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EVALUATION OF SOME ADDITIVES AS RELEASE RETARDANTS IN SUSTAINED RELEASE THEOPHYLLINE TABLETS

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ABSTRACT

Sustained release matrix tablets involve mixing the active ingredient(s) with proper release retarding agent(s). In this study, theophylline anhydrous (THF) matrix tablets were prepared using different concentrations of magnesium stearate or ethylcellulose as release retarding materials. At certain concentrations, both substances were capable of retarding the drug release. However, high concentrations of magnesium stearate has led to poor physical properties such as low hardness and increased friability. On the contrary, increasing the concentration of ethylcellulose has improved both hardness and friability which may be regarded due to its binding properties. The optimum formulation was chosen on the basis of tablet mechanical properties and in vitro drug release. The selected tablet formulations had optimum hardness, low friability and acceptable dissolution pattern regarding to USP XXX dissolution regulations. Through applying kinetic equation models, the release mechanism of the drug from the selected formulations was found to follow Higuchi's kinetic model. This indicates that the drug release from the selected formulated tablets was mainly due to diffusion rather than matrix erosion.

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by variable airway obstruction, airway inflammation, and increased responsiveness to a variety of stimuli [1,2]. Theophylline has remained the cornerstone for asthma management, especially for patients with moderate-to-severe symptoms [3]. Due to its short half life which is about 7-9 hrs in adults [4] and narrow therapeutic index (5-20 µg/mL) [5-7], there is an important need for theophylline sustained release dosage form.

Sustained release dosage forms are designed to maintain uniform therapeutic concentration of the drug for an extended period of time leading to reduced dosing frequency, customer compliance, lower incidence of side effects and maximum drug effectiveness [8,9]. Matrix systems are still one of the most attractive approaches in sustained release preparations from both the economic as well as the process development points of view [10,11].

Many retarding materials have been used to control and modulate drug release properties of tablets. Magnesium stearate is a hydrophobic material consisting of a mixture of magnesium salts with different fatty acids mainly used as a lubricant [12]. It is an additive that is capable of forming films on other tablet excipients during mixing, leading to a prolonged drug liberation time [13,14]. It has been reported that magnesium stearate can be used as a release controlling excipient [15,16].

Another release modifying material is ethylcellulose which is a non-toxic, stable, compressible, inert and hydrophobic polymer. It has been used as a binder, in preparing microcapsules and as a matrix forming material in sustained release formulations [17].

In this study, simple formulations consisting of two principal components were investigated. These components were theophylline anhydrous (THF) and a release retarding agent. Highly drug loaded matrix tablets with different concentrations of magnesium stearate or ethylcellulose were prepared. Formulation selection was based upon physical properties and *in vitro* drug release. The release mechanisms of the selected formulations were analyzed according to zero

order, first order, Higuchi and Hixson-Crowell kinetic models.

MATERIAL AND METHODS

Materials :

Theophylline anhydrous (Gift from MUP Pharmaceutical Company, Abu Sultan, Egypt). Ethylcellulose (45cp) (Carl Rothe GmbH, Chemical Company, Germany). Lactose (Aldriche Chemical Company, St. Louis, USA). Magnesium Stearate (NF, Merck, Dramstadt, Germany). All other chemicals were of analytical grades.

Methods :

Formulation of theophylline tablets.

Different tablet formulations were prepared by either direct compression or wet granulation techniques containing 300 mg of THF. Table 1 shows the composition of the suggested formulations. In case of direct compression, drug, lactose and magnesium stearate were individually sieved then mixed. For wet granulation, the drug and lactose were sieved, mixed and granulated using ethylcellulose alcoholic solution, and passed through a sieve of pore size 500 µm. The prepared granules were dried, sieved and the fraction retained between 500 µm and 250 µm sieve was collected. Magnesium stearate was sieved, added to the dried granules and mixed. Each formulation was compressed using press tablets machine (Chamunda Pharma Machinary Pvt. Ltd, Ahmedabad, India), oblong punches, 18 L, 8 W mm die, at constant compression force (3.5 tons).

