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INTRODUCTION

To overcome the problem of difficulty in swallowing tablets, the new drug delivery dosage forms known as oral disintegrating tablets (ODTs) were developed. These tablets can be dissolved or suspended within 60 s in the mouth for easy swallowing [1)]. Disintegration time and taste masking are primary considerations in the formulation of ODTs. Current taste-masking methods, including sweeteners and flavors [2)], are not sufficient for use in ODTs. Thus, new taste-masking techniques have been developed recently, i.e. ion exchange resins and cyclodextrins [1, 3)]. An ion exchange resin consists of two components: a cross-linked polymer matrix and a functional component with bound counter ions [4)]. Exchange of an ionized drug molecules with counter ions binds the drug to the resin, forming a "resinate". The drug resinate does not come in contact with the taste buds, and so its bitter taste is masked. However, the controlled release of drugs from resinates can delay the onset of action [3)]. To circumvent this effect, taste masking by cyclodextrins has been developed. A cyclodextrin molecule has a lipophilic cavity that forms an inclusion complex by accepting a molecule or the nonpolar part of a molecule into the cavity. The encapsulating the drug molecules at the molecular level reduces the unpleasant odor and taste [5)]. Moreover, an inclusion complex is rapidly wetting than the free drug, and it enhances the dissolution of the drug. Therefore, the combination of ion exchange resins and cyclodextrin has promise for the development of ODTs for weakly water-soluble drugs with bitter taste. Meloxicam (MX), a class of non-steroidal anti-inflammatory drugs (NSAIDs) with poor aqueous solubility and bitter taste was selected as a model drug to formulate ODTs. Tablets containing various drug forms (free drug, resinate, MX/HPβCD complexes, and the mixture of resinate and MX/HPβCD complexes) were prepared and evaluated for properties that included disintegration time, taste, and dissolution profiles.

MATERIALS AND METHODS

Materials Meloxicam, 2-hydroxypropyl-β-cyclodextrin (HPβCD) with molar substitution 0.6, poly (styrene-co-divinylbenzene) sodium sulfonate (Amberlite® IRP-69), and poly(styrene codivinylbenzene) with dimethylamine functional group in the chloride form (Dowex® 1x2-200) were purchased from Sigma Chemical Co., USA. Microcrystalline cellulose (Comprecel® M102 D+; Mingtai chemical, Taiwan.), spray dried lactose (Super-Tab® 11SD; DMV-fonterra excipients GmbH & Co., Germany), Crospovidone (Kollidon®CL; BASF, Germany), mannitol (Merck, Germany), icing sugar, and magnesium stearate were purchased and used as received. Deionized water was used in this work.

Preparation of MX resinate First, saturated MX solutions were prepared as follows. An excess amount of MX was added into phosphate buffer solution at pH 8. The mixture was vigorously shaken on a magnetic stirrer for 24 h. Then, the sample was filtered through a 0.45 μm membrane filter to remove any undissolved solids. The dissolved MX was assayed at a wavelength of 362 nm by UV–Visible spectrophotometry (NanoVue™, GEHealthcare, UK). A MX resinate was prepared by a batch method. The saturated MX solution were equilibrated with Dowex® 1x2-200 resin at 2:1 weight ratios of MX to resin while stirring magnetically for 48 h. After equilibration, the resinate was collected by filtration, washed several times with copious amounts of deionized water, and dried at 50°C overnight in a hot air oven. The percentage of MX loading was determined by an elution method. The resinate was accurately weighed and placed in a volumetric flask that contained 2 N potassium chloride (KCl) solution. The mixture was stirred magnetically for 24 h and the eluted MX was assayed by spectrophotometry. The MX loading (% w/w) of the resinate was calculated with the following equation: %MX loading = (MX_{EL}/W) x 100% where MX_{EL} and W are the amounts of eluted MX and resinate, respectively.

MX/HPβCD complexes Meloxicam and HPβCD were mixed at 1:1 molar ratio of meloxicam and HPβCD that were blended in a plastic bottle for 10 min.

