약제학회지(2005), 제 35 권 제 3 호
J. Kor. Pharm. Sci., Vol. 35, No. 3, 151-155 (2005)

A Novel Drug Delivery System Design for Meloxicam

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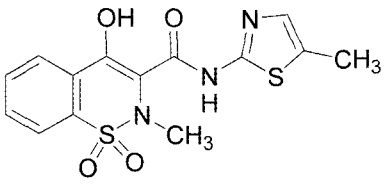
(Received March 25, 2005 · Accepted April 11, 2005)

ABSTRACT – A drug delivery system(DDS) for practically insoluble meloxicam was developed and evaluated by dissolution study. A novel DDS is two layered system, where the first layer is consisted of gas-forming agent for an immediate release and the second layer is composed of metolose SR(HPMC) for sustained release. This bilayered tablets were manufactured by using manual single punch machine. The results of dissolution study showed an initial burst release followed by sustained release for the experimental period time. From a pharmaceutical point of view, the designed DDS for meloxicam would be informative system in terms of poorly soluble analgesic medicines.

Key words – Drug delivery system, practically insoluble drug, meloxicam, effervescent tablet, HPMC, analgesics

In general, analgesics are drugs that relieve pain without producing unconsciousness or impairing mental capacities. Many of these drugs also have an antipyretic and/or an anti-inflammatory effect. This analgesics are classified into two groups such as opoid-analgesics and non-narcotic analgesics which are non-steroidal anti-inflammatory agent(NSAID).[1] Meloxicam(MOBIC®)[2] an oxicam derivative, is a member of the enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs) and specially designed to inhibit cyclo-oxygenase (prostaglandin synthetase). It is chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide. The molecular weight is 351.4. Its empirical formula is $C_{14}H_{13}N_3O_4S_2$ (Scheme 1).

Meloxicam is a yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P)app=0.1 in n-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.[3] Many enhancement methodology of solubility for meloxicam has been reported, which are water-soluble meloxicam granulates,[4] nanoparticulate meloxicam formulations,[5] complexation with β-cyclodextrin.[6-9] It was reported that an inclusion of β-cyclodextrin increased the solubility and the dissolution rate of meloxicam was significantly enhanced by it in the formulations up to 30%.[9] With the presence of β-cyclodextrin the mean pharmacokinetic parameters such as C_{max}, K_{el}, and AUC were increased significantly.[9] On the other hands, the absolute bioavailability of meloxicam capsule was 89% following a single oral dose of 30 mg compared with bioequivalent MOBIC® tablet according to Rxlist.[2] The main adverse events of meloxicam are serious gastrointestinal toxicity risk, such as inflammation, bleeding, GI ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with non-steroidal anti-inflammatory drugs (NSAIDs).[10] The different therapeutic dose strengths of meloxicam ranged from 7.5 mg to 15 mg were investigated and it was revealed that gastrointestinal side effect is shown consistently regardless of dose in the results of four placebo clinical trials.[11-14] Thus, the complexation theory into meloxicam with β-cyclodextrin was applied in order to improve the solubility and dissolution rate as well. In addition to it, we have developed a novel drug delivery system for meloxicam which is composed of two layers, where the first layer is consisted of gas forming agent for an immediate and effervescent release to approach fast-acting, the second layer is consisted of Metolose SR for sustained release for the purpose of decreasing or elimination of side effect maintaining the blood concentration of meloxicam within the therapeutic window in other words, to reach long-acting with strong strength (15 mg).



Scheme 1–The chemical structure of meloxicam.

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Materials and Methods

Materials

Meloxicam as a model drug and β-cyclodextrin were purchased from Sigma chemicals (USA).

Ludipress (Lactose, Povidone, Crospovidone) was used for direct compression and obtained from BASF, Germany. Metolose SR(HPMC K4M, hydroxypropylmethylcellulose) was purchased from ShinEtsu, Japan and other excipients such as Sodium Citrate, Avicel (Microcrystallinecellulose), and Mg stearate were obtained from Hwail Chemicals, Korea.

Methods

Granulation – A model drug, meloxicam was blended with β-cyclodextrin in the ratio of 1 to 1 mole ratio using incorporation methodology. Both active ingredient, meloxicam and β-cyclodextrin were sieved through US sieve No. 20 seperately. The accurately weighted molar portion of meloxicam was incoporated into grounded β-cyclodextrin in the micronized state. The β-cyclodextrin inclusion complex was blended in a motar with pestle and the granule agent including 10% povidone(PVP) w/v EtOH was added into it gradually. The formed granules were dried over night in the oven at 60°C. After drying the moisture content was less than 3%, which was confirmed and these granules were used for tablet manufacturing process unless otherwise stated.

