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Dissolution Profile of Theophylline Extended Release Caplets Based On Metolose 90 SH – 4000SR With Accelerated Stability Study

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Abstract:
To avoid consume theophylline oftenly, we need an extended release dosage form to maintain the therapeutic dose on the blood plasma for a long interval time. The most common dosage form in the market is coated tablet, but that needs a long procedure and quite expensive to be produced. Recently, there is a brand new polymer derived from Hydroxypropylmethyl cellulose is Metolose 90SH-4000SR. This kind of polymer is able to form high viscosity hydro gel with a suitable solvent. Gel which is formed from the polymer physically restrain the active ingredient released on a short period. Through this study, presented practically easy to use metolose as the matrix of a binder in wet granulation method. The study found that efficient solution consistency for binder solution of the matrix gel of Metolose is 10%. In the manufacturing process of the caplets, metolose as gel is used on low concentration at 4,5-5% (18-20 mg of 400 mg total weight of caplet). Both caplets shows similiar quality in terms of physical properties and dissolution rate profile. After 6 months storage at 40^{O}C and humidity 75% (accelerated stability condition storage) the dissolution profile and theophylline contents not change or decrease significantly.
Keywords : Teophylline, Metolose 90SH-4000SR, Extended release dosage form, accelerated stability test.

Introduction:

Teophylline as a drug of choice in the treatment of bronchial asthma, cardial asthma, and pulmonary emphysema. Bronchodilator effects of the drug closely related to the concentration in serum. In patients with asthma required treatment levels at least5-8µg/mL and toxic effects of theophylline beginning at levels above 15 µg/mL, especially when given in combination with other bronchodilators. While theophylline has short half-life of3-7 hours and a narrow therapeutic index that is 10-20 µg/mL[1].

With an arrow therapeutic index, it is necessary to modify the drug to be controlled release so that the concentration of drug in the blood is relatively constant in arelatively long period of time, thereby reducing the frequency of drug use and can reduce the total dose of the drug, thereby minimizing side effects[2]. For that purpose need an extended release dosage form to maintain the therapeutic dose on the blood plasma for a long interval time. Slow or an extended-release preparations are widely used today[3,4,5,6]. Recently, solid dosage forms in such like tablets and capsules already produced in micro granule forms with various materials such as cellulose derivatives and methacrylic acid derivatives.

In this study we used variation concentration of the cellulose derivatives as a matrix. That matrix is Metolose 90SH-4000SR HPMC(Hydoxy propyl methyl celullose) which is specific to slow-release preparation[7]. To elaborate performance and mechanism of drug release from the matrix, we can study it at in vitro method with dissolution test. Performance of drug release from initial product will differently with performance of product after stored in such a long time. The differences generally trending decrease

proportionally to the length of storage time. For that reason after learning the effect of matrix concentration variation thenwe studied also the influence of storage time in dissolution profile.

Materials and Methods

Theophylline anhydrous (ex JilinShulan, China), Metolose 90SH-4000SR (ex ShinEtsu, Japan), Lactose SD (ex Grande, USA), Talcum (ex Haicen, China) and Magnesium stearate (ex Faci, Indonesia), artificial gastric fluid pH 1,2 and artificial intestinal fluid pH 6,8 without enzymes (attempt to match USP 30 NF 25) and reagents appropriate analysis of Merck grade.

Matrix Solution optimization:

Make a variety of binding solution consistency with different concentration between matrix (Metolose 90SH–4000SR) and water. All those binding solution used for wet granulation in caplet formulation.

Caplet formulation:

All of matrix variation solution used in wet granulation methods to make a Theophylline caplet. The quality of granule for caplet was evaluated including loss on drying, flow ability, compressibility, and angle of repose. The caplet quality was evaluated including content uniformity, weight uniformity, size uniformity, hardness, friability, and dissolution.

