Kinetic Analysis of Drug Release from Compounded Slow-release Capsules of Liothyronine Sodium (T3)

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INTRODUCTION

Over the past several decades, liothyronine (T3) along with its precursor levothyroxine (T4), have often been prescribed, alone or in combination, for the initial treatment of clinical underactive thyroid in hormone replacement therapy.[1-6] Underactive thyroid is the prevalent disease-state hypothyroidism, a common condition in which the thyroid gland neglects to produce sufficient amounts of thyroid hormones.[2-3] This condition precipitates life-altering and potentially life-threatening symptomologies, including ataxia, intractable chronic fatigue, bradycardia, cold intolerance, hyperlipidemia, mental impairment, weight gain, impaired concentration, and depression,[2,3,7,8] in approximately 5.8 million people within the U.S., as reported by the American Association of Clinical Endocrinologist.[7]

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ABSTRACT

The purpose of this study was to formulate extemporaneously compounded Liothyronine Sodium (T3) slow-release capsules and to evaluate their *in vitro* drug release performance. Twenty-one formulations containing T3 (7.5 µg) with various compositions of two different grades of Methocel E4M and K100M premium (30% to 90%), and/or SimpleCap/Lactose (10% to 70%) were examined. Quality assessment of the capsules was conducted by standard quality control criteria of the *United States Pharmacopeia* (i.e., weight variation, content uniformity) to ensure their compliance. The dissolution release profile of the formulations was evaluated using *United States Pharmacopeia* Apparatus type II (paddle method) at a speed of 50 rpm and temperature of 37°C in phosphate buffered saline media (pH = 7.2 to 7.4). Aliquots from the media were taken periodically up to 24 hours and analyzed using a validated enzyme-linked immunosorbent assay method. The cumulative percentage of drug release for each formulation was fitted to eleven major release kinetic equations to determine the best-fit model of drug release, as well as the mechanism of release. Assay sensitivity was as low as 1 ng/mL and the optimal calibration range was found to be between 0 ng/mL and 7.5 ng/mL, which corresponded well with the average physiological plasma concentrations of T3. Liothyronine sodium with either SimpleCap (100%) or Methocel E4M (100%) exhibited slow-release kinetic patterns of *Peppas* and *Zero Order*, respectively. The formulation with SimpleCap (100%) had a higher percentage of drug release (as compared to 100% Methocel E4M) within the first four hours; this formulation released 80% of the drug within 12 hours when the release was plateaued thereafter. The formulation with 30% Methocel E4M and 70% SimpleCap released 100% of the drug within the initial 12 hours and exhibited a *Zero Order* slow-release kinetic pattern. In general, the release kinetic rate of the formulations containing Methocel K100M appeared to be slower than Methocel E4M. This alteration may be due to a higher molecular weight and apparent viscosity of Methocel K100M. While most of the formulations were fitted to a slow-release kinetic pattern, several others including Methocel E4M 100%, 30% Methocel E4M+ 70% SimpleCap, 40% Methocel K100M+ 60% SimpleCap, 50% Methocel K100M+ 50% SimpleCap, 30% Methocel E4M+ 70% Lactose, 90% Methocel E4M+ 10% Lactose, 40% Methocel K100M+ 60% Lactose, and 50% Methocel K100M+ 50% Lactose followed an ideal slow-release kinetic pattern of *Zero Order* or *Higuchi*. The results of this study successfully demonstrated the optiomal composition of slow-release compounded capsules of T3. Future studies are warranted to evaluate the *in vivo* performance of the optimal formulations and to establish an *in vitro-in vivo* correlation.

