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Modification of the Release Profiles of Theophylline Matrix Tablets by inclusion of Water Leachable or Water Swellable Excipients

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ABSTRACT

Matrix system is an attractive oral controlled release dosage form due to convenience in process development and low production. This study was undertaken to investigate the effects of leaching and swelling agents on sustained release theophylline tablets. Twelve batches of theophylline matrix tablets were prepared with ten batches containing varied amount of the swellant or channeling agents. The matrix tablets were prepared by either melt granulation or simple coacervation technique. Release studies were carried out for 12 h in 0.1 N HCl. Data obtained were fitted into zero order, first order, Higuchi and Korsmeyer equations. The initial release after 60 min and maximum release from only carnauba wax and Eudragit based tablets were 13%, 50% and 12.5%, 46% respectively. With the inclusion of 10% sucrose, these values were increased to 22%, 80% and 22%, 86% respectively. Both the rate and extent of release were significantly increased with the inclusion of either channeling agents or swellant. Kinetic study revealed that the mechanism of release was mainly by diffusion and partly by erosion. Thus, the inclusion of excipients in the right proportion can produce matrix tablets with desired release profiles.

KEYWORDS: Matrix tablets, controlled release, Eudragit, carnauba wax, Release kinetic

INTRODUCTION

In recent years, considerable attention has been geared towards the development of novel drug delivery systems, NDDS (Bhagwat and Vaidhya, 2013). Of the various approaches so far, osmotic pumps and matrix systems are at the fore front of this development (Tiwari *et al*, 2012; Sammour *et al*, 2015). Among these two classes, matrix tablets which is made up of the active drug and release retardants (polymers) provide the simplest and cost-effective approach in development of controlled release formulations (Nokhodchi *et al*, 2012; Roy *et al*, 2013). Hydrophobic polymer (e.g. ethyl cellulose, acrylate/methacrylate co-polymer), hydrophilic polymers (polyacrylic acid, polymethacrylate) and waxes (carnauba wax, bees wax) have all been investigated in the development of controlled release matrix tablets. However, initial release from matrix tablets that consist of these polymers and active pharmaceutical ingredient (API) is always very low, and often times not therapeutic. This may necessitate the inclusion of pharmaceutical excipients such as channeling agents (e.g. sucrose) and swelling agents (e.g. microcrystalline cellulose) to modulate drug release (Nokhodchi *et al* 2012; Rios and Ghaly, 2015). One of the therapeutic agents (API) that has been so investigated and reported is theophylline.

Theophylline (1, 3 - dimethyl xanthine) is used in the management of asthma. Its use as bronchodilator in chronic asthma has declined, however, it has been shown more recently to have anti-inflammatory action in asthma and chronic obstructive pulmonary disease, COPD (Barnes, 2013). The drug is also highly effective in treatment of infant apnea (Damodharan *et al*, 2009; Schultz and Martin, 2013). However, many developed countries have relegated it to third line treatment that is only used for patients that are poorly controlled. Various national and international guidelines on asthma and COPD therapy have reinforced this, but others have emphasized the special benefit of theophylline which still places it in an important position in management of asthma (Barnes, 2010). Theophylline has very short plasma half-life (6 to 8 h in adult) and narrow therapeutic window. Its effective plasma concentration is 10 to 20 µg/mL; with toxic symptom appearing once plasma concentration exceed 20 µg/mL (Sarojini *et al*, 2010; Barnes 2013). Thus, there is obvious need for continuous search for development of better delivery systems especially the ones that will reduce dosing frequency of theophylline (i.e. sustained or controlled release dosage forms). Such well formulated dosage form with the incorporation of the necessary excipients will help maintain therapeutic blood level throughout the 24 h which will result in reduced dosing frequency, better adherence, reduced plasma drug fluctuations and minimal side effects (Gad *et al*, 2012, Vo *et al*, 2016)..

