotherapeutic drug delivery, Circadian rhythm, Diclofenac sodium, Dual pulse release, Microspheres, Bi functional capsule formulation, MATICS.

INTRODUCTION

Chronotherapeutic drug delivery system is the application of biological rhythm to pharmacotherapy and the special drug delivery system to synchronize drug concentration to rhythms in the disease condition[1]. This system is used for the treatment of rheumatoid arthritis and to overcome the symptoms like severe pain, inflammation and stiffness in joints, which occur in early morning and usually follow circadian rhythms[2]. Non - steroidal anti-inflammatory drugs are prescribed for relieving morning pain and stiffness of rheumatoid arthritis. Diclofenac sodium is an anti-inflammatory drug which is more effective in the treatment of rheumatoid arthritis. Diclofenac sodium possesses two main disadvantages first, when it is taken orally it causes serious gastrointestinal side effects second, its biological half life is short i.e.1-2 h and so it requires frequent administration[3].

MATERIALS AND METHODS

Diclofenac sodium, Crospovidone, hydroxy propyl methyl cellulose K4M, Eudragit RS100, Croscarmellose sodium, Microcrystalline cellulose, magnesium stearate, di-butyl phthalate, lactose, talc and ethyl cellulose, cellulose acetate phthalate, acetone, ethyl acetate, ethanol and liquid paraffin, n-hexane and petroleum ether were used in this study.

Preformulation study was performed by physical appearance like colour, odour and taste of the sample. Melting point was determined by open capillary method. Solubility was determined by the saturation solubility method[4]. Drug identification and compatibility study of drug with excipients was done by using Fourier transform infrared spectrophotometer. Bifunctional capsule shell was prepared. Capsule cap was coated with cellulose acetate phthalate solution. Capsule body was coated with the help of ethyl cellulose solution. Solution was poured into capsule body, then solvent allowed to evaporate overnight in a refrigerator (4 ^{o}C)[5]. Formulations of diclofenac sodium microspheres were prepared by solvent evaporation method by using various quantities of Eudragit RS 100 and evaluation test performed[6]. Core tablets were prepared by direct compression method by using various quantities of super-disintegrates and evaluation test performed[7]. Hydrogel plug tablets were prepared by adding various quantities of HPMCK4M and evaluated[8]. Microsphere and tablet in capsule system assembly was prepared. The diclofenac tablet was fixed in the base of the impermeable body and plugged with the help of hydro gel and tablet plugged at the capsule body mouth. Diclofenac microspheres were placed in enteric coated capsule cap and then the *in vitro* drug release was performed. Paddle type apparatus was used.

In vitro drug release study was first carried out in 900 mL of HCl, having pH 1.2 at 37 ^{o}C±1 ^{o}C for 2 h. After 2 h, the media was replaced by phosphate buffer pH 7.4 and sampling was carried out for another 6 h. 5 mL sample was withdrawn every hour and assayed at 275.6 nm. After 8 h, the medium was replaced by phosphate buffer (pH 6.8) to continue release study another 2 h. 5 mL aliquot of the dissolution medium was withdrawn at intervals of 0, 5, 10, 15, 20, 25, 30 and 60

Table I: Evaluation of microsphere formulation

Formulation	Yield (%)	Particle size (µm)	Entrapment efficiency (%)	Drug content (%)	Cumulative drug release (%)	Higuchi (r^2) (best fitted model)
MP1	67±0.42	90.44±0.01	50.53 ± 0.572	97.73±0.057	91.49±0.20	0.9183
MP2	75±0.45	114.48±0.04	63.01 ± 0.65	87.76±0.057	84.40±0.041	0.9151
MP3	77.6±0.20	133.79±0.04	69.88 ± 0.96	93.33±0.057	75.03±0.044	0.9253
MP4	80.18±0.02	148.03±0.03	77.77 ± 0.45	93.76±0.401	61.74±0.92	0.9187
MP5	81.43±0.16	152.63±0.03	81.98± 0.25	90.68±0.076	53.31±0.038	0.9174
MP6	94.3±0.25	299.66±0.01	90.22± 0.78	96.55±0.05	36.58±0.200	0.9117