Characterization of Theophylline Extended release Caplets:

Dissolution profile of theophylline extended release caplets follow in USP 30 NF 25. The apparatus type 2 of dissolution test from SOTAX and for analytical method using spectrophotometer UV–Vis from Analytic Jena (SPECORD).

Accelerated Stability Test:

Only caplet that complies with the requirements as an extended release caplets made with the more unit of batch. The products from that batch then tested with the accelerated stability as ASEAN Harmonization Guidelines 2005. The climatic chamber is from PharmaTehnik, years 2006, Serial No. 40/PT-CC-06.

Results and Discussion

Among those variety of matrix solution between 3–10% of matrix as binding in wet granulation for caplet formulation below. Found that matrix solution between 8.5% and 10% was practically better. Cause more efficient with a shorter drying time and the equitable distribution of granular particles.

From those matrix solution, we have to select the best performance of caplet release profile which suitable in all of requirement. The result seen that caplets from 10% of matrix solution has more an extended release profile then other. As show in figure 1 below. Beside that with 10% of matrix solution give practically easier, shorter drying time with apportionment granular size. Then 10% of matrix solution consistency became a wet binder solution recommendation to use in Theophylline caplet.

Table 1. Theophylline caplet composition

Ingredients	Amount (%)	Amount (mg)
Theophylline Anh.	75	300
Lactose SD	18.5	74
Metolose 90SH–4000SR	5	20
Mg Stearate	1	4
Talcum	0.5	2

Table 2. Theophylline extended release caplet requirement in HCl medium pH 1.2 and buffer phosphate pH 6.0 as required at USP 30 NF 25

Time (hours)	% dissolve
1	Between 3% and 15 %
2	Between 20% and 40%
4	Between 50% and 75 %
6	Between 65% and 100%
8	No more than 80 %

After we used the 10% of matrix solution to the formula in table 1.above. We found some data has Theophylline content more than 100% (fig.1). On the alert if the API content become too high then we test also the decrease levels of matrix in caplets till 4.5% (18 mg) and Lactose SD become 19% (76 mg). Evaluation quality of those caplets formula (4.5% and 5% of matrix) has fulfill all requirement as a good quality caplet. Then we proceed evaluation with dissolution and accelerated stability test. As accelerated stability guideline we took sampling after 0, 1, 2, 3, and 6 months from *Climatic Chamber* at condition 40^{O}C and 75%.

Table 3. Evaluation of granule and caplet quality

Test Parameter	4.5%	5%	Req.
Granule properties			
LOD (%)	1.05	0.41	1–2
Flowability (g/s)	17.65	16.30	>10
Angle of repose (^{O})	14.39	17.20	<25
Bulk density (g/cc)	0.69	0.71	-
Tap density (g/cc)	0.76	0.82	-
Compressibility (%)	9.35	13.18	12–18
Caplet properties			
Weight uniform (mg)	400.48	413.825	380–420
Length uniform (mm)	16.98	17.02	-
Thick uniform (mm)	3.67	3.75	-
Hardness (N)	107.37	86.87	80–120
Friability (%)	0.29	0.43	<0.8

Content uniform (%)	113.76	113.66	94–106

Result from the data of dissolution test after accelerated stability in 6 months storage for both formulation (fig. 2.) shown that after 6 months the dissolution profile and theophylline contents not change or decrease significantly.