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Therefore, in the present study, controlled release theophylline matrix tablets were formulated and the possibilities of improvement in initial percentage drug release using channeling agent (e.g. sucrose) and swelling agent (microcrystalline cellulose) were carried out

MATERIALS AND METHODS

Materials: Sucrose (Guangdong Guanghua Sci-Tech Co., Ltd. Shantou, Guangdong, China); microcrystalline cellulose (BDH, Poole England); Samples of Eudragit®RL100 and Eudragit®RS100 were received as gift from Evonik Industries AG – Werk Röhm, Darmstadt. Theophylline powder (was a product of Vital Biotic, Nigeria Ltd.); carnauba wax and absolute ethanol (BDH, Poole England), Normal Saline (Unique Pharmaceutical Nigeria Ltd.) All other reagents were of analytical grade and were used without further purification.

Methods:

Melt granulation: To form granules for the matrix tablets by melt granulation technique, carnauba wax sample (4.5 g, i.e. 15% w/w) was melted in a stainless-steel jar in a water bath at 90 ± 0.5°C. A sample of theophylline powder (30 g) was added to the melt and stirred continuously with a glass rod. While still hot, the moist mass was passed through a sieve (aperture size 710 µm) and cooled in an air-conditioned room at 15°C.

Coacervation Technique*:* To form granules by coacervation technique, an ethanolic solution of theophylline (30 g) and 7.5 g (25% w/w) acrylate – methacrylate polymer (Eudragit®RS100) was formed; followed by addition of 270 ml of normal saline to co – precipitate the drug and the polymer. The mixture was allowed to stand for 30 min and the precipitates (coacervates) collected by filtration. The coacervates were dried in hot air oven at 60 ± 0.5°C for 24 h and the dried mass was passed through a sieve (710 µm) to obtain the granules. The procedure was repeated with 20% w/w of Eudragit®RS100 to obtained third set of granules. The sets of granules were characterized for flowability by measuring the angle of repose and stored in air tight container for further studies and compression to non-disintegrating matrix tablets.

Flowability*:* - A sample of each set of granules (20 g) was allowed to fall freely from a funnel clamped to a retort stand at a height of 7.5 cm to a horizontal surface. The angle (θ) formed by the powder heap was taken as measure of flowability. The diameter (D) and height (H) of the heap formed were measured and the angle of repose (θ) was computed from equation (1)

$$\theta = arc\ Tan\frac{2H}{D} \ldots . (1)$$

Preparation of theophylline matrix tablets*:* A sample of granules (18 g) prepared above was mixed with 3% w/w microcrystalline cellulose (swelling agent), 1%w/w talc and 1%w/w magnesium stearate. The mixture was then taken in a photo film container and mixed intimately in a laboratory designed small drum mixer for 20 min before compression to non-disintegrating matrix tablets containing 300 mg theophylline. The procedure was repeated with other sets of granules as shown in Table 1. Furthermore, different concentrations of channeling agent (sucrose) were substituted for microcrystalline cellulose to produce other set of tablets.

In vitro release studies*:* Theophylline release profiles from the different matrix tablets were determined by using dissolution tester (Erweka apparatus – type: DT, Nr: 56263, Heidenstam, Germany), U.S.P dissolution apparatus 1. The baskets rotating at 100 rpm in 900 ml of 0.1 N HCl. Aliquots, of 5 ml was withdrawn at specified time intervals. The withdrawn portions were replaced with fresh equal volume of blank medium (0.1 N HCl). The withdrawn media were properly diluted and the concentration of theophylline was determined with UV Spectrophotometer (PG Instrument, USA) at a wave length of 272 nm. The percentage of drug released was computed using an equation obtained from standard theophylline calibration curve. The dissolution study was done for 12 h and drug dissolved at specified time was plotted against time (min). The amounts of drug released were fitted into four well known mathematical models: Zero order, First order, Higuchi model and Korsmeyer-Peppas model as to determine the release mechanism.

Kinetic of drug release*: In vitro* data obtained from the dissolution study were fitted into four popular mathematical models (equations 2 to 5):

Zero Order: $P = k_0 t \ldots . (2)$

First Order: $InP_1 = InP_0 + k_1 t \ldots . (3)$

Higuchi Model: $P = k_H t^{1/2} \ldots . (4)$

Korsmeyer-Peppas: $P = k_{KP} t^n \ldots . (5)$

Therefore, $LogP = Logk_{KP} + nLogt \ldots . (6)$

Where P_0 is the initial amount of drug in the dosage form, P is percentage amount of drug released, and P_1 is percentage of residual drug at time t. K_0, K_1, K_H, and K_{KP} are Zero order, First order, Higuchi and Korsmeyer-Peppas rate constant respectively.

