Studies on Commercially Available Sustained- or Controlled-Release Theophylline Products Commonly Used: Characterization of In-vitro Dissolution Properties and Kinetics

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Abstract:

Purpose: Theophylline (TP), is an one of the most popular drugs used in the therapy of the respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma under a variety of commercially brand names of oral sustained- or controlled-release products in the local market. The objective of this work is to endow an overview of type and dissolution characteristics of various sustained- or controlled-release products presently available.

Method: The dissolution characteristics of TP from its commercially available sustained- or controlled-release products were studied in simulated gastric fluid for 2 hr and in simulated intestinal fluid for 8 hr using the USP dissolution apparatus with the paddle assembly. The kinetics of the dissolution profiles were determined by analyzing the dissolution data according to 4 kinetic equation models, namely; zero-order equation, first-order equation, Higuchi square root equation and Hixson-Crowell cube root law.

Results: All the investigated commercially available TP products displayed good sustained-release patterns. The dissolution rate of TP from its commercially available capsule products was higher than that of TP commercially available tablet products. Further, the progress increase in the dissolution rate of TP from its commercially available capsule products along the dissolution period was more regular than that of TP commercially available tablet products. The kinetics study demonstrated that Zero-order and Hixon-Crowell's models displayed sufficiently linearity with minimal differences between them suggesting that the release mechanism of TP from most of the investigated commercially available TP products   may be a coupled release pattern between diffusion and dissolution mechanisms.

Conclusion: The study demonstrated that most of the investigated commercial available TP products satisfied the requirements of good sustained-release products.

Key Words: Theophylline, commercial available, sustained-release, controlled-release, products and dissolution kinetics.

1. Introduction:

TP, structurally classified as methyl xanthine (1,3-dimethylxanthine), is an one of the most popular drugs used in therapy of the respiratory diseases as a bronchodilator in patients with airflow limitation diseases such as bronchial asthma and chronic obstructive pulmonary diseases (COPD) [1,2]. TP is also used as a prophylactic drug and as a means to prevent acute exacerbations of asthma [1,2]. The main actions of TP involve relaxing bronchial smooth muscle, increasing heart muscle contractility and efficiency, anti-inflammatory effects and central nervous system stimulatory effect mainly on the medullar respiratory center [1,2]. Moreover, it has recently been proved that TP could be used as a novel form of adjunct therapy in improving the clinical response to steroids in smoking asthmatics [1, 2].

TP has an average half-life of 6-8 h but in case of smokers, it is 4.4 h [3, 4]. Hence, it requires frequent dosing for achieving therapeutic drug concentration in the target tissue. Conventional oral dosage forms do not offer any control over drug delivery and cause great fluctuations in plasma drug concentrations [3, 4]. Furthermore, patient compliance is fairly poor with such frequent dosing regimens [3, 4].

In the last two decades, sustained- or controlled-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance [5]. Hence, the clinical benefits and related advantages are likely to happen if such a drug was to be administered as a sustained- or controlled-release dosage forms. A variety of commercially brand names of oral sustained- or controlled-release dosage formulations containing TP have

become relatively prevalent in medicine today because of their ability to reduce noncompliance and perhaps, to increase efficacy [2,5].

However, there are many patient- and drug-related factors that may present special problems in the selection of the appropriate TP product. Further, the work done on the sustained- or controlled-release TP commercial available oral products is a very little and not enough to describe and explain the diversity of the formulation techniques affecting the drug release process.

The objectives of this work are aimed to endow an overview of type and dissolution characteristics of the most popular seven sustained- or controlled-release oral TP products presently available.

2. Materials and methods:

2.1. Materials:

Commercial lots of sustained- or controlled-release TP oral products presently available were purchased on the open local market. The composition of the commercial TP sustained- or controlled-release oral products purchased was listed in table (1). TP powder was gifted by Nile Company for Pharmaceutics & Chemicals, Cairo, Egypt. Methanol, ethanol and chemicals of dissolution media, all obtained from El-Nasr Company, Abu-Zabal, Cairo, Egypt.

Table (1): The composition of commercial available TP sustained- or controlled-release oral products presently available.