Evaluation of physical properties of formulated tablets.

The formulated tablets were evaluated according to their physical properties. Thickness of tablets was measured using multi-purpose thickness tester (Shanghai, China). Tablet hardness was determined using digital tablets hardness tester (Campbell Electronics, Maharashtra, India). Friability was evaluated using friabilator (S.B.S. Instruments, Barcelona, Spain). Disintegration time was evaluated using disintegration tester (S.B.S. Instruments, Barcelona, Spain). All the previous evaluation tests in addition to drug content and weight variation tests were done according to the USP XXX standards [18].

***In vitro* dissolution study.**

Dissolution test was done according to USP XXX with six cups dissolution tester (S.B.S. Instruments, Barcelona, Spain) using apparatus 1(basket) at 100 rpm. Dissolution was carried out using 900 ml simulated intestinal fluid (SIF) phosphate buffer pH 7.5 as dissolution medium. Samples were withdrawn at predetermined time intervals (0.5, 1, 2, 4, 6, 8 hr). Sink conditions were kept throughout the test. Samples after being properly diluted were assayed using UV spectrophotometer (Shimadzu Corporation, Kyoto, Japan) at 272 nm. Each data represents the mean ± standard error (S.E.).

Kinetics of theophylline release.

In order to study the kinetics of drug release from the formulated matrices, the dissolution data were kinetically analyzed according to zero order kinetics, first order kinetics, Higuchi diffusion model as well as Hixson- Crowell model.

Statistical analysis.

All the data represents the mean±S.E. The differences were considered to be significant at a level of $p<0.05$,using one way ANOVA test and paired T test.

Results and discussion

Physical characteristics.

The physical characteristics of the formulated tablets: thickness, weight variation, drug content, hardness, friability and disintegration time expressed as mean ± S.E are shown in Table 2. Increasing the concentration of magnesium stearate has dramatically affected tablet hardness, friability and disintegration time in formulations from F-1 to F-6. Lubricants can alter tablet's blend hydrophobicity which may affect tablet manufacturing processes such as compaction, and tablet hardness [19]. The hardness reduction caused by magnesium stearate may be considered as a result of reduction of interparticle bonding leading to tablet relaxation [20]. Disintegration time has increased with the increase in magnesium stearate which is may be due

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to its hydrophobic nature [21]. In case of formulations from F-7 to F-11, increasing the concentration of ethylcellulose improved both hardness and friability of the prepared tablets of F-7 to F-11 which could be attributed to its binding property [17].

In vitro drug release.

Figure 1 illustrates the release data of THF from F-1 to F-6 formulations in SIF pH 7.5 using basket at 100 rpm. *In vitro* dissolution data indicated that the dissolution of THF was strongly affected by the concentration of magnesium stearate. As magnesium stearate concentration increased from F-1 to F-6, the dissolution rate decreased. In case of F-6 only 81.11%± 1.57 was released after 8 hr while F-1 achieved nearly 100 %± 1.43 after that time. Water soluble excipients usually increase the drug release rate from matrix tablets, whereas, water insoluble excipients decrease drug release rate [22]. So, due to the hydrophobic nature of magnesium stearate, the drug release rate was expected to decrease.

Although the hardness of formulated tablets from F-1 to F-6 has decreased (Table 2), there wasn't a concomitant increase in the release rate; on the contrary, the dissolution rate was decreasing. There was a slight decrease in release between F-1 and F-2 which may be caused by two counteracting effects. The first effect may be due to the decrease in hardness and the increase in tablet porosity. The second opposing effect is supposed to be the hydrophobic nature of magnesium stearate. These two effects are nearly equal at low concentrations of magnesium stearate. However, as the concentration of magnesium stearate increased starting from F-3 formulation, the hydrophobicity had a greater influence on the dissolution rather than hardness.

