Akreditasi LIPI Nomor : 452/D/2010
Tanggal 6 Mei 2010

INFLUENCE OF HIDROXYPROPYL METHYLCELULLOSE AND PECTIN MATRIX ON THE SOLUBILITY PROFILE AND CRYSTAL STABILITY OF THEOPHYLLINE

Yoga W. Wardhana and Mulyadi G. Tedjasaputra
Faculty of Pharmacy-Universitas Padjadjaran
Jl. Raya Bandung-Sumedang Km. 21 Jatinangor 45363, Sumedang, Indonesia
e-mail : ayodhna@gmail.com or ayodhna@yahoo.co.id

ABSTRACT

INFLUENCE OF HYDROXYPROPIL METHYLCELULLOSE AND PECTIN MATRIX ON THE SOLUBILITY PROFILE AND CRYSTAL STABILITY OF THEOPHYLLINE. Humidity is one of a factor affecting drug stability. Theophylline is a good sample which easily modified by humidity. In this study, we investigate the effect of polymer matrix of hidroxypropyl methylcelullose (HPMC) and pectin to inhibit the humidity-caused crystal stability changes of theophylline. Theophylline anhydrous (Ta) and mixture of Ta and matrix (80 : 20, 70 : 30 and 60 : 40) were used as the object of the study. The mixture was pressed to tablets using a Single Punch 12 mm flat E. Korsch machine. Humidity exposure was performed using a desiccator in room temperature (27 °C), with 94 % of relative humidity for 3 weeks of storage. The ability of matrix in inhibiting the change of Ta to theophylline monohydrate (Tm) was determined by comparing the result of dissolution test and X-Ray diffraction patterns from material test before and after humidity exposure. The results suggest that both polymers inhibited the changes of Ta to Tm. However, pectin was more superior than HPMC in inhibiting the hydration.

Key words : Humidity, HPMC, Pectin, Solubility, Crystal stability, Theophylline

ABSTRAK

PENGARUH MATRIKS *HYRDROXYPROPYL MEHTYLCELLULOSE* DAN *PECTIN* TERHADAP PROFIL KELARUTAN DAN STABILITAS KRISTAL DARI *THEOPHYLLINE*. Kelembaban merupakan salah satu faktor yang mempengaruhi stabilitas obat. *Theophyline* merupakan contoh yang menarik karena mudah terpengaruh oleh kelembaban. Studi ini mempelajari pengaruh dari matriks polimer *hidroxypropyl methylcelullose* (*HPMC*) dan *pectin* dalam menghambat perubahan stabilitas kristal *theophyline* yang diakibatkan oleh kadar air. *Theophylline anhydrous* (Ta) dan campuran dari Ta dan matriks (80 : 20, 70 : 30, 60 : 40) menjadi obyek dalam penelitian ini. Campuran ini dicetak hingga membentuk tablet dengan mempergunakan *punch* tunggal 12 mm *flat* E (*korsch machine*). Pemaparan terhadap kelembaban dilakukan dengan menggunakan desikator pada suhu ruang (27 °C), dengan tingkat kelembaban relatif (*RH*) 94 % selama 3 minggu. Kemampuan matriks untuk menghambat perubahan pada Ta menjadi *theophyline* monohidrat (Tm) ditentukan dengan membandingkan hasil pada tes dissolusi dan pola *XRD* dari material sebelum dan sesudah pemaparan kepada kelembaban. Hasil menunjukkan bahwa kedua polimer yang diuji mampu menghambat perubahan dari Ta menjadi Tm. Meskipun demikian, *pectin* cenderung lebih unggul dari pada *HPMC* dalam menghambat proses hidrasi.

Kata kunci : Kelembaban, *HPMC*, *Pectin*, Kelarutan, Stabilitas kristal, *Theophylline*

INTRODUCTION

Theophylline is known as the drug of choice for asthma. Theophylline has three crystalline forms, including one monohydrated and two anhydrous crystalline. Two anhydrous forms are obtained by different crystallization process, one is obtained by cooling a solution with a higher melting point than the crystals, the other is obtained by vacuum dehydration of the monohydrate. All forms have a different physical and chemical properties. Regard to their solubility, the anhydrous form dissolves in water faster than the monohydrate form. Furthermore, anhydrous form can transform to the monohydrate form in humid environment through recrystallization following the dissolution of anhydrous form in sorbed water [1].