Experimental design – Solid dosage formulations for meloxicam were designed in order to optimize tablet composition and to develop bilayered system which is consisted of an immediate release(IR) and sustained release(SR). Four different simple matrix compositions of meloxicam were shown in Table I.

Tablet manufacturing – Tablets whose bilayers are consisted of the first effervescent layer for immediate release and the second sustained layer for modified release were manufactured into and this schematic illustration is shown in Figure 1.

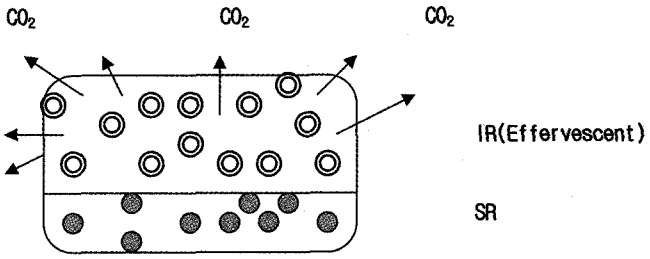

Figure 1–The schematics of the designed drug delivery system for meloxicam.

An experimental design for dosage formulations (Table I) was investigated throughly with observation of matrix changes and the final composition of meloxicam DDS (Table II) was optimized according to the performance of dissolution study.

The prepared second layer components dyed with iron dioxide to distinguish layer from layer were poured into die and those were tapped with upper punch slightly and then the first layer components were added upto final compression under single punch machine (Model SF-6, Sejong Instrument Co., Korea).

Dissolution study – The dissolution study was performed on Vankel Dissolution Tester (VK-8000, Apparatus II method) with Waters 717 Plus Autosampler UV 620 and the absorbance was measured at the wavelength of 365 nm. The manufactured 6 tablets were tested in dissolution medium, deionized water 300 ml at 37°C with 125 rpm and sampling was carried out at the planned time intervals during whole experimental period.

Results and Discussion

Many prestigious reports showed that the mixture of meloxicam and β-cyclodextrin was identified using X-ray diffraction (XRD) and differential scanning calorimetery(DSC) method.[7]

Table I–*The Designed Experimental Compositions of Meloxicam Matrix*

Matrix Composition \ RUN NO.		N=1	N=2	N=3	N=4
Active Ingradient	Meloxicam	15mg	15 mg	15 mg	15 mg
	β-cyclodextrin	-	48.45 mg	48.45 mg	48.45 mg
Disintegrant	Avicel	50 mg	50 mg	50 mg	50 mg
Diluent	Lactose	133 mg	84.55 mg	-	14.55 mg
Effervescent	Na Citrate			50 mg	
Direct compress	Ludipress			34.55 mg	
Sustained	Metolose SR				70 mg
Lubricant	Mg stearate	2 mg	2 mg	2 mg	2 mg
Total weight		200 mg	200 mg	200 mg	200 mg

Table II–*The Tablet Composition of the Designed DDS for Meloxicam*

Layer	Composition	Weight(mg)	Remark
1(IR)	Meloxicam granule (equivalent to 7.5mg meloxicam)	31.73	Meloxicam with β-cyclodextrin (1:1 mole ratio)
	Na Citrate	25	Gas forming agent
	Ludipress	25.27	Lactose, Povidone, Crospovidone
	MCC	25	
	Mg Stearate	1	
2(SR)	Meloxicam granule (equivalent to 7.5 mg meloxicam)	31.73	Meloxicam with β-cyclodextrin (1:1 mole ratio)
	HPMC K4M	35	Sustained release
	Ludipress	39	Lactose, Povidone, Crospovidone
	MCC	25	
	Mg Stearate	1	

The calorimetery thermogram and powder X-ray diffractometry are very useful methodology for the detection of cyclodextrin complexation in power or micronized state.[15,16] It is well known about these inclusion technology has been used to improve the stability and solubility of model drugs resulted in increasing dissolution rate and bioavailability, which is described in the literature of Naidu et al[7]. In our laboratory, the incoporation methodology explained in experimental part was introduced in order to make meloxicam and β-cyclodextrin complexation. The granulated binary system was evaluated through performance of dissolution study and drug release profiles from prepared matrix both N=1 and N=2 (Table I) were shown in Figure 2. The dissolution rate was calculated based on the results given in Figure 2. It showed the dissolution rate of β-cyclodextrin complexation tablet increased more than double times in comparison to that of meloxicam simple compact (Figure 3). The percent drug release from β-cyclodextrin inclusion meloxicam is lower than that from meloxicam itself.