Data analysis

All data were expressed as mean ± SD of three determinations. Differences between means were

determined with one-way analysis of variance (ANOVA) at $P < 0.05$.

Table 1: Composition of theophylline matrix tablets

BATCH	THEO-CW GRANULES (mg)	THEO-EuRS GRANULES (mg)	M-CELL (%)	SUCROSE (%)
B2	360	-	-	-
F	360	-	3.0	-
H	360	-	7.5	-
J	360	-	-	5.0
K	360	-	-	7.5
L	360	-	-	10.0
B6	-	330	-	-
F	-	330	3.0	-
H	-	330	7.5	-
J	-	330	-	5.0
K	-	330	-	7.5
L	-	330	-	10.0

THEO = Theophylline; CW = Carnauba wax; EuRS = Eudragit®RS100; M. CELL = Microcrystalline Cellulose

RESULTS AND DISCUSSION

Effects of swelling and leaching agents: From Table 1, batches B2 and B6 did not contain swelling agent (microcrystalline cellulose) or leaching agent (sucrose). Figures 1 and 2 showed both batches (i.e. B2 and B6) have least rate of drug release. In other words, the rate of drug release in these two batches is slow. When swelling agent was included in formulations, the rate of drug release was greatly improved. This was also the case when leaching agent (sucrose) was included in some of the formulations (J, K and L). It was also noted that as the concentrations of leaching and swelling agents increased, the rate of drug release also increased. Razzak *et al* (2008) also observed the same trend when NaCl and PEG1500 were used as channeling agents to increase the release of theophylline from METHOCEL K4M based matrix tablets.

Tables 2 and 3 illustrates the values of the release rate constants (K) and the regression coefficients (R^2) for each model in addition to 'n' values of Korsmeyer - Pepas model for the twelve (12) batches of tablets in 0.IN HCl using basket at 100 rpm. It is expected that the model that best fit the release data should be the one with highest R^2 values when analyzed for Zero Order, First Order and Higuchi model. The theophylline release fitted Higuchi more with the highest R^2 value of 0.9973, which implies that release of theophylline from the various matrix tablets is by drug diffusion. But it must be remembered that Higuchi model is only applicable to ideal situation without putting into consideration certain matrix complication such as swelling and erosion (Shannon, 2000; Gad *et al*, 2012). Observation at the end of the dissolution study showed that erosion has also occurs. This is expected since most of the formulations contain swellant and leaching agents. Hence, the data were also evaluated with Korsmeyer–Peppas equation. A good correlation with Korsmeyer–Peppas model was observed ($R^2 > 0.98$). The 'n' values indicate whether Fick's diffusion has taken place ($n = 0.45$). When 'n' is above 0.45 but less than 0.89, non-Fick (anomalous transport) has occurred which involves both diffusion and erosion. It is case II transport when $n = 0.89$ and super case II when $n > 0.89$ (Gad *et al*, 2012; Hayashi *et al*, 2005). The 'n' values obtained for all twelve batches is $0.45 < n < 0.89$ except batches B6h that has 'n' values of 0.375. However, since Higuchi R^2 values are higher than those of the Zero and First Order, one can conveniently say that both diffusion and erosion had occurred with diffusion being the major mechanism.

CONCLUSION

Controlled release theophylline matrix tablets were successfully prepared via melt granulation and coacervation techniques. Channeling and swelling agent significantly affected drug release from the matrix tablets. Both channeling and leaching agents have similar effect on drug release. All the formulations fit better with Korsmeyer-Peppas equation which helps defined drug release rate and mechanism of release.

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TABLE 2: Mathematical modeling / *in vitro* theophylline release kinetic of matrix tablets prepared with carnauba wax as matrix former.