Figure 2 illustrates the release data of THF from F-7 to F-11 formulations in SIF pH 7.5 using basket at 100 rpm. In such formulations, high concentrations of magnesium stearate were substituted with different concentrations of ethylcellulose while magnesium stearate was kept at constant concentration of 2% w/w as a lubricant. There was an obvious retardation in drug release rate from these formulations. As the concentration of ethylcellulose increased from F-7 to F-11, the dissolution rate decreased. In case of F-7, 90.1%±1.3 of theophylline was released after 8 hr compared to 75.8%±0.55 in case of F-11 tablets. Such retardation in dissolution may be due to the hydrophobic nature of ethylcellulose which prevents the penetration of the dissolution medium within the matrix. In addition, increasing ethylcellulose concentration has lead to increased tablet hardness which may cause a slower drug release rate.

Table 1: Composition of different formulated theophylline tablets

Formulation No.	Applied technique	Magnesium stearate (mg)	ethylcellulose (mg)	Theophylline anhydrous (mg)	Lactose (mg)
F-1	D.C.[a]	-	-	300	40
F-2	D.C.[a]	6.8	-	300	33.2
F-3	D.C.[a]	13.6	-	300	26.4
F-4	D.C[a]	20.4	-	300	19.6
F-5	D.C.[a]	27.2	-	300	12.8
F-6	D.C.[a]	34	-	300	6
F-7	W.G.[b]	6.8	3.4	300	29.8
F-8	W.G.[b]	6.8	10.2	300	23
F-9	W.G.[b]	6.8	17	300	16.2
F-10	W.G.[b]	6.8	23.8	300	9.4
F-11	W.G.[b]	6.8	30.6	300	2.6

[a] Direct compression [b] Wet granulation

Table 2: Physical characteristics of theophylline anhydrous formulated tablets.

Formulation no.	Thickness (mm)	Weight (mg)	Drug content (%)	Hardness (Kg)	Friability (%)	Disintegration time (min)
F-1	2.1±1.1	333.3±1.5	97.2±0.4	6.6 ± 0.4	0.55	45.9±1.5
F-2	2.1±2.0	330.8 ± 1.0	97.0±0.2	5.7±0.2	0.85	66.8 ± 2.1
F-3	2.0±1.0	337.5± 1.0	97.5±0.1	4.8±0.4	Failed	70.0±1.0
F-4	2.0± 1.1	340.7±0.9	100.8±0.8	4.5±0.9	Failed	80.5±1.2
F-5	2.1 ± 1.1	341.5±1.1	101.5±1.0	3.5±0.3	Failed	84.0±1.5
F-6	2.1± 1.4	340.9±0.5	98.6±0.8	2.8± 0.5	Failed	150.0±2.5
F-7	2.0 ±0.0	339.2±0.6	99.7±0.7	6.2±0.8	0.59	138.3±1.9
F-8	2.0±1.1	341.5± 2.1	100.1±0.8	7.5±1.3	0.35	178.4±0.9
F-9	2.0±0.1	337. 7±0.9	99.1±2.0	8.2±1.0	0.27	205.7±3.1
F-10	2.1±2.0	340.1±0.8	98.0±1.1	9.2±0.8	0.14	225.1±2.2
F-11	2.0±0.7	337.9±1.4	99.5±0.5	10.1±0.5	0.13	245.3±1.7

All tests were done according to USPXXX. Each data represents the mean ± S.E (n=6).