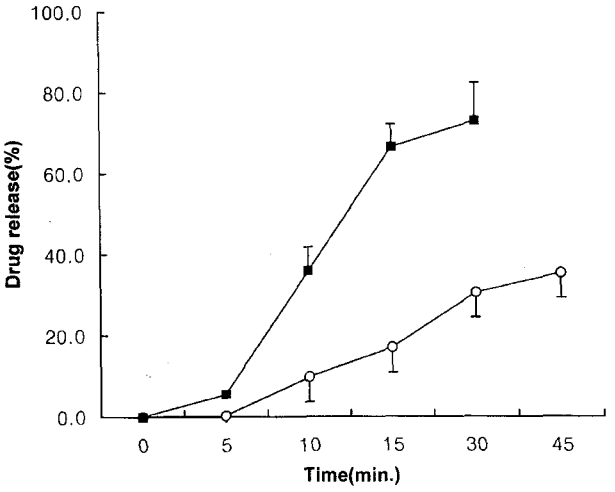

Figure 2–Drug release profiles from the designed matrix of meloxicam itself (■) and meloxicam with beta-CD(○).

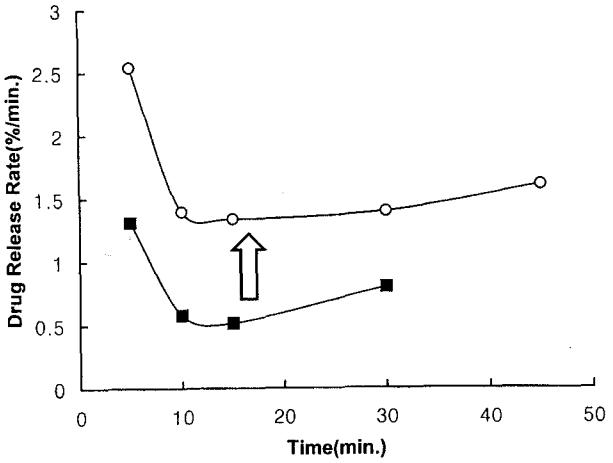

Figure 3–Dissolution Rate of meloxicam itself (■) compact in comparison study with meloxicam included in beta-CD(○).

Nevertheless, the dissolution rate of meloxicam inclusion was significantly increased thus we conclude that the binding force between β-cyclodextrin and meloxicam may influence on the drug diffusion and its viscosity is high enough not to release drug from an inclusion complex induced by viscosity of povidone (PVP) used as a granulation agent.

According to experimental solid dosage formulations given in Table I the meloxicam release profiles from both 1 N=3(IR) and N=4(SR) were shown in Figure 4. These results showed that meloxicam from the effervescent IR(Immediate Release) compacts were released 100% almost within 45 minutes, on the contrary meloxicam from the SR(Sustained Release) compacts were released slowly about 20% for 5 hours. Ludipress® is free-flowing granules composed with three components such as 93% lactose monohydrate, 3.5% Kollidone 30®, and 3.5% Kollidone CL.[17] Owing to the ability of the Kollidon CL disintegrant to swell the channel could be permeated by dissolution medium is easily formed, which drives incoporated drug come out rapidly. Thus, it resulted in fast-acting meloxi-

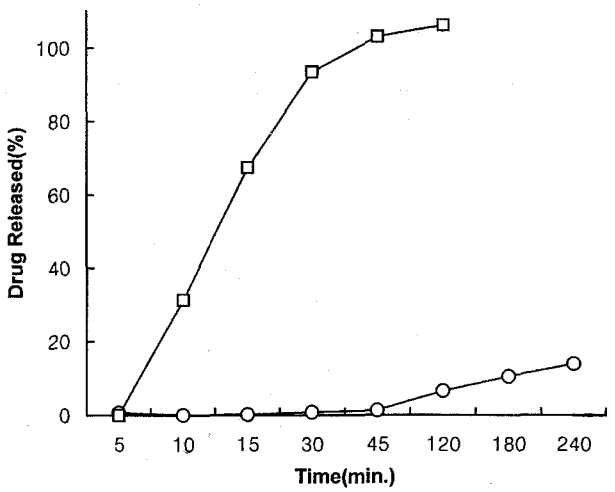

Figure 4–The meloxicam release profiles from IR effervescent tablets(□) and SR compacts (○).