In pharmaceutical dosage forms, solubility play an important role for their efficacy. Drug with higher

Vol. 12, No. 2,Februari 2011, hal : 141 - 144
ISSN : 1411-1098

solubility will easily absorbed on gastrointestinal tract, and therefore will give a faster pharmacological effect. One of the method to study the drug solubility is by a dissolution test, where the drug with high solubility will reach a high concentration faster [2].

As the drug of choice for asthma, theophylline has to be used with caution due to its toxicity to central nervous system. For many drugs and therapeutic indications, conventional multiple dosing of immediate release formulations provides satisfactory clinical performance with an appropriate balance of efficacy and safety. Use of hydrophilic matrices for oral controlled release of drugs is a common practice in the pharmaceutical industry [3].

In this study, we examined the changes in hydration and release profiles of a direct compression anhydrous tablets with two hydrophilic matrices in some variation, which has differing in water binding characteristic. The hydrophilic matrices we used were pectin and cellulose derivative (Hidroxypropylmethyl cellulose/ HPMC).

Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an α-(1-4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. It has been used in a colon biodegradable pectin matrix with a pH sensitive polymeric coating, which retards the onset of drug release, overcoming the problems of pectin solubility in the upper GI tract [4]. Pectin has hygroscopic characteristic to make a viscous gelation forming with sweetly taste [5].

HPMC or hypromellose as The PhEur 2005 describes is a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. Hypromellose defined in the USP 28 specifies the substitution type by appending a four digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. In oral products, hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended-release tablet formulations.

Pectin has been used in film coating formulations containing chitosan and hydroxypropyl methylcellulose in the investigation of the biphasic drug release properties of film-coated paracetamol tablets [4].

In this work, we put theophylline anhydrous and those matrices as tablets under extremely relative humidities for 3 weeks. The high capacity of those matrices for water uptake, gelling and for the formation of hydrogen bonds can crucially affect the hydration and solubility of the drug during storage.

EXPERIMENTAL METHOD

Materials

The following materials were used, theophylline anhydrous (ex china, batch J0450/09(200805015), expiry april 2012), pectin (ex Shin Etsu) and Hypromellose 2910 (ex Shin Etsu).

Methods

All materials were dried for 24 hours at 70 °C, and mixed at the composition of Ta and matrices (HPMC or Pectin) 100 : 0; 80 : 20; 70 : 30 and 60 : 40. The materials were then compressed to tablets with a nominal weight of 125 mg using 12 mm flat punches at Single Punch E. Korsch tablet machine. Ten tablets of all formulation were individually tested for weight, diameters, hardnesses and thicknesses homogenity.

Tablets from each formulation were then taken as samples for dissolution test and recorded for the X-Ray diffraction patterns using Multi-Purpose X-Ray Diffractometer (X'Pert Pro MRD Type PW 3050/60 PANalytica, BATAN Bandung). The rest of the tablets were then stored at desiccator in a room temperature (27 °C) and 94 % relative humidity for 3 weeks. After 3 weeks, each tablets from all formulation were checked for its release profile and X-Ray diffraction patterns. The results were then compared to those of before 3 weeks of storage.

RESULT AND DISCUSSION

Pectin and HPMC gave different tablet characteristics (Table 1). Tablets made from pectin gave brown-white colour, while those made from HPMC gave clear white colour.

All Ta were changed to Tm under 3 weeks extreme relative humidity (27 °C, 94% RH). Polymer matrices were proved to inhibit the hydration during humidity exposure (Figure 1 and Figure 2).