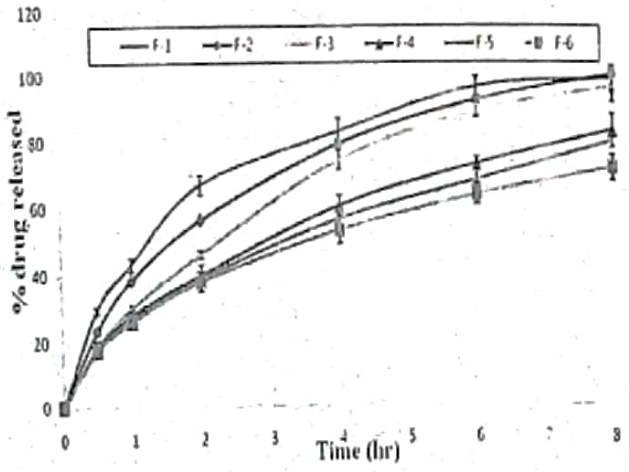

Fig. 1: *In vitro* release profile of theophylline from F-1 to F-6 formulas in simulated intestinal fluid pH 7.5 using basket 100 rpm.

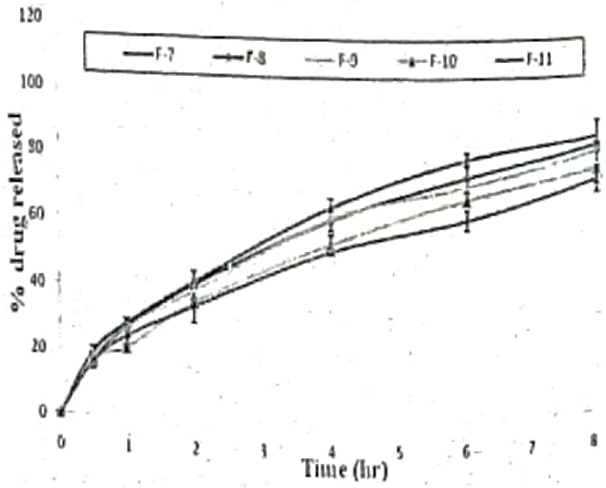

Fig. 2: *In vitro* release profile of theophylline from F-7 to F-11 formulas in simulated intestinal fluid pH 7.5 using basket at 100 rpm.

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Selection of formulation.

The release profiles of theophylline from different formulated tablets were evaluated according to USP Test 8 for theophylline extended release capsules [18]. Only F-4, F-5, F-7, F-8 and F-9 formulations have fulfilled the requirements while the rest of formulations were out of the range of tolerance established in such test. F-1, F-2 and F-3 formulations have shown fast release while F-6, F-10 and F-11 formulations have shown much slower drug release. The latter formulations seemed to be impermeable due to the high content of magnesium stearate in F-6 tablets or ethylcellulose in F-10 and F-11 tablets. Both F-4 and F-5 formulations did not pass the friability or hardness tests requirements. Therefore, none of the magnesium stearate based matrices was selected indicating that magnesium stearate was not a reliable release retardants. This contra verses with [16] who mentioned that for highly loaded matrix tablets containing sparingly soluble drugs, such as theophylline, magnesium stearate at appropriate levels can act as an effective release-controlling excipient. According to USP XXX dissolution test requirements and acceptable physical properties only F-7, F-8 and F-9 formulations have been selected for further studies.

Kinetics of theophylline release.

In order to understand the release mechanisms, mathematical models were applied. The rate and extent of release from matrix tablets depends on many factors including the solubility of the drug [22]. Since the drug is soluble in SIF pH=7.5 therefore, the solubility was not the limiting factor here [21]. The dissolution data (from the values of 0.5 to 8 hr drug release) of F-7, F-8 and F-9 in SIF pH 7.5 using basket at 100 rpm were fitted to zero-order (Fig. 3), first-order (Fig. 4), Higuchi models (Fig. 5) and Hixson –Crowell models (Fig.6). Table 3 shows the regression coefficient values for the three formulations for the kinetics models. The model that best fitted the release data was determined by the highest regression coefficient (r^2).

As clearly indicated in Table 3 and Fig. 3, the prepared formulations did not follow zero-order release kinetics. The best fit with highest regression for the three formulations was found with the Higuchi's equation which expresses a diffusion drug release mechanism. As for the Hixson–Crowell equation, it indicates an erosion-depended drug release mechanism [23]. This indicates that the release of drug from the formulated tablets using hydrophobic matrix may be due to drug diffusion. These findings agree with the fact that at the end of the experiment, the integrity of ethylcellulose tablets was maintained, suggesting that water and theophylline diffused through the tablets without a noticeable erosion of the matrix structure.