Commercial available TP oral products	Abbr. name	TP content (mg)	Manufacture	Form
Theo 100 SR capsules	**T-1**	100	SmithKline Beecham, Egypt.	Capsules contain coated spherical pellets
Theo 200 SR capsules	**T-2**	200	SmithKline Beecham, Egypt.	Capsules contain coated spherical pellets
Theo 300 SR capsules	**T-3**	300	SmithKline Beecham, Egypt.	Capsules contain coated spherical pellets
Quibron SR tablets	**Q**	300	GlaxoSmithKline, Egypt.	Cylindrical flat-shaped dividose tablets
Minophlin SR tablets	**M**	300	Alexandria Co. for Pharmaceut., Egypt.	Cylindrical flat-shaped dividose tablets
Uniphlline® Continus 300 tablets	**U-1**	300	Nile Co./Pharmaceut. & Chemicals Egypt.	Capsule-shaped tablets
Uniphlline® Continus 400 tablets	**U-2**	400	Nile Co./Pharmaceut. & Chemicals Egypt.	Capsule-shaped tablets

2.2. Drug content:

Ten capsules or tablets of each of TP investigated commercial products; T-1, T-2, T-3, Q, M, U-1 and U-2 were randomly selected, placed in a mortar and grinded with a pestle. The drug content was extracted several times using a phosphate buffer solution (PH 7.1). The solutions were filtered, suitably diluted and assayed for TP contents spectrophotometrically at λ_{Max} 272 nm.

2.3. Dissolution studies:

The dissolution studies were carried out in U.S.P dissolution apparatus II with paddle assembly (Shimadzu-UV 160A Spectrophotometer). One capsule or tablet of each of TP investigated commercial products; T-1,T-2, T-3, Q, M, U-1 and U-2 was immersed under sink conditions in 900 ml dissolution medium of simulated gastric fluid for 2 h and then, in simulated intestinal fluid for 8 h. The dissolution contents were kept at $37\pm 0.5°C$, and stirred at 50 rpm. A 5-ml sample was withdrawn and replaced with another 5-ml of a suitable fresh dissolution medium at the preselected intervals. The concentration of the drug was determined spectrophotometrically at λ_{Max} 272 nm. Each test was performed in triplicate.

2.4. Release Kinetics [6]:

The in vitro release of TP from its different investigated products was evaluated by fitting the dissolution data obtained to the following equations:

1. Zero order equation:

$$C_t = C_0 - K_0 t \qquad\qquad (1)$$

where C_t is the amount of the drug released at time t, C_0 is the initial amount of drug in the tablet and K_0 is the zero-order release rate constant.

2. First order equation:

$$Log\ C_t = log\ C_0 - K_1 t / 2 0 3 0 3 \tag{2}$$

where C_t is the amount of drug remaining as a solid state at time t, C_0 is the total amount of drug in the matrix and K_1 is the first-order release rate constant.

3. Higuchi model equation:

$$Q = 2\ C_o\ (D t / \pi)^{1/2} \tag{3}$$

where C_o is the initial drug concentration, t is time of release, Q is the amount of drug released/unit area and D is the diffusion coefficient constant.

4. Hixon-Crowell's root equation:

$$[1 - (M_t / M_\infty)]^{1/3} = -K t \tag{4}$$

where M_t / M_∞ is the fraction released by the drug at time t, K is a constant related to dissolution rate limitation of the drug particles species.

3. Results and Discussion:

3.1. Drug content:

The actual drug contents of the investigated commercial available TP oral products; T-1, T-2, T-3, Q, M, U-1 and U-2 are listed in table (2). From the results shown in this table, it can be concluded that all the investigated commercial available TP oral products satisfied the pharmacopeia limits for their drug content.

Table (2): The drug contents of the investigated TP products

Product Abbr. name	Claim TP content (mg)	Actual TP content (mg)
T-1	100	97 ±1.53
T-2	200	193 ±2.64
T-3	300	292 ±2.95
M	300	287 ±3.55
Q	300	293 ±2.87
U-1	300	288 ±3.15
U-2	400	386 ±2.23

3.2. Dissolution studies:

The commercial pharmaceutical products, particularly sustained- or controlled-release types, should be subject to the in-vitro dissolution studies. Where, the drug delivery systems are theoretically designed to release their drug contents according to certain profiles depending on the drug release mechanisms built by the processing manufacture. But in practice, some difficulties in the manufacturing processes may be lead to deviation from the proposal behavior. Furthermore, the in-vitro dissolution studies can be used to explain the release process and the reasons for therapeutic differences that are noted in-vivo, where in-vitro performances showed by products reflected highly how they would behave in-vivo [7].