Table 1. Tablet Characteristics

Evaluation	Ta 100 %	Ta 80 %		Ta 70 %		Ta 60 %	
		Pectin	HPMC	Pectin	HPMC	Pectin	HPMC
Weight (mg)	124 ± 0,562	124,95 ± 0,825	125,05 ± 0,605	125,3 ± 0,657	125,2 ± 0,617	126 ± 0,725	125,3 ± 0,733
Thickness (mm)	3,454 ± 0,014	3,363 ± 0,012	3,684 ± 0,014	3,484 ± 0,017	3,942 ± 0,015	3,628 ± 0,019	3,996 ± 0,018
Diameter (mm)	6,075 ± 0,009	6,094 ± 0,008	6,096 ± 0	6,095 ± 0,005	6,096 ± 0	6,096 ± 0	6,096 ± 0
Hardness (N)	40,75 ± 4,064	39 ± 3,84	41,05 ± 3,471	41,75 ± 3,72	40,75 ± 3,726	43 ± 2,51	40,5 ± 3,348

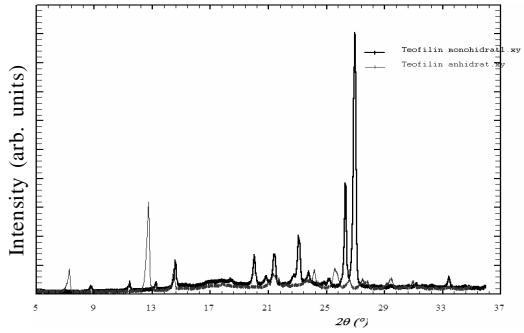

Figure 1. X-Ray diffraction patterns of Ta and Tm

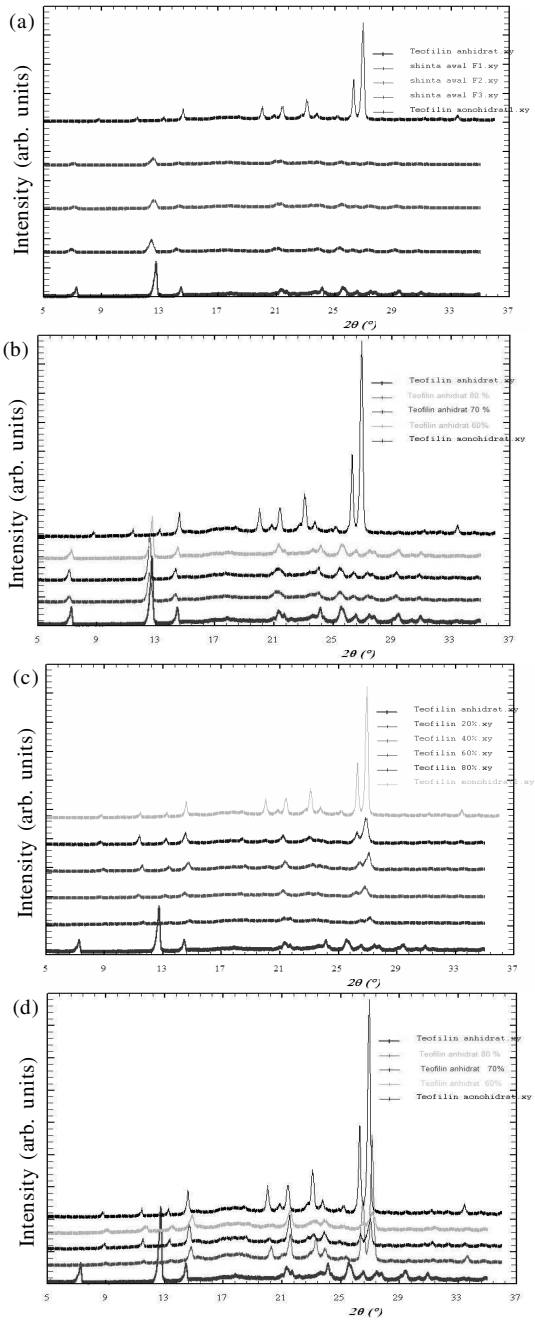

Figure 2. X-Ray diffraction patterns : Ta before storage and Ta with matrices before and after 3 weeks humidity exposure (a). Pectin matrix before storage, (b). HPMC matrix before storage, (c). Pectin matrix after storage and (d). HPMC matrix after storage