ORDER OF DRUG RELEASE	FORMULATIONS / BATCHES B2	B2F	B2H	B2J	B2K	B2L
ZERO ORDER						
R^2	0.9426	0.9463	0.9317	0.9541	0.9646	0.9613
K_0	0.0686	0.0746	0.1189	0.0818	0.0947	0.1013
FIRST ORDER						
R^2	0.9753	0.9782	0.9716	0.9899	0.9809	0.9750
K_1	$1.2*10^{-3}$	$1.2*10^{-3}$	$3.3*10^{-3}$	$1.4*10^{-3}$	$1.9*10^{-3}$	$2.1*10^{-3}$
HIGUCHI MODEL						
R^2	0.9960	0.9920	0.9950	0.9973	0.9905	0.9938
K_H	2.0926	2.2678	3.6485	2.4821	2.8503	3.0562
K-PEPPAS MODEL						
R^2	0.9974	0.9809	0.9891	0.9934	0.9964	0.9892
K_{KP}	2.3190	2.3867	2.3302	2.4866	2.6971	2.9580
N	0.4840	0.4875	0.5720	0.4969	0.5058	0.4990

TABLE 3: Mathematical modeling / *in vitro* theophylline release kinetic of matrix tablets prepared with Eudragit®RS100 as matrix former.

ORDER OF DRUG RELEASE	FORMULATIONS / BATCHES B6	B6F	B6H	B6J	B6K	B6L
ZERO ORDER						
R^2	0.9187	0.9473	0.9647	0.9670	0.9773	0.9725
K_0	0.0543	0.0727	0.0771	0.0779	0.1084	0.1152
FIRST ORDER						
R^2	0.9537	0.9787	0.9824	0.9864	0.9828	0.9890
K_1	$7.0*10^{-4}$	$1.2*10^{-3}$	$1.4*10^{-3}$	$1.4*10^{-3}$	$2.3*10^{-3}$	$2.8*10^{-3}$
HIGUCHI MODEL						
R^2	0.9906	0.9915	0.9845	0.9924	0.9932	0.9933
K_H	1.6725	2.2078	2.4005	2.3419	3.2427	3.4560
K-PEPPAS MODER						
R^2	0.9894	0.9925	0.9610	0.9968	0.9917	0.9946
K_{KP}	2.2213	1.4086	5.4664	2.3259	2.0907	2.3491
N	0.4643	0.5653	0.3751	0.4965	0.5557	0.5478

