Thai Journal of Pharmaceutical Sciences (TJPS)

5th International Conference on Pharmaceuticals,
Nutraceuticals and Cosmetic Science (IPNaCS 2017)

Release Behaviors and Kinetics of Ambroxol Sustained Release Matrix Tablets

Wipada Samprasit*, Benchawan Chamsai

Department of Pharmaceutical Technology, Faculty of Pharmacy, Rangsit University, PathumThani, Thailand.

* Corresponding author: Tel. +66(0)29972000 ext 1404; Fax. +66(0)29972000 ext 1403;
E-mail address: swipada@hotmail.com

Keywords: Ambroxol, Sustained release, Matrix tablets, Release kinetics

Introduction

Sustained release is a kind of controlled release systems that can slow drug release and provide medication over extended period. These become the reducing frequency of administration and improving patient compliance of oral dosage forms. There are numerous approaches to design sustained release dosage forms such as matrix, reservoir-type and coated systems. Among the different approaches, matrix tablets have been the most widely used because of the simple and low-cost manufacturing process.[1] Matrix polymers of sustained release tablets act as a key role to control the release of drug, including hydrophilic and hydrophobic polymers. Hydrophilic matrices control the diffusion of drug by creating the polymer hydration to delay drug release. The polymers used in the preparation of hydrophilic matrices are cellulose derivatives, i.e. hydroxypropymethylcellulose (HPMC) sodium carboxy methyl cellulose (SCMC) and methylcellulose (MC), non-cellulose natural polymers and semi-synthetic polymers. HPMC are frequently used as the basis for sustained release hydrophilic matrix tablets. Their properties are responsible for the hydration, diffusion and erosion-resistant gel layer which is able to control drug release.[2] Sustained release tablets based upon hydrophobic matrices have been also used. The delayed drug release is due to the dissolved drug has to diffuse through capillary network between the polymers. Ethyl cellulose (EC) is a hydrophobic polymer that has been widely used to prepare sustained release matrix tablets. In addition, the combined hydrophilic/hydrophobic matrix polymers may modify drug release by changing the ratio of polymers.

Ambroxol hydrochloride (ABX) is classified as a class I drug by Biopharmaceutics Classification System. According to its high water solubility, absorption and short biological half-life (4 h)[3], resulting in the frequent daily dosing (2-3 times) to act as a mucolytic agent used in the production of excess or thick mucus. The therapeutics of ABX usually use in chronic respiratory diseases that necessitates its formulation into sustained release dosage forms. Therefore, it is an ideal candidate to be designed as sustained release dosage forms. Thus, the aim of work was is to develop sustained release matrix tablets of ABX using hydrophilic, hydrophobic and combined hydrophilic/hydrophobic polymer. Microcrystalline cellulose (MCC, Avicel® PH 101), HPMC (Methocel® F4M) and EC (Ethocel®) were used as matrix polymers. Tablets were evaluated for physical characteristics, ABX release profiles and kinetic mechanisms.

Methods

ABX sustained release tablets formulation

Matrix Tablets containing an equivalent dose (75 mg) of ABX (Vitalife Laboratories, India) were developed. Compositions were presented in Table 1. Super-tab® (spray dried lactose, the lactose company of New Zealand Ltd, New Zealand) and Emcompress® (Dicalcium Phosphate, Aldrich Chemical Co., USA, USA) were selected as water soluble and insoluble fillers, respectively. HPMC (Methocel® F4M, Srichand-united dispensary Ltd, Thailand), MCC (Avicel® PH 101, FMC, USA) and EC (Ethocel®, Rama chem., Thailand) were used as matrix polymers at the various amounts. Fixed amounts of talcum (Srichand-united dispensary Ltd, Thailand) and magnesium strearate (Trade mark, Italy) were used as lubricant. All ingredients, except talcum and magnesium stearate, were shaken in a plastic bag for 10 min. Then, the lubricants were added and mixed further for 5 min. The mixture was transferred to compress using manual single stroke tablet machine (Yeoheng Co., Thailand) with stainless flat-face punches with a diameter of 3/8 inch.