In the present study the dissolution patterns of TP from the investigated products; T-1, T-2, T-3, Q, M, U-1 and U-2 in phosphate buffer medium of PH 7.1 are displayed in Fig. (1). As shown in this figure, all the investigated TP products displayed good sustained-release patterns over prolonged period of time. Both U-1 and U-2 showed the most sustaining release patterns among the other investigated products. The percent release of TP from U-1 and U-2 are 35.o3 and 26.33% respectively, while, the percent release of TP from the other investigated TP products; T-1, T-2, T-3, M and Q exceeded 80% at the end of dissolution studies (8 h). The dissolution profiles of TP from its investigated products of the same manufacture and having different drug contents showed closely similar dissolution patterns.
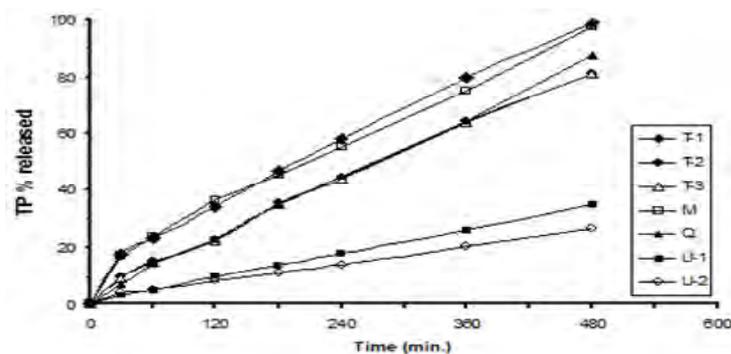
Fig. (1): Dissolution profiles of TP from its commercial available products in a phosphate buffer of PH 7.2.

It is worth to note that the dissolution patterns of TP from its commercial products investigated; T-1, T-2, T-3, Q, M, U-1 and U-2, in acidic medium of PH 1.2 behave in a similar fashion as those at phosphate buffer medium of PH 7.1.

3.3. Release Kinetics:

There is a number of drug release mechanisms can be anticipated to explore in vitro release profile of TP from its investigated commercial available sustained- or controlled-release oral products. Four kinetic equation models of particular relevance to the release process of TP from its investigated commercial available sustained- or controlled-release oral products have been used for describing the kinetics of the release process as followed: zero-order equation describes the release process when the release rate is independent of the concentration of the dissolving species [8], first-order equation describes the release process when the release rate is dependent of the concentration of the dissolving species [9], Higuchi's equation describes the release process when the solid drug is dispersed in an insoluble matrix and the drug release rate is related to the rate of drug diffusion [10] and Hixon-Crowell's cub root equation describes the release process when there is a change in the surface area and diameter of the drug particles species reflected by a change in the weight of the particles [11].

The plots of the dissolution data obtained by the investigated TP commercial products; T-1, T-2, T-3, Q, M, U-1 and U-2 in phosphate buffer of pH 7.1, in accordance to these equation models; zero-order, first-order, Higuchi's equation and Hixon-Crowell's cub root equation model, were demonstrated in Figs. (2-5), respectively.
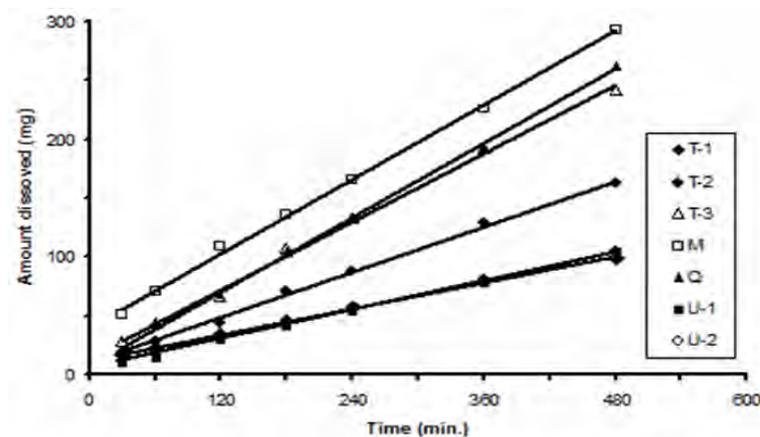