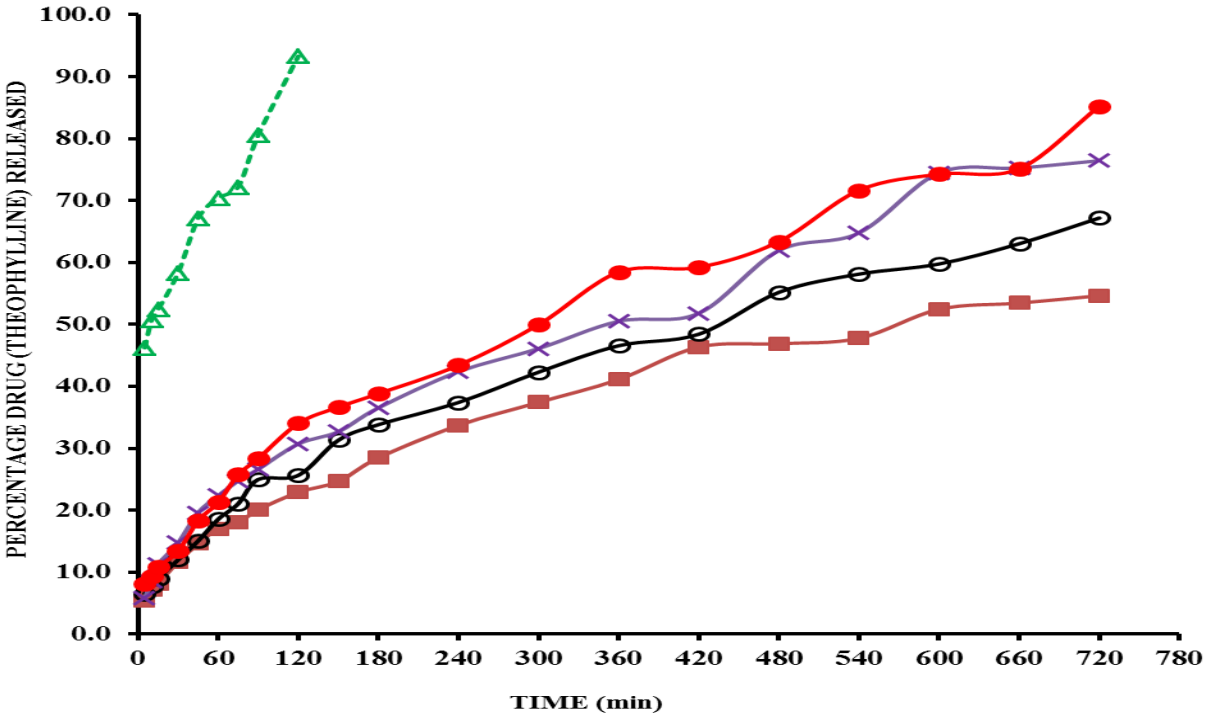

Figure 1a: - Drug release profiles of conventional theophylline tablets (▪▪▪Δ▪▪▪); matrix tablets by melt granulation with carnauba wax (B2, —■—) and matrix tablets containing channeling agent - sucrose - 5% (B2j —O—), 7.5% (B2k —x—), 10% (B2*l*—●—)

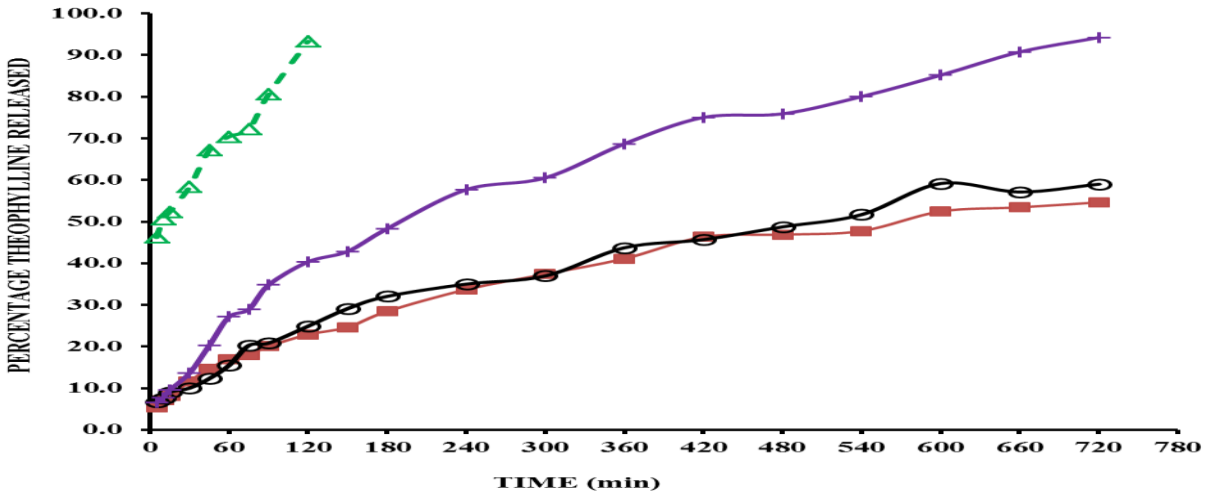

Figure 1b: - Drug release profiles of conventional theophylline tablets (▪▪▪Δ▪▪▪); matrix tablets by melt granulation with carnauba wax (BF2, —■—) and matrix tablets containing swelling agent – microcrystalline cellulose: - 3% (BF2f —O—) & 7.5%w/w (BF2h —|—)