The benefits and drawbacks of commercially available formulations of T3 have been studied in the past.[1,3-6,8] Recent studies have also reviewed the effectiveness of T4 and T3 as the single active ingredient versus a fixed amount of T3 and T4 as a combination therapeutic.[1,2,4-12] However, the findings of these studies have shown discrepancy, hence controversial; some studies have reported a positive effect of combination therapy on overall wellness of the patients, whereas others have deemed the therapy ineffective or even harmful.[1,5,7,9,10,12] Most recently, it has been shown that a slow-release T3 or a specific blend of T4 with slow-release T3 may grant more benefit to the patients and resolve many of the limitations on a patient's quality of life.[7] Indeed, these results have highlighted the individual needs of patients and have brought to spotlight the fact that one size does *NOT* fit all. Compounded T-4, T-3, or a combination of both at mathematical ratios other than 4.22:1 can help a certain patient population that otherwise would experience therapeutic failures.

Currently, T3 is commercially available as 5-, 25-, 50-µg immediate-release (IR) tablets of liothyronine sodium (Cytomel), which are typically administered up to 2 to 4 times daily.[7,8] T3 is a biologically active moiety that is rapidly absorbed into the bloodstream with a high reported bioavailability (69% to 99%).[13] T3 is 3 to 4 times more potent as compared to T4, yet exhibits a relatively short half-life of less than 2 days, versus that of T4 (6 to 7 days).[8] Thus, following the administration of any IR formulation, T3 plasma levels often fluctuates, which leads to an inconsistent and often undesired serum levels.[7,11,14,15] In addition, some patients can be under or over treated using the only available three dosages.

Compounded slow-release (SR) capsules are intended for prolonged drug release over several hours,[12,16-18] which can result in decreasing dosing frequency, obtaining more constant plasma concentration levels, and reducing adverse effects, which ultimately translates into improving the overall clinical efficacy.[14,15,19] This release profile mimics the pulsate hormone release profile of the thyroid gland better than an immediate-release pattern. Since SR formulations of T3 as mono/combination therapy are not commercially available, compounding pharmacists have often been requested to compound SR capsules of T3 for the treatment of hypothyroidism. By compounding an optimal and precise amount of T3 and/or T4 SR formulation, pharmacists are able to improve patients' overall health and well-being by giving the clinician the ability to achieve targeted serum levels and desirable therapeutic objective while minimizing the adverse drug effects.[4,7,12,20] For many patients, this is also associated with the improvement of their symptoms (e.g., cold tolerance, foggy thinking, menses in women) and "feeling better."

There is a dearth of literature regarding the optimal composition of T3 and/or T4 slow-release capsules or whether the compounded preparations have the desirable SR characteristics. Often, compounded capsule formulations employ controlled-release grades of Methocel E4M or K100M.[21,22] Methocel polymers, also known as hydroxypropyl methylcellulose, are water-soluble polymers derived from cellulose and are among the most abundant polymers in nature.[23] These products have been commonly used as popular key ingredients in pharmaceuticals for decades.[21,23] The main purpose of Methocel is to attenuate drug release when no other commercially available slow-release dosage forms are accessible.[18]

There are various reasons for the high popularity of Methocel in controlling the release kinetics of drugs. Methocel polymers are very versatile with non-ionic characteristics that minimize the excipient-drug interaction problems. They may be used in different conditions including acidic, basic, or other electrolytic systems.[21,23] These polymers work well with soluble and insoluble drugs at high and low strengths while possessing an excellent safety record.[18,21,23] Moreover, Methocel systems are relatively simple to compound, which in turn allow the formulations to have robust, reliable, and consistent drug systems (based on 30% to 40% w/w of specific types of Methocel).[12,16-18,21] Commercially, Methocel has been utilized mainly to compound extended-release tablet formulations. However, the optimal utilization of Methocel in compounding SR capsules has only been examined in a limited number of cases.[16-18] There is a lack of literature regarding the optimal composition of Methocel alone or in combination with other excipients in order to achieve optimal SR characteristics in capsules. In addition, the utilization of Methocel in compounded SR capsule formulations has not yet been recommended by DOW Chemical Company, the manufacturer of Methocel, although it has been extensively used for sustained-release tablets.[21] Therefore, there is a need for investigation of the optimal composition of Methocel in SR capsule formulations in order to achieve adequate SR characteristics; therefore, the objective of this study was to examine the optimal composition of Methocel in combination with other excipients for use in T3 compounded SR capsules. These type of studies will provide compounding pharmacists the information they need in order to compound appropriate formulations with confidence and to minimize the potential harms to their patients.