Evaluations of ABX sustained release tablets

The ABX content was evaluated by crushing a tablet in a mortar, weighed and transferred into a 100 volumetric flask, and methanol was added to adjust the volume. The dissolved ABX was assayed by UV-visible spectrophotometer (Spectronic genesys 5, U.S.A.) at wavelengths of 307.5 nm. The ABX content was calculated and expressed a % labeled amount. Tablets were individually weighed on an analytical balance, and the average weight and standard deviation were calculated. The thickness was measured using a micrometer (Mitutoyo Thickness Gage, Japan). The hardness was measured using a Monsanto hardness tester (K.S.L. Engineering Co., Thailand). The friability was determined using a Roche friabilator (K.S.L. Engineering Co., Thailand). Tablets were weighed (W_1) and placed into the friabilator which were rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fines (W_2), and the friability was calculated by $100\times(W_1-W_2)/W_1$. Twenty tablets were used in each testing.

Table 1 Formula of ABX sustained release tablets

Formula	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
ABX (mg)	75	75	75	75	75	75	75	75	75	75	75	75	75	75
HPMC (mg)	-	-	30	50	70	-	-	-	-	-	-	42	34	26
MCC (mg)	-	-	-	-	-	30	50	70	-	-	-	-	-	-
EC (mg)	-	-	-	-	-	-	-	-	30	50	70	8	16	24
Talcum (%)	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate (%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Super-tab® (mg)	200	-	-	-	-	-	-	-	-	-	-	-	-	-
Emcompress® (mg)	-	200	100	100	100	100	100	100	100	100	100	100	100	100

Release behaviors and kinetics of ABX sustained release tablets

In *vitro* dissolution studies were performed in 0.1 N HCl (1000 ml) for 2 h using a USP dissolution testing apparatus I (VANKEL Techonology Group Cary, North Carolina) at 37 ± 0.5 °C with a rotation speed of 100 rpm. After 2 h, the release medium was changed to phosphate buffer pH 6.8 (1000 ml), which was equilibrated to 37 °C. The ABX release was measured at predetermined times; samples of medium (10 ml) were collected and replaced with fresh medium, and analyzed by UV-visible spectrophotometer at wavelengths of 307.5 nm. The obtained data were carefully analyzed to determine the cumulative amount of ABX release at each immersion time point. The marketed product (Mucosolvan® PL) was also evaluated to compare the release profiles with the tablets.

The release kinetics of tablets and Mucosolvan PL® were investigated using a zero-order model, a first-order mode, the Higuchi model and Korsmeyer–Peppas model, as follows:

Zero-order model	$Q_t = k_0 t$	First-order model	$\ln C = \ln C_0 - k_1 t$
Higuchi model	$Q_t = k_H t^{0.5}$	Korsmeyer–Peppas model	$\frac{M_t}{M_\infty} = kt^n$

where Q_t is the amount of ABX released at time t; k_0 is the zero-order release constant, C_0 is the initial concentration of ABX, k_1 is the first-order rate constant, k_H is the Higuchi release rate constant, M_t/M_∞ is a fraction of ABX released at time t, k is the release rate constant and n is the release exponent. The value of n is used to characterize the release mechanism of ABX. For the case of cylindrical tablets, $0.45 \leq$ n corresponds to a Fickian diffusion mechanism, 0.45 < n <0.89 to non-Fickian transport, n = 0.89 to Case II (relaxational) transport, and n > 0.89 to super case II transport.[4]