Fig. (2): Dissolution profiles of TP from its commercial available product in a phosphate buffer of 7.2, plotted in accordance to zero order model.
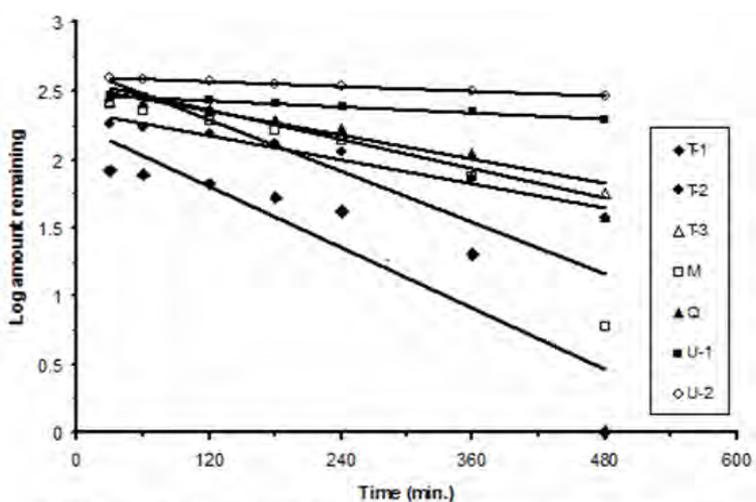
Fig.(3): Dissolution profiles of TP from its commercial available product in a phosphate buffer of 7.2, plotted in accordance to first order model.
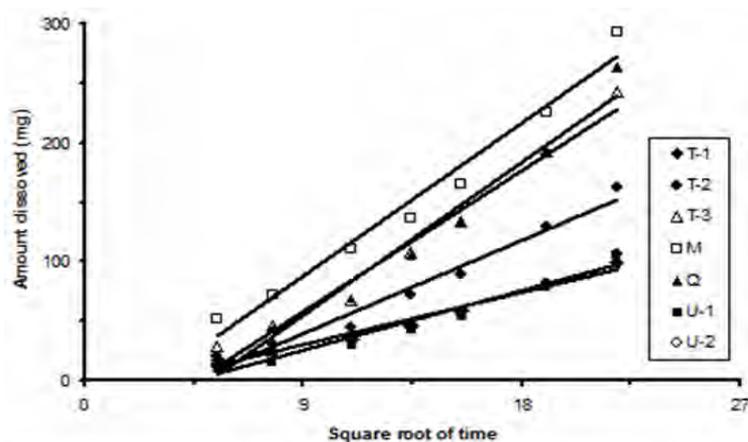

Fig. (4): Dissolution profiles of TP from its commercial available product in a phosphate buffer of 7.2, plotted in accordance to Higuchi model.
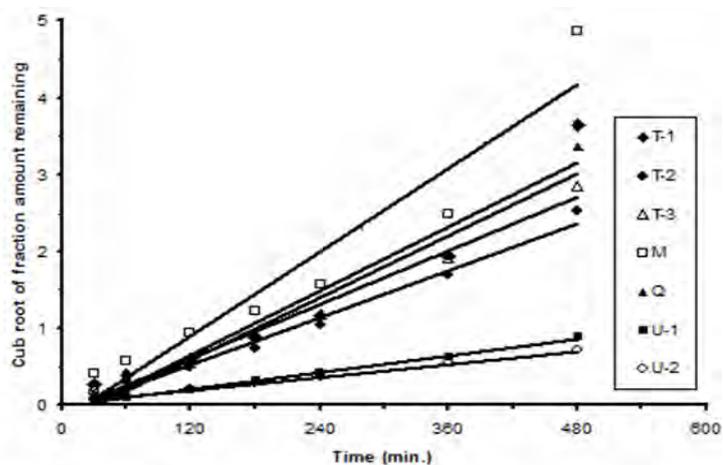

Fig. (5): Dissolution profiles of TP from its commercial available product in a phosphate buffer of 7.2, plotted in accordance to Hixon Crowell model.