MATERIALS AND METHODS

MATERIALS

Liothyronine (T3) sodium (Lot 06302015:2122) was purchased from Sigma Aldrich, USA. Blue Locking Gelatin Capsules #3 United States Pharmacopeia (USP) (Lot 1401210060) were purchased from Letco Medical Inc. (Decatur, Alabama). Methocel E4M (Hypromellose 2910 USP) (Lot F10623-3, 17), Methocel K100M (Hypromellose 2208 USP) (Lot F11146), premium CR), lactose monohydrate (Lot F11226-05, 06), and Freedom SimpleCap powder (Lots F10865-4 and 15D01-F001) were donated by Freedom Pharmaceuticals Inc. (Broken Arrow, Oklahoma). Triiodothyronine enzyme-linked immunosorbent assay (ELISA) kits were purchased from Sigma-Aldrich (Model SE120132; St. Louis, Montana) and Abcam Inc. (Model AB108685; Cambridge, Massachusetts). Purified water was from a Direct-Q 3 UV laboratory water purification system (Model F1CA39722). Phosphate Buffer Saline (PBS) Tablet

USP (Lot 74199080A) was purchased from Gibco (Waltham, Massachusetts).

METHODS

EXPERIMENTAL DESIGN

T3 capsules (7.5 µg active ingredient) were compounded at Carolina Compounding Pharmacy & Health Center, Cary, North Carolina. All preparations were compounded under the supervision of Dr. Hamid Bakhteyar (the registered pharmacist member of the research team). The compositions of the various formulations examined in this study are summarized in Table 1. In Groups 1 and 3, different compositions of Methocel E4M with SimpleCap/or lactose were tested, whereas in Groups 2 and 4, Methocel K100M was utilized as the primary excipient in combination with SimpleCap/or Lactose.

PREPARATION OF LIOTHYRONINE SODIUM (7.5 µg) SLOW-RELEASE CAPSULES

Liothyronine sodium and all other excipients were weighed using an analytical balance. Aliquot method of weighing was utilized to make T3 capsules. The powder mixture was blended using a V-mixer machine for 10 minutes to ensure content uniformity. Capsules were filled at batches of 50 using a Capsule Machine USP Size #3. Three lots of each formulation were randomly selected for the dissolution studies.

PERFORMING QUALITY-CONTROL ASSESSMENT OF SLOW-RELEASE CAPSULES

Quality-control assessments including weight variation and content uniformity tests, dissolution of capsules, active drug assay, physical appearance, and physical stability were performed on all formulations. Weight variation and content uniformity was conducted according to *USP* Chapter <795>.[24] According to the *USP*, the compounded preparations are to be prepared to ensure that each contains no less than 90.0% and no more than 110.0% of the theoretically calculated and labeled quantity of active ingredient per unit of the preparation.[24] Additionally, a representative number of dosage units (10 capsules) should weigh no less than 90% and no more than 110% of the average weight of all capsules in the batch, and the relative standard deviation should be below 6%. The content uniformity assay was also conducted on 10 individual capsules from each formulation bath. The capsules were then shipped to Western New England University, College of Pharmacy, for further characterization.

TABLE 1. COMPOSITION OF T3 SLOW-RELEASE CAPSULES BASED ON VARIOUS W/W PERCENTAGE OF METHOCEL (E4M OR K100M) AND EXCIPIENTS (SIMPLECAP OR LACTOSE).