Table 2. Hydration rate percentages for each formula

Ta	Hydration at 2θ : 26,925° Before		Hydration at 2θ : 26,925° After		Differences	
	Pectin (%)	HPMC (%)	Pectin (%)	HPMC (%)	Pectin (%)	HPMC (%)
100 %	1.89	1.89	100.7	100.7	98.81	98.81
80 %	1.81	1.86	34.84	17.6	33.03	15.74
70 %	1.71	1.75	14.63	16.27	12.92	14.52
60 %	1.33	1.71	7.64	14.10	6.31	12.39

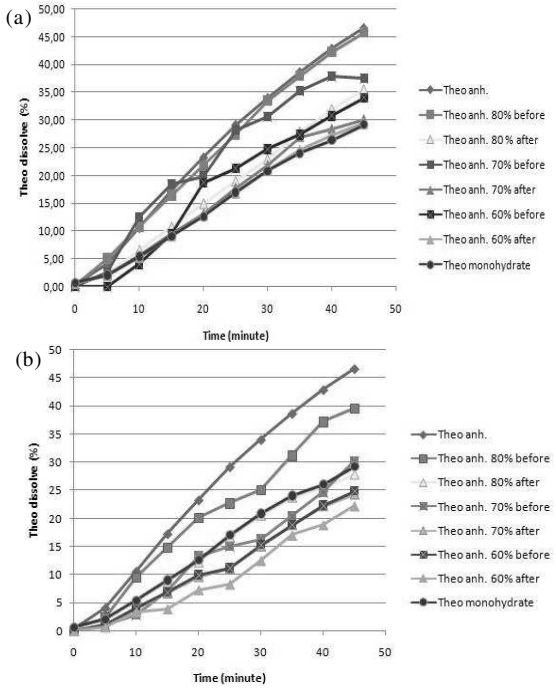

Figure 3. Dissolution profile (a). Pectin matrix and (b). HPMC matrix

The diffraction patterns showed that pectin matrix patterns on 2θ degrees was not as displaced as those of HPMC matrix. It suggest that pectin was more superior than HPMC in inhibiting the hydration of theophylline. When we calculated the 2θ intensity between materials tested before and after storage, the result show that on the ratio of Ta and matrix at 60 : 40 the hydration at pectin was 6,31 % whereas HPMC was 12,39%. It suggest that pectin has ability to detain hydration 2 folds stronger than HPMC. This calculation result were given on Table 2.

Result of the dissolution test showed that pectin matrix has ability to mantain stability of Ta from hydration during dissolution process more superior than HPMC matrix. Figure 3 showed that the profile of HPMC matrix release before and after humidity exposure, except on 20 % HPMC matrix, were below those of Tm. The results of pectin, however, were on the contrary.

CONCLUSION

Ta under humidity exposure will be degraded to Tm that have a lower solubility. This changes can be

Vol. 12, No. 2,Februari 2011, hal : 141 - 144
ISSN : 1411-1098

inhibited by highly hydrophilic polymer matrix such as pectin. The overall effect of hydration on drug release is the result of conflict between the tendency of theophylline hydration to slow drug release and the tendency of tablet swelling to accelerate drug release. The later tendency can cancel the initial tendency with hygroscopic polymer matrices and reducing particle size that favors gelling of the polymer.

ACKNOWLEDGMENT

The authors would like to thanks to Indonesian Atomic Agency (BATAN) Bandung for their collaboration, and to Shinta R. P. and Ria P. for the data collection.

REFERENCES

[1]. C. ALVAREZ-LORENZO, J.L. GÓMEZ-AMOZA, R. MARTINEZ-PACHECO, C. SOUTO and A. CONCHEIRO, *Drug Development of Industrial Pharmaceutical*, **26** (1) (2000) 13 - 20

[2]. A.A. DESPHANDE and C.T. RHODES, *Drug Development of Industrial Pharmaceutics,* **22** (1996) 531-539

[3]. JAIN and K. KEWAL, *Drug Delivery Systems*, Humana Press, Switzerland, (2008) 217

[4]. R.C. ROWE, SHESKEY, J. PAUL, QUINN and E. MARIAN, *Handbook of Pharmaceutical Excipients*, 6th Ed. RPS Publishing, London, (2009) 478-479

[5]. D. MUHIDIN, *Agroindustri Papain dan Pektin*, Penebar Swadaya, Jakarta, (2001)1-34