Results and Discussion

Development of ABX sustained release tablets

The ABX tablets were successfully prepared by direct compression method. Results showed that the type of fillers and matrix polymers affected the characteristics of tablets (Table 2). The formulation using Emcompress® (F2) provided higher hardness and friability than that using Super-tab® (F1). Because of Emcompress® is calcium phosphate, dibasic anhydrous which has excellent compressibility. In addition, its brittle fracture exhibits the lamination and capping when compacted at higher pressures.[5] However, the friability of tablets was below the acceptant limit (< 1%), indicating that tablets was high enough to withstand erosion on handling and storages. No matter fillers used, labeled amount, weight and thickness of tablets were not significantly different. The ABX content of both F1 and F2 was found to be within the assay limit (90-110%) specified in the monograph of USP ABX tablets.[6] Release profiles of tablets using Super-tab® and Emcompress® as diluents are shown in Figure 1a. Both F1 and F2 provided a burst release pattern. The complete ABX release was observed within 2 h of study. Moreover, F1 gave the faster dissolution rate than that F2. This finding supported a well-established property of Super-tab® to increase wettability and promote drug release.[5] In the case of Emcompress®, water insoluble diluent property

caused the slow ABX release. Thus, Emcompress® was selected as a diluent to develop ABX sustained release tablets.

The matrix polymer, i.e. HPMC, MCC and EC was added into the tablets at the various amounts. Tablets formulated with HPMC (F3-F5) and MCC (F6-F8) could compress into the tablets, whereas EC (F9-F11) could not. This was due to the low compressibility of EC than that HPMC and MCC.[5] This result was corresponded with the study of Enayatifard, et al that demonstrated the low compressibility of EC, resulting the lower hardness compare to HPMC.[7] The HPMC/EC mixtures were formulated to improve the compressibility and hardness of tablet (F12-F14). Tablets containing the various amount of HPMC, MCC and HPMC/EC mixtures showed the insignificant different in the ABX content, weight, thickness, hardness and friability. The ABX labeled amount was within the assay limit (90-110%) specified in the monograph of USP ABX tablets.[6] The acceptable hardness (> 3 kg) and friability (< 1%) revealed that tablets was high enough to withstand erosion on handling and storages. MCC has excellent compressibility that is widely added in tablet formulations to improve hardness and prevent capping. HPMC is hydrophilic polymer with a good compressibility.[8] EC is a compressible, hydrophobic polymer that has been used to prepare sustained release products. These results indicated that all tablets presented acceptable physical properties to be candidates for ABX sustained release tablets.

Table 2 Characteristics of ABX sustained release tablets

Formula	Labeled amount (%)	Weight (mg)	Thickness (mm)	Hardness (kg)	Friability (%)
F1	104.25 ± 0.35	288.68 ± 4.49	3.919 ± 0.055	2.7 ± 0.27	0.5286
F2	104.48 ± 1.18	290.89 ± 2.99	3.463 ± 0.167	3.4 ± 0.55	0.6069
F3	105.69 ± 0.69	220.47 ± 3.01	3.908 ± 0.050	3.8 ± 0.84	0.7407
F4	106.02 ± 0.70	239.30 ± 2.73	3.293 ± 0.036	5.0 ± 0.35	0.5714
F5	106.55 ± 1.40	254.81 ± 2.59	3.276 ± 0.020	4.4 ± 0.42	0.5317
F6	109.30 ± 0.58	215.69 ± 4.82	2.792 ± 0.053	4.3 ± 0.84	0.7343
F7	109.12 ± 0.55	228.75 ± 3.44	3.069 ± 0.062	4.1 ± 0.22	0.6664
F8	107.60 ± 0.45	259.27 ± 4.44	3.424 ± 0.155	4.0 ± 0.35	0.4283
F12	107.54 ± 3.98	234.96 ± 2.06	2.119 ± 0.015	4.0 ± 0.61	0.6755
F13	106.01 ± 3.51	235.07 ± 1.76	2.173 ± 0.042	4.5 ± 0.71	0.8753
F14	107.54 ± 0.01	234.79 ± 1.93	2.106 ± 0.060	4.4 ± 0.55	0.7254