GROUP NO.	FORMULATION ID	COMPOSITION
1	F1 (control)	T3 + SimpleCap (100%)
	F2 (control)	T3 + Methocel E4M (100%)
	F3	T3 + Methocel E4M (40%) + SimpleCap (60%)
	F4	T3 + Methocel E4M (30%) + SimpleCap (70%)
	F5	T3 + Methocel E4M (50%) + SimpleCap (50%)
	F6	T3 + Methocel E4M (90%) + SimpleCap (10%)
2	7 (control)	T3 + Methocel K100M (100%)
	F8	T3 + Methocel K100M (40%) + SimpleCap (60%)
	F9	T3 + Methocel K100M (30%) + SimpleCap (70%)
	F10	T3 + Methocel K100M (50%) + SimpleCap (50%)
	F12	T3 + Methocel K100M (90%) + SimpleCap (10%)
3	F13 (control)	T3 + Lactose (100%)
	F14	T3 + Methocel E4M (40%) + Lactose (60%)
	F15	T3 + Methocel E4M (30%) + Lactose (70%)
	F16	T3 + Methocel E4M (50%) + Lactose (50%)
	F17	T3 + Methocel E4M (90%) + Lactose (10%)
4	F18	T3 + Methocel K100M (40%) + Lactose (60%)
	F19	T3 + Methocel K100M (30%) + Lactose (70%)
	F20	T3 + Methocel K100M (50%) + Lactose (50%)
	F21	T3 + Methocel K100M (90%) + Lactose (10%)

Formulations 1 through 6 are different compositions of Methocel E4M with SimpleCap; formulations 7 through 12 contain various compositions of Methocel K100M and SimpleCap; formulations 13 through 17 contain various compositions of Methocel E4M and lactose; and formulations 18 through 21 contain various compositions of Methocel K100M and lactose. One batch of each formulation (n=50) was compounded, and three random capsules were selected from each batch to conduct dissolution studies.

SAMPLE ASSAY METHOD

Samples were analyzed for T3 concentrations by commercially available ELISA kits. The assays were conducted in direct accordance with the manufacturer's instructions verified for *in vitro* use. Assay sensitivity was achieved in the ng/mL range (0 ng/mL to 7.5 ng/mL), which correlated well with physiological plasma range of T3. The absorbance was measured spectrophotometrically at 450 nm wavelength, using a (BioTek Model ELX808; Winooski, Vermont) spectrophotometer. Validation of each kit was based upon comparison between serial dilutions of standardized test samples with the reproducible standard calibration curve (0 ng/mL to 7.5 ng/mL) provided by the manufacturers of the kit. A blank control of PBS buffer was included in triplicate in the assay plates to examine any significant absorbance interference by the dissolution media components.

DRUG-RELEASE EXPERIMENTS

The *in vitro* dissolution of the various extemporaneously compounded SR capsules were evaluated utilizing a paddle (type II) apparatus (Model 2100C; DISTEK, North Brunswick, New Jersey) recommended by the *United States Pharmacopeia* at a temperature of 37°C ± 0.2°C and RPM of 50 ± 0.1 per minute. The dissolution media consisted of 1000 mL of PBS (pH =7.3 ± 0.1). Each formulation was tested in triplicate. Samples were withdrawn at given time points of 0, 1, 2, 4, 6, 8, 12, 20, and 24 hours.

DATA ANALYSIS

The amount of T3 in each time point within the 24-hour interval was utilized to calculate percentage release of T3 versus time. The calculated cumulative percent release was plotted with respect to time, and the standard deviations were calculated using GraphPad Prism, version 7, (GraphPad, California). Cumulative percentage of drug release for each formulation was fitted to eleven most common release kinetic equations (Table 2) to find out the best model of release profile as well as the mechanism of drug release. The mathematical equations for the models used to describe dissolution profiles are summarized in Table 2 where Q is the percent of released at time t and k_0, k_1, k_h, and kp are the coefficients of the equations. An empirical equation of Korsmeyer–Peppas model [$Q = kp\ (t)^n$] was utilized to describe general solute behavior from controlled-release polymeric matrices, where n is the release exponent indicative of the mechanism of release. When n approximates between 0.43 and 0.50 (*Higuchi* release kinetics), a Fickian/diffusion-controlled release is implied, whereas a 0.5 <n < 1.0 value indicates a non-Fickian transport. If the value of n approaches 1.0, phenomenologically one may conclude that the release is approaching *Zero Order* kinetic, which has been idealized as an ultimate goal for a slow-release delivery system. The best-fit model for each formulation was identified by evaluating the coefficient of determination (RSQ) and mean percent error (MPE) using the following equation:

$$MPE = \frac{100x\ \Sigma\ \frac{|Fcal\text{-}Fobs|}{Fobs}}{N}$$

where *Fobs* and *Fcal* are the measured and calculated fraction of the drug released in each sampling time, and N is the number of sampling times. For a given release profile, the highest RSQ value and smallest MPE values indicated the best fit model.

TABLE 2. SUMMARY OF EQUATIONS DESCRIBING DRUG RELEASE KINETICS FROM THE SLOW-RELEASE SYSTEMS.

KINETICS	EQUATION
Zero order	$Q = k_0\ t$
Higuchi model (1963)	$Q = k_h\ (t)^{0.5}$
Korsmeyer–Peppas model (1983)	$Q = k_p\ (t)^n$
First Order	$Ln\ (1\text{-}Q) = -k_1\ t$
Hixon-Crowell	$1\text{-}\sqrt[3]{1\text{-}Q} = k_{1/3}\ t$
Weibull	$Ln[-\ Ln(1\text{-}Q)] = \beta Ln\ t_d + \beta Lnt$
Wagner Linear	$Z = Z0 + qt$
Wagner Log Probability	$Z' = Z_0\ ' + q\ 'Ln\ t$
Square root of mass	$1\text{-}\sqrt[3]{(1\text{-}Q)} = k_{1/2}\ t$
Three seconds root of mass	$1\text{-}\sqrt[3]{(1\text{-}Q)^2} = k_{2/3}\ t$
Non-conventional order 1	$1\text{-}(1\text{-}Q)^{1\text{-}n} = (1\text{-}n)k_{1\text{-}n}\ t$

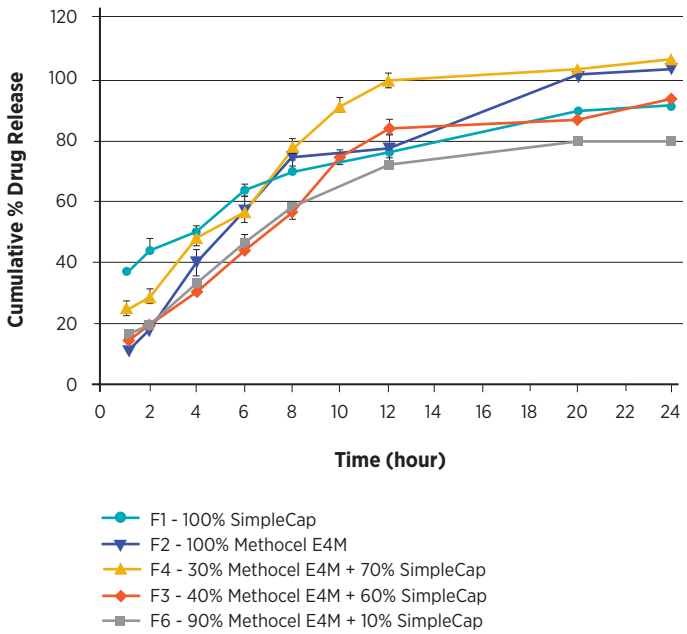
Q denotes the percent of drug released at time t. k0, kh, kp, p, k, k1/3, k1/2, k2/3, td, β, Z0, Z0′, q, q′ are parameters of the models. Z and Z′ are probits of fraction of drug released at any time. Z0 and Z0′ are the values of Z and Z′ when t=0 and t=1, respectively.