The values of release rate constants and the corresponding correlation coefficients (r^2) of the applied models (zero-order, first-order, Higuchi's equation and Hixon-Crowell's cub root equation) for TP commercial products investigated; T-1, T-2, T-3, Q, M, U-1 and U-2 in phosphate buffer medium of PH 7.1 were listed in table (3).

From the results shown in Figs. (2-5) and table (3), it can be concluded that the kinetic of the release data of TP from its investigated commercial products showed that the best fitting models with the highest correlation coefficients (r^2) were given by zero-order model and Hixon-Crowell's cub root model among the other investigated models. Both zero-order (r^2 ranged from 0.9981 to 0.9998) and Hixon-Crowell's cub root (r^2 ranged from 0.9681 to 0.9994) models displayed sufficiently linearity.

To further the exact release mechanism, the dissolution data were fitted to the well-known exponential Ritger and Peppas model [12], which is often used to describe the drug release behavior from polymeric matrix systems:

$$M_t / M_\infty = K t^n \quad (5)$$ -where M_t / M_∞ is the fraction released by the drug at time t, K is a constant incorporating the structural and geometric characteristic of the polymeric systems and n is the release exponent characteristic for the drug transport mechanism and is used to characterize the operating transport mechanism. Where, the values of n are listed as followed: ≤ 0.45 for Fickian (Case I) release, >0.45 and <0.89 for non-Fickian (Anomalous) release, equals to 0.89 for Case II (Zero order) release and >0.89 for super case II type of release [13]. The values of n for the investigated TP commercial products have been calculated to identify the drug release mechanism and listed in table (3). The n vales are ranged from 0.731 to 0.897, suggesting that a near zero-order kinetics (Case II transport or super Case II transport) was assumed to be appropriate to describe the release data. The linear applicability of the dissolution data to Hixson-Crowell cube root law indicates that during the dissolution process there is an alteration in the surface area and diameter of the matrix system as well as in the diffusion path length from the matrix drug load.

Table (3):The values of release constant (k) and correlation coefficient (r^2) of different kinetic models for fitting the release process of TP from its investigated products.

Abbr. name	Zero-order model		First-order model		Higuchi model		Hixon-Crowell model		Release exponent
	R^2	$K_Z.10^{-1}$	R^2	K_F	R^2	$K_H.10^{-1}$	R^2	K_{HC}	(n)
T-1	0.9986	1.30	0.8124	2.25	0.9783	1.64	0.9781	0.20	0.731
T-2	0.9983	1.02	0.9623	2.35	0.9732	4.08	0.9839	0.07	0.825
T-3	0.9981	1.50	0.9620	2.53	0.9729	6.14	0.9861	0.08	0880
M	0.9982	4.04	0.8149	2.66	0.9739	4.24	0.9755	0.18	0.897
Q	0.9988	0.77	0.9190	2.57	0.9675	7.46	0.9681	0.21	0.896
U-1	0.9998	0.29	0.9947	2.48	0.9703	3.04	0.9984	0.01	0.751
U-2	0.9993	0.72	0.9953	2.60	0.9746	2.51	0.9994	0.04	0.746

In summary, it can be concluded that the release mechanism of TP from its commercial products investigated; T-1, T-2, T-3, Q, M, U-1 and U-2 was a coupled release pattern mechanism between the diffusion and dissolution mechanisms from these matrices. Similar results were obtained by Juarez et al. [14].

4. Conclusion:

The present work proved that a significant variation exists in the in-vitro release patterns of TP from its investigated commercial available sustained- or controlled-release oral products. This variation is related to the drug release mechanisms built by the processing manufacture. The analysis of the kinetics of dissolution process showed that both zero-order and Hixson-Crowell cube root models can best describe the kinetics of the dissolution process of TP for most of its investigated commercially available sustained- or controlled-release oral products. These results indicated that the release process of TP is a coupled release patterns between the diffusion and the dissolution mechanisms for its investigated commercial available sustained- or controlled-release oral products.

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