Increasing the concentration of Ethylcellulose from F-7 to F-9 tablets has increased the r^2 value obtained from first order model and decreased that obtained by Hixson- Crowell as shown in table 3. This indicates that erosion of the matrix system decreased by increasing ethylcellulose concentration.

Table 3: *In vitro* release regression coefficient values of theophylline release from selected formulations.

Formulation No.	Zero order r^2	First order r^2	Higuchi model r^2	Hixson-Crowell r^2
F-7	0.9517	0.9771	0.9951	0.9915
F-8	0.9630	0.9894	0.9981	0.9874
F-9	0.9747	0.9954	0.9983	0.9864

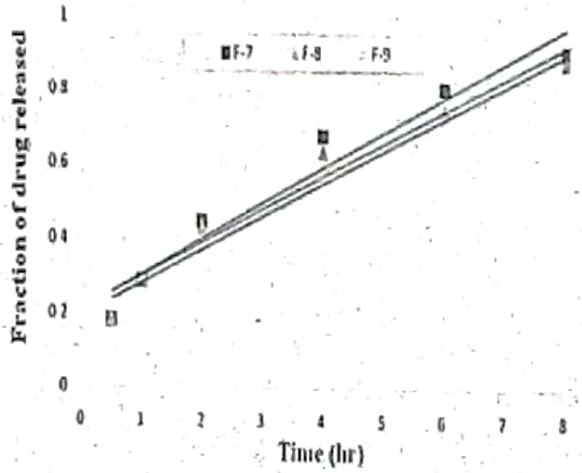

Fig. 3: Zero order plot of theophylline release from selected formulations in simulated intestinal fluid pH 7.5 using basket at 100 rpm.

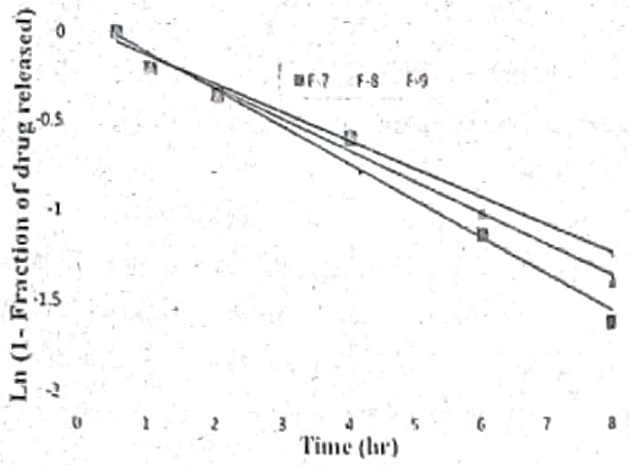

Fig. 4: First order of theophylline release from selected formulas in simulated intestinal fluid pH 7.5 using basket at 100 rpm.

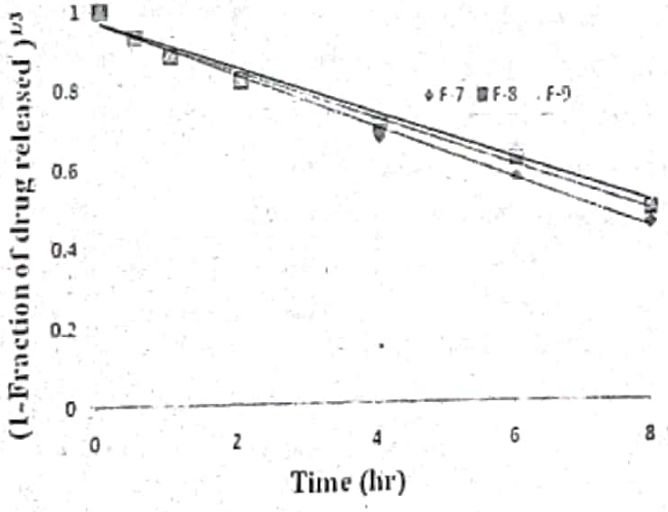

Fig. 5: Higuchi plot of theophylline release from selected formulations in simulated intestinal fluid pH 7.5 using basket at 100 rpm.