RESULTS

The cumulative percent release of T3 for various formulations was plotted with respect to time, and the standard deviations were calculated for each time point within 24 hours (Figures 1 through 6). Moreover, for each formulation, the cumulative percentage of the release was fitted to eleven major release kinetic equations, which are listed in Table 2. The results of the kinetic analysis and the best model fit for formulations 1 through 21 are summarized in Table 3.

Figure 1 displays the release profiles of the formulations composed of Methocel E4M and SimpleCap with varing percentage (ranging from 10% to 100%) of the excipients (F1 through F6; Note: For simplicity, only selective, more informative plots have been shown. In both F1 (100% SimpleCap) and F2 (100% Methocel

FIGURE 1. DISSOLUTION PROFILES OF VARIOUS METHOCEL E4M AND SIMPLECAP COMPOSITION (F1 THROUGH F6).



E4M), approximately 75% of the T3 was released within the initial 12 hours. F1 and F2 both exibited slow-release kinetic profiles of *Peppas Power Law* and *Zero Order*, respectively. While F1 (100% SimpleCap) exhibited a higher percentage of drug release within the initial six hours compared to F2 (100% Methocel E4M), yet, ultimately 80% of the total T3 content was releasd after 24 hours; wheras F2 showed 100% drug release within 24 hours. Additionally, by increasing the percentage of Methocel E4M, the release-rate

FIGURE 2. DISSOLUTION PROFILES OF VARIOUS METHOCEL K100M AND SIMPLECAP COMPOSITION (F7 THROUGH F12)

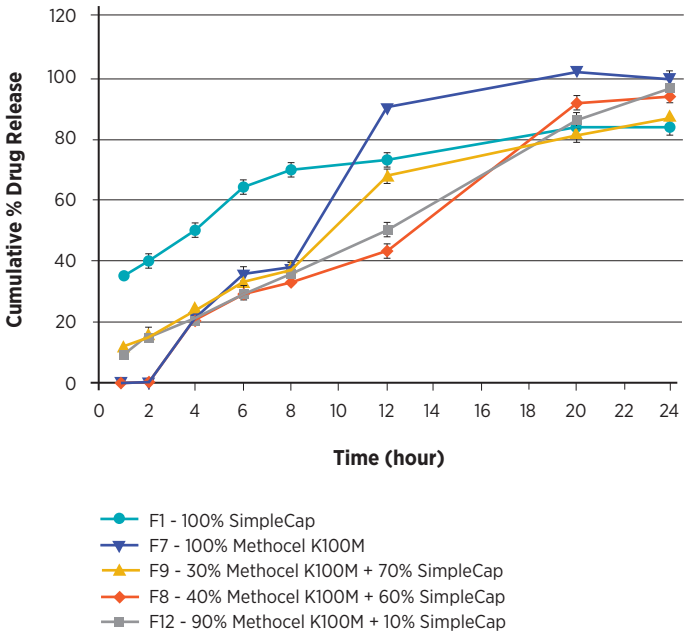


FIGURE 3. A COMPARISON OF TWO DIFFERENT FORMULATIONS UTILIZING 30% METHOCEL E4M.