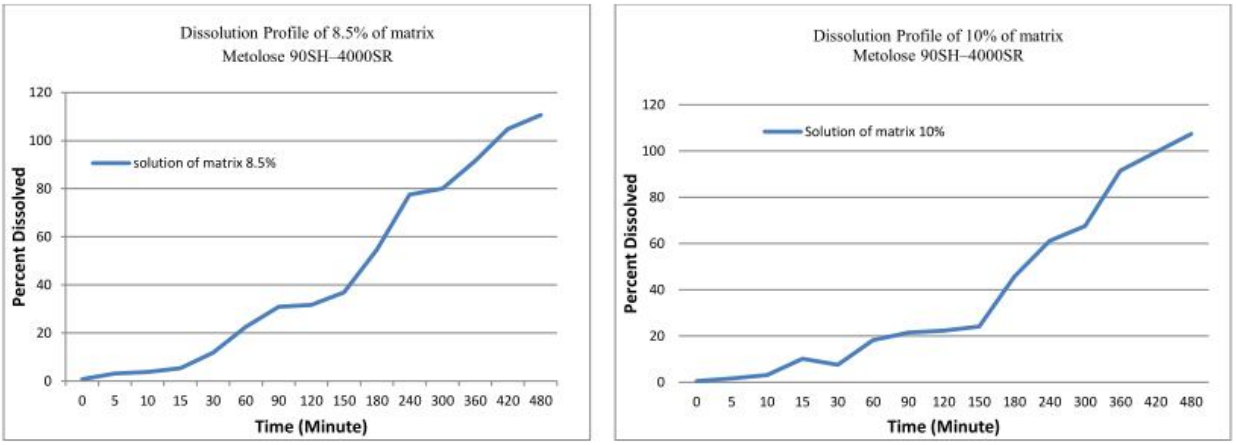

Fig. 1. Dissolution Profile of Matrix Solution between 8.5% and 10% of Metolose 90SH–4000SR

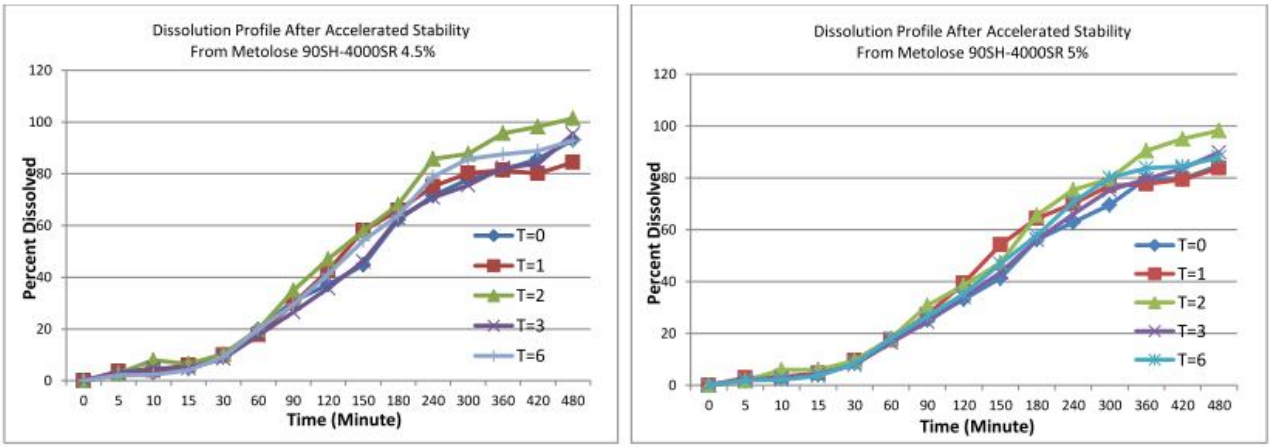

Fig. 2. Dissolution Profile After Accelerated Stability from Metolose 90SH–4000SR

All data represent were fulfill the requirement of extended release profile dosage form despite of 6 months storage. We found that using 4.5% of matrix have no significantly different with 5% of matrix. Then we can recommend to using 4–5% of metolose 90SH–4000SR as an extended release matrix. The accelerated stability condition equivalent with 2 years stress condition at real time storage (25–30^{O}C, RH 70–90%). Meaningly that the theophylline caplets product still stable after 2 years real time storage. We suggest for other research in different accelerated stability condition which have equivalent with 5 years real time

storage to determine lifetime (expire date) of product.

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