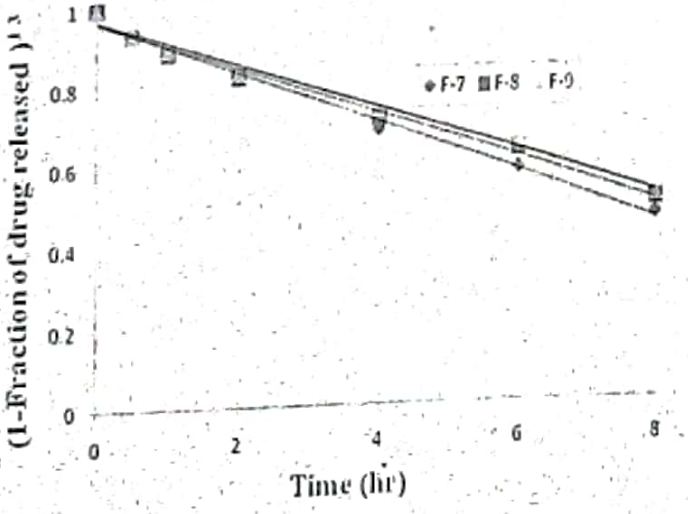

Fig. 6: Hixson-Crowell plot of theophylline release from selected formulations in simulated intestinal fluid pH 7.5 using basket at 100 rpm.

CONCLUSION

The approach of the present study was to evaluate magnesium stearate and ethylcellulose separately as release retarding materials in sustained release tablets for a sparingly soluble drug such as THF. Both substances had the ability to prolong drug release. However, the incorporation of high concentrations of magnesium stearate required to achieve such retardation has led to poor tablet physical properties the most important of which is decrease in hardness and increase in friability. The hydrophobicity of magnesium stearate had a stronger effect on the release of theophylline from matrix tablets than hardness. In case of ethylcellulose, increasing its concentration improved both hardness and friability suggesting that ethylcellulose acted both as a binder and drug release retardant. Selection of the most appropriate formulations was based upon physical and dissolution properties. Ethylcellulose has proven to be a better release retardant than magnesium stearate. The drug release mechanism from selected formulations was best fitted to Higuchi's kinetic model suggesting that the release was may be due to diffusion rather than matrix erosion. In addition, according to the r^2 values, the matrix erosion was found to decrease with the increase of ethylcellulose concentration.

REFERENCES.

1. Minoguchi, K., Kohno, Y., Oda, N., Wada, K., Miyamoto, M., Yokoe, T., Hashimoto, T., Akabene, T., Kobayashi, H., Mita, S., Kihara, N. and Adachi, M.; **Clin. Exp. Allergy.** 28, 57-63 (1998).
2. Lüllmann, H., Ziegler, A., Mohr, K.and Bieger, D., (Ed.). Color atlas of pharmacology. 2nd ed. NY: Thieme Stuttgart. pp: 328- 330 (2000).
3. Riahi, S., Mousavi, M.F.; **Anal. Chem. Acta.** 548, 192-198 (2005).
4. Serafin, W.E., in: Goodman and Gilman's the pharmacological basis of therapeutics. (Hardman, J.G., Limbird, L.E., eds.) 9th ed. 659-683 (1996).

Zagazig J. Pharm. Sci., June 2009
Vol. 18 , No. 1, pp. 23-29.