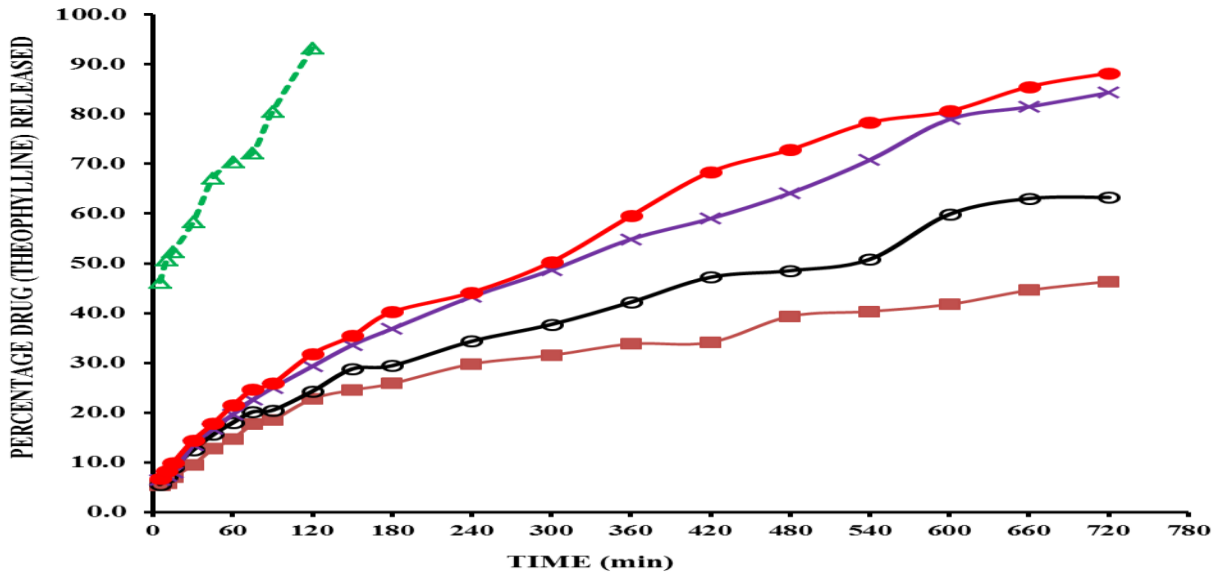

Figure 2a: - Drug release profiles of conventional theophylline tablets (▪▪▪Δ▪▪▪); matrix tablets prepared by coacervation technique using Eudragit®RS100 (BF6, —■—) and matrix tablets containing channeling agent - sucrose - 5% (BF6j —O—), 7.5% (BF6k —x—), 10% (BF6l —●—)