The mixture ratio of resinate and MX/HPβCD complexes The resinate and MX/HPβCD complexes were mixed at 1:2 weight ratio of resinate to MX/HPβCD complexes that was blended in a plastic bottle for 10 min.

Preparation of Meloxicam ODTs Several ODTs containing equivalent doses (7.5 mg) of MX in the free drug, resinate, MX/HPβCD complexes and the mixture ratio of resinate and MX/HPβCD complexes were developed. The formulae of meloxicam ODTs are summarized in Table 1. All materials, except magnesium stearate were blended in a plastic bottle for 10 min. Then, magnesium stearate was added and materials were mixed for an additional 3 min. A portion of the mixture was accurately weighed (200 mg), transferred to a hand hydraulic press machine (Specac P/N 15011/25011, UK), and compressed at a constant force (29.4 kN) using stainless steel flat-face punches with a diameter of 9.53 mm.

Table 1 Composition of meloxicam ODTs

Ingredient (mg)	F1	F2	F3	F4	F5	F6
Meloxicam (MX)	7.5	-	-	-	-	-
MX resinate	-	15	-	5	-	5
MX/HPβCD complexes	-	-	7.5/29.45	5/19.65	7.5/29.45	5/19.65
Mannitol (10%)	20	20	20	20	20	20
Icing sugar (10%)	20	20	20	20	20	20
Comprecel® M102 D+ (20%)	40	40	40	40	40	40
Kollidon®CL (5%)	10	10	10	10	10	10
Amberlite® IRP-69 (20%)	-	-	-	-	40	40
Magnesium stearate (0.5%)	1	1	1	1	1	1
Super-Tab® 11SD q.s. to	200	200	200	200	200	200

Evaluation of Meloxicam ODTs (1) The amount of MX in a tablet was determined by crushing the tablet in a mortar. Then, the crushed powder was transferred into a 250-ml volumetric flask, and 2 N KCl, pH 8, solution was added to adjust the volume. The mixture was stirred magnetically for 24 h. The supernatant was filtered and assayed by UV–Visible spectrophotometry. The MX content was calculated and expressed as % labeled amount. (2) The tablets were evaluated for uniformity of weight, diameter hardness, and friability. Tablets were individually weighed on an analytical balance. The thickness and diameter were measured with amicrometer (Sylvac S229, Switzerland). The hardness was measured with a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). The friability was determined with a Roche friabilator (Yeoheng Co., Thailand). (3) In vitro disintegration time. A modified method was used to determine the disintegration time of tablets simulating the conditions similar to mouth cavity [6]. The 6 ml of artificial saliva was placed inside vessel in such way that 2 ml of artificial saliva was below the sieve and 4 ml above the sieve. The tablet was placed on the sieve no 10 and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. (4) In vivo disintegration time and taste evaluation was performed with six healthy human volunteers. This study was approved by an Investigational Review Board (Human Studies Ethics Committee, Faculty of Pharmacy, Silpakorn University, approval no. 24-2553). Each volunteer randomly took a tablet and kept on their tongue, the time required for complete disintegration of tablet was recorded as in vivo disintegration time and the bitterness after a tablet completely disintegrated was determined immediately. The taste was evaluated and assigned a numerical value, i.e., 0 = tasteless, 1 = slightly bitter, 2 = moderately bitter and 3 = strongly bitter, respectively. (5) In vitro dissolution studies were performed in 0.1 N HCl for 2 h using a USP dissolution testing apparatus II (type PTW, Pharmatest, Germany) at 37±0.5°C with a rotation speed of 50 rpm. After 2 h, the pH was changed to pH 6.8 by the addition of 0.20 M solution of trisodium phosphate, which was equilibrated to 37°C. The MX release was measured at predetermined times; samples of medium were collected and replaced with fresh medium, and analyzed by UV–Visible spectrophotometry.