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5. Bukowsky, M., Nakatsu, J. and Munt, P.W.; **Annals. Int. Med.** 101, 63-73 (1998).
6. Markham, A. and Faulds, D.; **Drugs.** 56, 1081-1091(1998).
7. Ohnishi, A., Kato, M., Kojima, J., Ushiama, H., Yoneko, M. and Kawai, H.; **Drug. Aging.** 20, 71-84 (2003).
8. Bertocchi, P., Antoniella, E., Valvo, L., Alimonti, S. and Memoli, A.; **J. Pharm. Biomed. Anal.** 37, 679-685 (2005).
9. Altinkaya, A.S. and Yenal, H.; **Biochem. Eng. J.** 28, 131-139 (2006).
10. Lafuente, C.S., Faucci, M.T., Arévalo, F.F., Fuentes, J.A., Rabasco, A.M. and Mura, P.; **Int. J. Pharm.** 234, 213-221(2002).
11. Tiwari, S.B., Murthy, T.K., Pai, M.R., Meht, P.R. and Chowdary, P.B.; **AAPS PharmSciTech.** 4, Article 31(2003).
12. European pharmacopoeia and supplements 5th ed. Strasbourg: Council of Europe. (2005).
13. Hussain, M.S.H., York, P. and Timmins, P., **Int. J. Pharm.** 78, 203-207 (1992).
14. Pather, S.I., Russell, I., Syce, J.A., Neau, S.H.; **Int. J. Pharm.** 164, 1-10 (1998).
15. Dürig, T. and Fassihi, R.; **J. Pharm. Sci.** 86, 1092-1098 (1997).
16. Dürig, T., Venkatesh, G.M. and Fassihi, R.; **J. Pharm. Pharmacol.** 51, 1085-1092 (1999).
17. Katekaneni, P.R., Upadrashta, S.M., Neau, S.H. and Amitra, A.K.; **Int. J. Pharm.** 123, 119-125 (1995).
18. United States Pharmacopeia. Theophylline, in: *USP 30 – NF 25*. Electronic version (2007).
19. Chambin, O., Champion, D., Debray, C. Rochet-Gomphir M.H., Mestel M.L. and Pourcelot, Y.; **J. Controlled Release**, 95, 101-108(2004)
20. Zuurman, K., Maarschalk, V.V. and Bolhuis, G.K.; **Int. J. Pharm.** 179, 107-115 (1999).
21. Chambin, O., Champion, D., Debray, C., Rochet-Gonthier, M. H., Meste, M. L. and Pourcelot, Y.; **J. Control. Release.** 95, 101-108 (2004)
22. Rao, V.M.; Haslam, J.L. and Stella, V.J.; **J. Pharm. Sci.** 90, 807-816 (2001).
23. Gil, E.C., Colarte, I.C., Bataille, B., Pedraz, J.L., Rodriguez, F. and Heinamaki, J.; **Int. J. Pharm.** 317, 32-39 (2006).

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تقييم تأثير بعض الإضافات على إنطلاق الثيوفيللين من الأقراص الممتدة المفعول

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تعد الأقراص الممتدة المفعول خليط من المواد الفعالة و بعض المواد الأخرى التى لها تأثير على الإنطلاق المعملى للعقار. تتناول هذة الدراسة تحضير أقراص ممتدة المفعول تحتوي على الثيوفيللين الاماني بالإضافة الى تركيزات مختلفة من شمعات المغنيزيوم أو الإيثيل سلليولوز واللتان لهما القدرة على إطالة مدة إنطلاق العقار. أظهرت النتائج أنه مع زيادة تركيز شمعات المغنيزيوم تقل صلابة الأقراص بينما زيادة تركيز الإيثيل سيللولوز تؤدى الى زيادة صلابتها. ولقد تم إختيار أنسب الصياغات تبعا لمعدل الإنطلاق المعملى للعقار و الخواص الفيزيائية للأقراص. أخيرا، تم إستنباط ميكانيكية إنطلاق العقار من الصياغات المختارة و ذلك بتطبيق قوانين الحركية المختلفة.