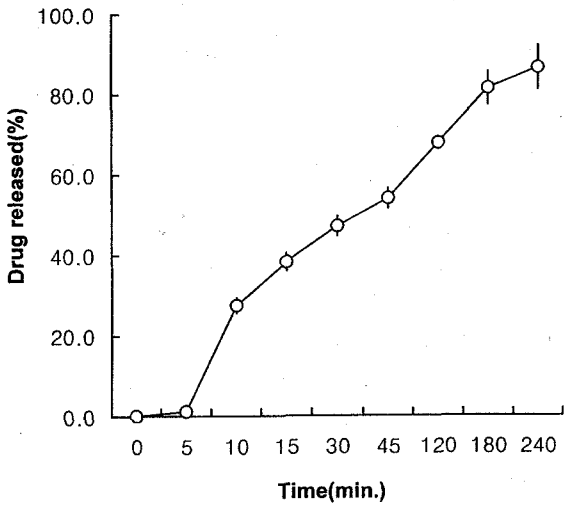

Figure 5-1–The meloxicam release profiles from the designed drug delivery system consisted of two layers, where the first layer is an immediate release layer and the second layer is sustained release layer.

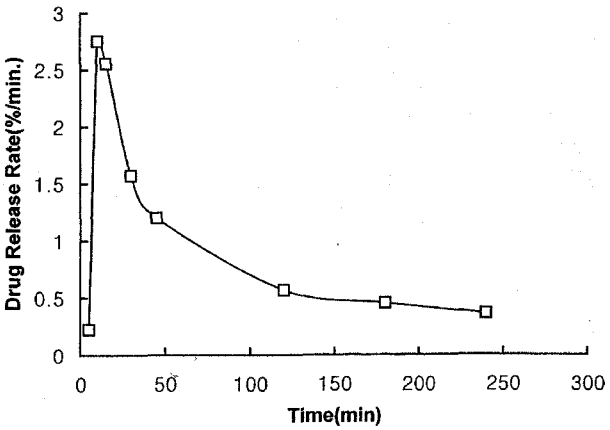

Figure 5-2–The dissolution rate of meloxicam bilayered tablets, a novel DDS during an experimental period of time over 5 hours.

cam release from IR matrix. Metolose SR®(Hydroxypropylmethylcellulose, substituition type 2208, 90SH, USP) which has methoxyl content 22~24% and hydroxypropyl content 8~10% is water soluble high molecular weight polymer[18]. Furthermore, it has been used for sustained hydrophillic matrix system since its viscosity is approximately 4,000 cps which could be applicable to achieve controlled release technology easily for oral dosage forms specially.[19,20] Due to the high viscosity of Metolose 4000(correspond to viscosity in unit, cps) SR polymer entanglement in the designed matrix is more compacted structure and the drug release is sustained over 16 hours until high molecular weight of polymer structure is distangled as shown in Figure 4. A novel drug delivery system for meloxicam which is consisted of two layers was evaluated as shown in Figure 5-1. An initial 30% burst release for 15 minutes resulted from effervescent IR formulation during the beginning of dissolution time period followed by controlled release for 5 hours resulted from SR formulation during entire time period of dissolution study except for initial 30 minutes. These result data have been manipulated into dissolution rate described in Figure 2 and remarkably improved rapid dissolution rate is decreased for an half hour approximately and then the dissolution rate is reduced slowly as time goes on. Therefore, the burst release is suitable for fast-acting of analgesics and followed sustained release would be better for long-acting of analgesics with strong strength 15 mg applied to this study. The mechanism of this release kinetics would be influenced by some parameters such as used polymer concentration, the mole ratio of model drug to β-cyclodextrin, viscosity, cloud point, drug diffusion coefficient, and hydrophobicity of model drug. Pose-Vilarnovo *et al.*[21] investigated drug release modulation with cyclodextrin in HPMC matrices and found that certain proportion of drug/cyclodextrin enhanced drug diffusion and prevented hydrophobic interaction between polymer and drug. In addition to it, a higher cyclodextrin/lactose ratio significantly increased the release rate of hydrophobic drugs. From all these results and observations mainly the viscosity of polymer and swelling capacity of binding agent may play role in drug release from the bilayered system. In our laboratory, further study with the great concern on release kinetics would be performed near future.

Conclusions

A novel drug delivery system design for meloxicam with

modulation of various solid dosage formulation was approached and its evaluation was performed on dissolution sudy. From results the desired and expected drug release profile was achieved, which initial burst release for highly rapid resorption followed by sustained release for prolong response againt pain.

Acknowledgments

I would like to thank Richwood for donation of Metolose SR and BASF Korea for providing Ludipress used in our experiment.

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