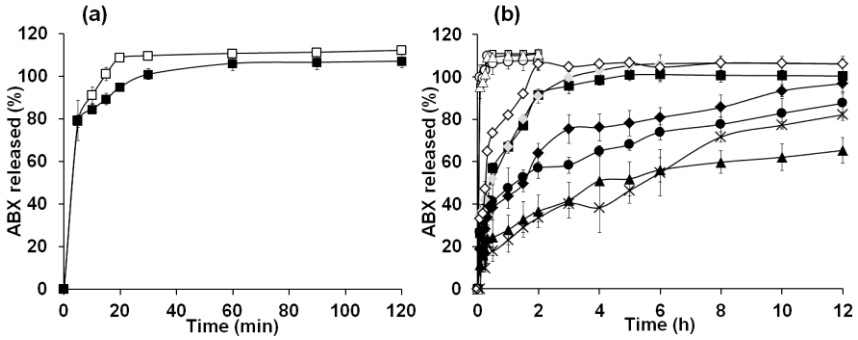

Figure 1 Release profile of ABX from tablets (a) using the different fillers; (□) F1 and (■) F2 and (b) using the different types and amount of matrix polymers; (■) F3, (●) F4, (▲) F5, (□) F6, (○) F7 (Δ) F8, (◆) F12, (◆) F13, (◇) F14 and (x) Mucosolvan® PL. Data are represented as mean ± SD (n=3).

Release behaviors and kinetics

Release profiles of ABX tablets are displayed in Figure 1b. Tablets incorporating MCC (F6-F8) provided the burst and complete ABX release within 2 h of study. MCC exhibit very good disintegrating property via wicking action. It functions by allowing water to enter the tablets by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals. While the tablets disintegrated, ABX also rapidly released into the medium. These results were contrast with the case of tablets containing HPMC and HPMC/EC mixtures. The ABX release data obtained over a period of 12 h. The release rate and ABX amount decreased as the amount of HPMC increased. HPMC matrix acted as gelling agents that generates swelling gel layer. The hydration, diffusion and erosion-resistant gel layer was able to control drug release.[9] At the higher amount of HPMC, the viscosity of gel matrix was increased which resulted in a decrease in the effective diffusion of drug.[10] The ABX had to diffuse through the gel layer, thus resulting in the sustained release. Figure 2 shows the image of ABX tablets (F5) during the dissolution study. It was seen that tablet was swelled and formed gel layer to control ABX release. The HPMC/EC mixtures were further designed to incorporate into the tablets (F12-14) which aimed to tailor the drug release. Incorporation of varying amounts of EC controlled the ABX release at 2 h of test. EC might attribute to

decrease the penetration of release medium in the presence of hydrophobic polymer, leading to reduce the drug diffusion from the matrix tablets.[7] However, the increase of ABX release was observed when incorporated the higher amount of EC. ABX release (over 12 h) from tablets with varying amounts of HPMC/EC mixtures (F12, F13 and F14) was 80, 100 and 100% , respectively. The reason might be that large hydrophobic molecules imposed a discontinuity in the gel structure, leading to formation of a weaker barrier than the HPMC gel alone.[11] According to the results, an addition of 50 and 70 mg of HPMC (F4 and F5) and HPMC/EC mixtures at 42/8 mg (F12) into the tablets obtained the most similar release pattern to Mucosolvan® PL.

F4, F5 and F12 were further determined the release kinetics to gain insight into the mechanism compare to Mucosolvan® PL. The release kinetics of ABX was examined by fitting with zero-order, first-order and Higuchi models. It was found that the release profiles were best fit by the Higuchi model with the highest R^2 (Table 3), indicating that the kinetics of the release of ABX was governed by the Higuchi model. This finding might be explained by the fact that the main mechanism of ABX release was diffusion. Moreover, a modeling analysis using the Korsmeyer–Peppas equation was carried out by fitting the ABX release data until 60% of the ABX was released. The values of exponential factor 'n' for the Korsmeyer–Peppas model were found to be less than 0.45. These results indicated a Fickian diffusion-controlled ABX release. The matrix polymers mainly controlled the diffusion of ABX from the tablets. HPMC forms a strong viscous gel on contact with aqueous media. EC decreases the penetration of aqueous media.