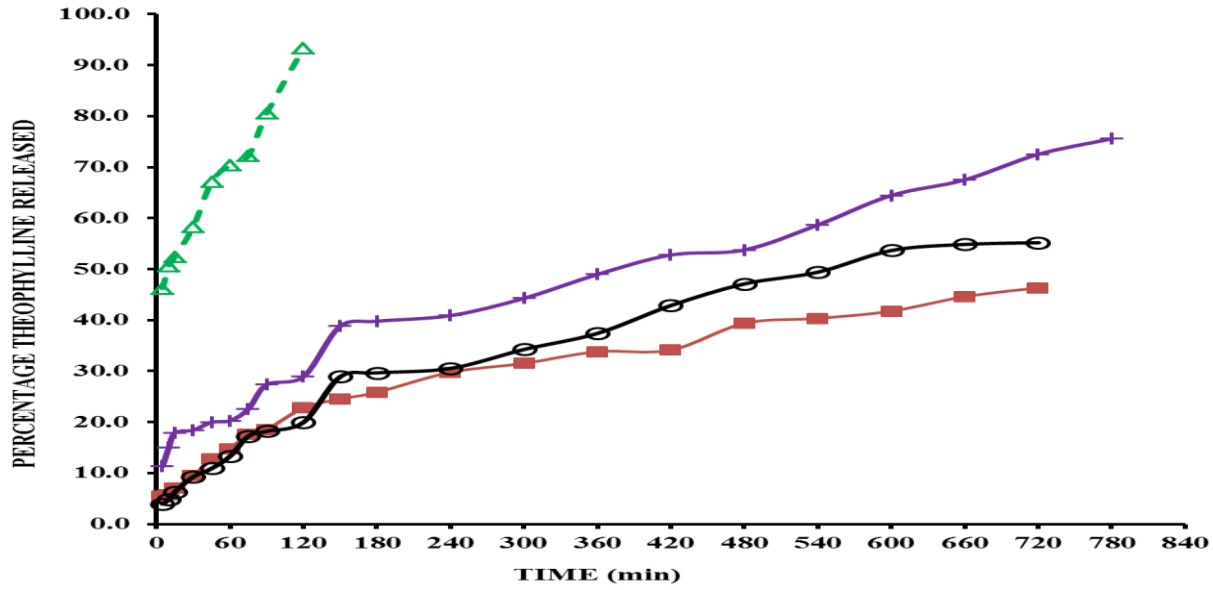

Figure 2b: - Drug release profiles of conventional theophylline tablets (▪▪▪Δ▪▪▪); matrix tablets prepared by coacervation technique using Eudragit®RS100 (BF6, —■—) and matrix tablets containing swelling agent, microcrystalline cellulose: - 3% (BF6f —O—) & 7.5% (BF6h —|—)

REFERENCES

Barnes PJ (2010). Theophylline: A review. *Pharmaceuticals.* 3(3): 725 – 747

Barnes PJ (2013). Theophylline. *Amm J Resp Cri Med.* 188: 901 – 906

Bhagwat RR and Vaidhya SI (2013). Novel drug delivery systems. An overview. *International J Pharm Sci and Res.* 4(3): 970 – 982

Damodharan N, Mothilal M, Madhavi M and Thejomayananthan P (2009). Formulation and evaluation of bi-layered floating tablets of theophylline. *Der Pharmacia letter,* 1(2): 227 - 233.

Gad S, Ghorab M, Khafagy E and Kamel M (2012). Formulation, characterization and comparative *in vitro - in vivo* evaluation of sustained release theophylline tablets. *International Journal of Pharmacy and Pharmaceutical Sciences,* 4(3): 721 - 728.

Hayashi T, Kanbe H, Okada M, Suzuki M, Ikeda Y, Onuka Y, *et al*. (2005). Formulation study and drug release mechanism of a new theophylline sustained release preparation. *Int J Pharm.*304: 91 – 101.

Nokhodchi A, Raja S, Patel P, Asare-Addo K (2012). The role of oral controlled release matrix tablets in drug delivery systems. *Bioimpacts*. 2(4):175 – 187

Razzak SM, Khan F, Khan ZR Fatema K, Islam MS and Reza S (2008). Effect of channeling agents on the release profile of theophylline from METHOCEL K4M based matrix tablets. *Dhaka Univ. J. Pharm. Sci.*7(1): 27 – 32.

Rios ZA, Ghaly ES (2015). The effect of formulation excipients and thermal treatment on the release properties of Lisinopril spheres and tablets. *BioMed Res Int.* Vol 2015, article ID 423615.

Roy H, Brahma C, Nandi S and Parida KR (2013). Formulation and design of sustained release matrix tablets of metformin hydrochloride: Influence of hypromellose and polyacrylate polymers. *Int J Appl Bio Med Res.* 3(1): 55 – 63.

Sammour RMF, Farah FH, Shahiwala A (2015). Publication trend of different novel drug delivery systems during 1980 – 2012: A pilot study using Pubmed search tool. *IOSR – JPBS*. 4(1): 01 – 08.

Sarojini S, Arivazagan D, Manavalan R, Jayanthi V (2010). Buoyant sustained release tablets based on polyethylene oxide. *Int J Pharm Pharm Sci.* 2 suppl 1: 144 – 149.

Schultz A, Martin AC (2013). Outpatients management of asthma in children. *Clin Med Ins: Ped*. 7: 13 – 34.

Shannon M (2000). Theophylline: its rise, demise and resurrection. *Clin Ped Emerg Med;* 217 – 221.

Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P and Bannerjee SK (2012). Drug delivery systems: An updated review. *Int J Pharm Investig*. 2(1): 2 – 11.

Vo AQ, Feng X, Morrott JT, Pimparade MB, Tiwari RV, Zhang F and Repka MA (2016). A novel floating controlled release drug delivery system prepared by melt extrusion. *Eu J Pharm and Biopharm*. 98: 108 – 121