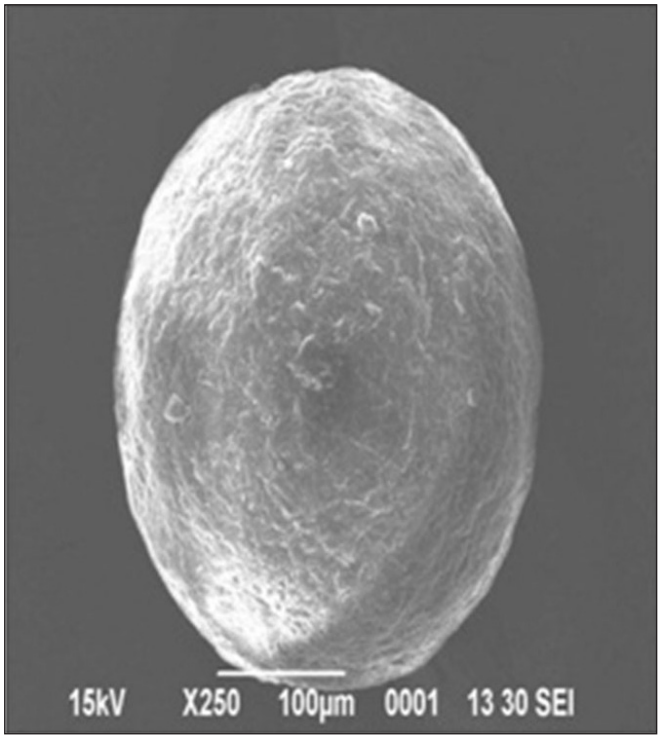

Fig.1: Scanning electron microscopy (SEM0 of microsphere (formulation 1)

min, filtered and analyzed spectrophotometrically at 275.6 nm. The drug release kinetics was studied by various kinetic models such as Korsmeyer-Peppas, Higuchi plot, first order plot and zero order plot[9,10].

RESULTS AND DISCUSSION

After visual inspection, the sample of diclofenac sodium was found to be white crystalline powder, odourless and bitter in taste and melting point was 285 to 288 °C. FTIR showed that there is no incompatibility between drug and polymer. Thickness of the ethyl cellulose coated impermeable capsule body ranged between 0.182 to 0.213 mm. With increased concentration of ethyl cellulose, the thickness of impermeable capsule body was increased, which is required for the avoidance of premature drug release and mechanical strength of capsule body[11]. The IB3 capsule body was selected for the MATICS formulations. Microspheres of diclofenac showed biphasic release pattern, primarily burst and release for 1 h due to surface allied drug, accompanied by sustained release for 6 h due to drug entrapped in the matrix of microspheres[12]. MP1 formulation showed highest cumulative drug release of 91.49±0.20 % and least particle size 90.44±0.01 µm (Table I, Fig.1). All the formulations were best fitted in Higuchi model. Core tablets evaluation tests viz. hardness, thickness, friability, weight variation, drug content and cumulative release were performed. The T3 formulation showed disintegration time 4 ±0.040 min due to high swelling and water uptake ability of Crosscarmellose sodium that leads to faster disintegration as compared to Crospovidone containing tablets. Decrease in disintegration time increased the cumulative drug release of tablets. The thickness, hardness, swelling index and lag time of hydrogel plug tablet was recorded and the plug tablets, thickness enhanced with the enhancement in weight of plug tablet. HP3 showed highest swelling index due to ability of HPMC to absorb water. HP2 formulation showed the value between 6 h and 5 min and lag time was near to intestine transit time[13]. MP1 formulation of microspheres showed highest % cumulative drug release 91.49±0.20 %, T3 formulation has less disintegration time 4±0.040 min and increased cumulative drug release 85.50±0.09 % and HP2 hydrogel plug tablet has similar lag time to intestinal transit time, so these formulations were selected for microsphere and tablet in capsule system. The microsphere MATICS cumulative drug release was

found to be 93.30 %. After 6.5 h, the HP2 tablet ejected out by itself from the impermeable capsule body, T3 tablet formulation in MATICS came in contact with phosphate buffer pH 6.8 and the release of the drug from the tablet started.

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