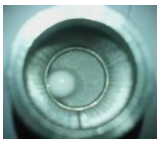

Figure 2 The image of tablet (F5) during the dissolution study.

Table 3 Kinetics models of release profile of ABX sustained release tablets and Mucosolvan® PL

Formula	Zero-order	First-order	Higuchi	Korsmeyer–Peppas	
	R^2	R^2	R^2	n	R^2
F4	0.7587	0.9036	0.9166	0.2211	0.9947
F5	0.8162	0.9591	0.9621	0.3457	0.9855
F12	0.7645	0.9225	0.9354	0.3411	0.9740
Mucosolvan® PL	0.9152	0.9288	0.9644	0.3112	0.7531

Conclusion

The proper amount of HPMC and EC offered as usable matrix polymers for developing ABX sustained release tablets by direct compression. HPMC and HPMC/EC mixtures could slow down the release profile of ABX. The gel layer of HPMC and hydrophobic nature of EC controlled the hydration and diffusion of ABX from the tablets. The sustained release of ABX was achieved with good characteristic of tablets including labeled amount, weight, thickness, hardness and friability. This approach may be suitable for development of controlled delivery of highly soluble drugs such as ABX.

Acknowledgements

The authors would like to acknowledge Faculty of Pharmacy, Rangsit University for materials and laboratory facilities supports. We also thank to Sarun Nimvorapun and Singhaphan Tithiratsanont for their research assistant.

References

1. Zhou X, Wang P, Wang J, Liu Z, Hong X, Xiao Y, et al. Hydroxyethyl Pachyman as a novel excipient for sustained-release matrix tablets. Carbohydrate Polymers. 2016;154(10):1-7.
2. Vasques MJ, Perez-Marcus B, Gomez-Amora JL, Martinez-Pacheo R, Souto C, Concheiro A. Influence of technological variables on release of drugs, from hydrophilic matrices. Drug Development and Industrial Pharmacy. 1992;18:1355-1375.
3. Nilesh VI. Preparation and evaluation of Ambroxol hydrochloride matrix tablet using different combination of polymers. International Journal of PharmTech Research. 2011;3(1):309-313.
4. Dash U, Murthy PN, Nath L, Chowdhury P. Review kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica. 2010;67(3):217–223.
5. Raymond D Rowe, Paul J Sheskey, Siân C Owen, editor. Handbook of Pharmaceutical Excipient Fifth Edition. London: Pharmaceutical Press; 2006.
6. The United State Pharmacopoeia XXXII/National Formulation XXVII. The United States Pharmacopoeial Convention. Rockville, MD; 2009.
7. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCl from matrices. Tropical Journal of Pharmaceutical Research. 2009;8(5):425-432.
8. Lapidusa H, Lordi NG. Some factors affecting the release of a water–soluble drug from a compressed hydrophilic matrix. Journal of Pharmaceutical Sciences. 1966;55:840-843.
9. Voinovich D, Moneghini M, Perissutti B, Filipovic- Gesic J, Grabnar I. Preparation in high shear mixer of sustained –release pellets by melt pelletisation. International Journal of Pharmaceutics. 2000;203:235-244.
10. Skoug JW, Mikelsons MV, Vigneron CN, Stemm NL. Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. Journal of Controlled Release. 1993;27:227-245.
11. Ahrabi SF, Madsen G, Dyrstad K, Sande SA, Graffner C. Development of pectin matrix tablets for colonic delivery of model drug Ropivacaine. European Journal of Pharmaceutical Sciences. 2000;10:43-52.