RESULTS AND DISCUSSION

Preparation of MX resinate MX has two dissociation constants (pKa), 1.09 and 4.18. The isoelectric point (pI) of MX, which was computed from $(pKa_1+pKa_2)/2$ [7], was 2.63. Therefore, the condition of pH>2.63 can increase the solubility and ionization of MX into anionic forms that can be exchanged with counter ions to form MX resinates. MX solubility increased when pH was raised from pH 3 to 8 [8]. The maximum solubility was observed at pH 8, which was used to prepare MX resinate. The resinate was successfully prepared by a batch process. After the resin was placed in the MX solution, ions from the

resin and MX solution diffused, and the dissolved MX in its ionized form (MX^-) exchanged with the counter ion (Cl^-) of resin and bound to the resin via ion exchange reactions, forming the resinate complex. The MX content was 49.69±0.35%w/w of MX to resinate, according to an elution method.

Preparation of meloxicam ODTs ODTs containing MX in various forms (free drug (F1), resinate (F2), MX/HPβCD complexes (F3), and the mixture of resinate and MX/HPβCD complexes (F4)) were formulated. The results showed that the MX form affected the disintegration time and hardness of the tablets (Figure 1). The disintegration times were longer and the tablets were harder for tablets formulated with MX/HPβCD complexes (F3) and the mixture of resinate and MX/HPβCD complexes (F4) than for tablets formulated with the free drug and the resinate (F1 and F2). The disintegration time was prolonged with increasing the hardness that was caused by the strengthening stronger attractive intermolecular forces among the particles increase the hardness, hinder water penetration and prolong the disintegration time. HPβCD contains waters of crystallization (14%) that increases binding among the particles, thus producing stronger tablets [9]. To improve the tablet disintegration times, the 20% of Amberlite® IRP-69 was selected as additional disintegrants for tablets containing MX/HPβCD complexes (F5) and the mixtures of resinate and MX/HPβCD complexes (F6). Rapid disintegration times were occurred due to increases in water uptake and swelling with of Amberlite® IRP-69 [10].

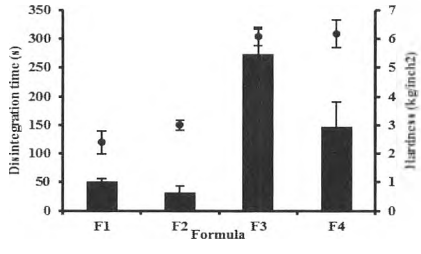

Figure 1 Disintegration times (bar graph) and hardness (dot graph) of meloxicam ODTs

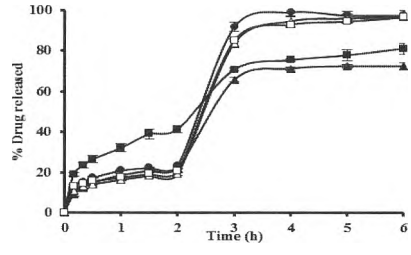

Figure 2 Dissolution profiles of MX from tablets; (filled circle) marketed product (mobic®), (filled upright triangle) F1, (filled square) F2, (open upright triangle) F5, and (open square) F6

Evaluation of meloxicam ODTs Tablets from F1, F2, F5, and F6 were selected and evaluated for optimal ODTs. There were no significant differences in the weight, diameter, and hardness of these tablets, Table 2. For all tablets, the hardness was approximately 3 kg/in.^{2}, and the friability was below the acceptable limit (<1%), indicating that tablet hardness was high enough to withstand erosion during handling and storage. Tablets disintegrated rapidly within 60 s, the acceptable limit for ODTs. The rapid disintegration of tablets was due to the two types of disintegrants (Kollidon®CL and Amberlite® IRP-69). Kollidon®CL has wicking ability that is a principal mechanism of disintegration, while Amberlite® IRP-69 has a combination of wicking and swelling properties for disintegration. When the tablet is exposed to water, disintegrants pull water through capillaries and the resin swelled, and the tablet disintegrated.

Table 2 Evaluation of parameters of meloxicam ODTs

Formula	weight (mg) n = 20	diameter (mm) n = 20	hardness (kg/inch2) n = 20	friability (%)	in vitro DT (s) n = 6	in vivo DT (s) n = 6	drug content (%LA) n = 3
F1	199.16 ± 3.27	9.61 ± 0.02	2.39 ± 0.39	0.99	52.17 ± 4.62	50.00 ± 11.98	106.51 ± 1.49
F2	202.99 ± 5.81	9.64 ± 0.05	3.00 ± 0.18	0.77	32.50 ± 11.24	42.17 ± 5.19	103.00 ± 4.62
F5	200.31 ± 3.72	9.60 ± 0.01	2.70 ± 0.39	0.62	50.67 ± 7.58	89.67 ± 15.16	100.62 ± 3.24
F6	207.43 ± 3.75	9.60 ± 0.01	2.94 ± 0.27	0.80	45.17 ± 11.13	62.67 ± 21.27	99.78 ± 3.16

The in vivo tablet disintegration times were slightly longer than the in vitro times, due to the very small volume of human saliva that penetrated the tablet relative to the large volume of disintegration medium [11]. The MX content (% labeled amount) in all formulations were within the assay limit (90%–110%) specified in the USP meloxicam tablet monograph. The dissolution profiles of formulated ODTs and the marketed product (mobic®) are shown in Fig. 2. In acidic medium (0.1 N HCl), all formulae except F2 released less than 20% of the MX due to its poor solubility at acidic pH values. When the pH was changed to pH 6.8, the MX release dramatically increased due to its greater solubility and ionization. The dissolution profile of the tablets containing the free drug (F1) released approximately 60% of the MX within 6 h, which was less than the other formulae. The tablets containing resinate (F2) released approximately 80% of the MX within 6 h, which was more than the free drug (F1) case. This finding can

be explained by the hydrophilicity of ion exchange resin. In the dissolution medium, the tablet disintegrated, which liberated the resinate from the tablet. The ion exchange resin allowed aqueous solutions to enter the three-dimensional resin structure and rapidly hydrate the MX resinate, thereby enhancing the dissolution rate. The anions in the release medium displaced the loaded MX from the resinate via ion exchange reactions, and the liberated MX was released. However, MX was not completely released, which might be attributed to the equilibrium of the release process via the ion exchange reaction. Tablets with MX/HPβCD complexes (F5) and the mixture of resinate and MX/HPβCD complexes (F6) provided complete MX release within 6 h. This finding indicated that HPβCD enhanced MX dissolution via the in situ inclusion complex with HPβCD during tablet disintegration and MX dissolution. In the case of tablets with the mixture of resinate and MX/HPβCD complexes (F6), the MX release was due to the combination of MX release by the MX/HPβCD complexes and MX resinate via in situ inclusion complexation and ion exchange reactions that provided complete MX release within 6 h. The complete MX release by F5 and F6 was similar to the release of the commercial product (Mobic®). Table 3 presents results from the taste evaluation of ODTs with various MX forms compared to the free drug (F1) reference. The level of bitter taste from F2 and F6 was significantly lower than F1 (p value<0.05 analyzed from Wilcoxon signed rank test), i.e., 0.012 and 0.019 for F2 and F6, respectively. In contrast, the bitterness level of F5 was not significantly different from F1. This finding confirmed that the tablets with resinate (F2) and the mixture of resinate and MX/HPβCD complexes (F6) successfully masked the bitter taste, while the MX/HPβCD complexes in F5 did not. However, only tablets containing the resinate and MX/HPβCD complexes (F6) successfully masked the bitter taste of MX and enhanced MX dissolution. Therefore, F6 was selected as the best formulation of MX ODTs.

Table 3 Taste Evaluation of Meloxicam ODTs

Volunteers	Bitter level*			
	F1	F2	F5	F6
1	2	1	2	1
2	1	0	1	1
3	2	1	2	0
4	2	0	1	1
5	2	0	2	0
6	2	1	2	1

*Bitterness levels: 0 = tasteless, 1 = slightly bitter, 2 = moderately bitter and 3 = strongly bitter

CONCLUSION

Taste-masked meloxicam ODTs with enhanced dissolution were successfully prepared using a combination of ion exchange resin and cyclodextrin with the MX resinate and MX/HPβCD complexes. This formulation demonstrated a good level of taste, rapid disintegration, and complete drug dissolution. Thus, this tablet is advantageous for poorly water-soluble drugs with bitter taste and increases the palatability of ODTs.

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