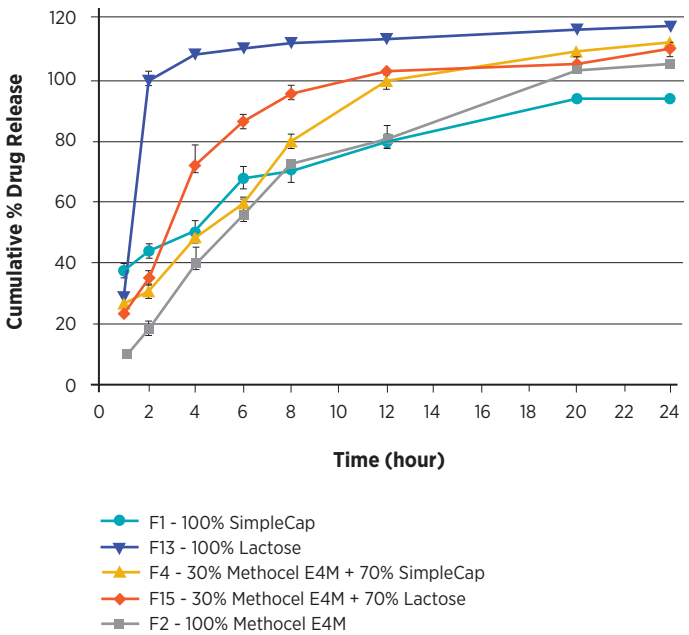


FIGURE 4. A COMPARISON OF TWO DIFFERENT FORMULATIONS UTILIZING 40% METHOCEL E4M.

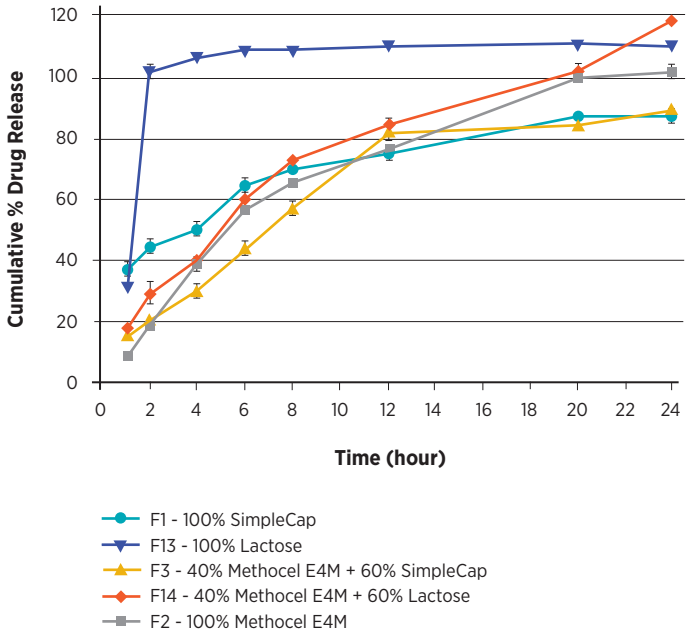


FIGURE 5. A COMPARISON OF TWO DIFFERENT FORMULATIONS UTILIZING 30% METHOCEL K100M.

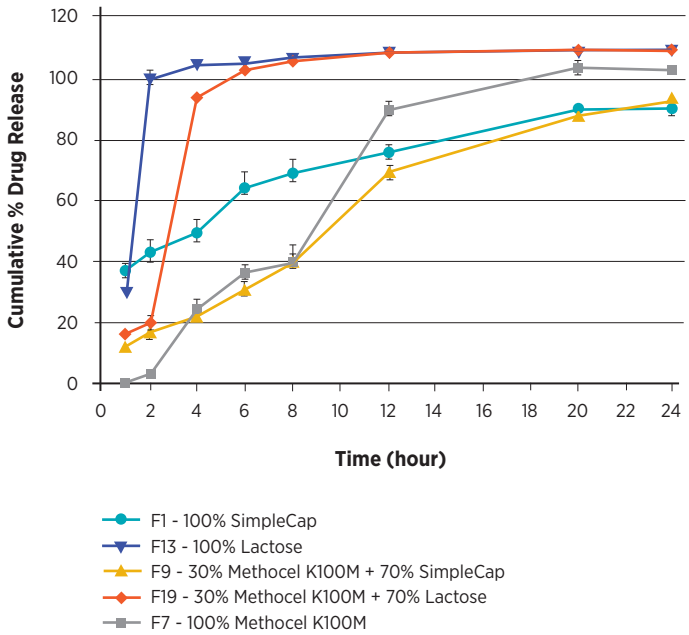
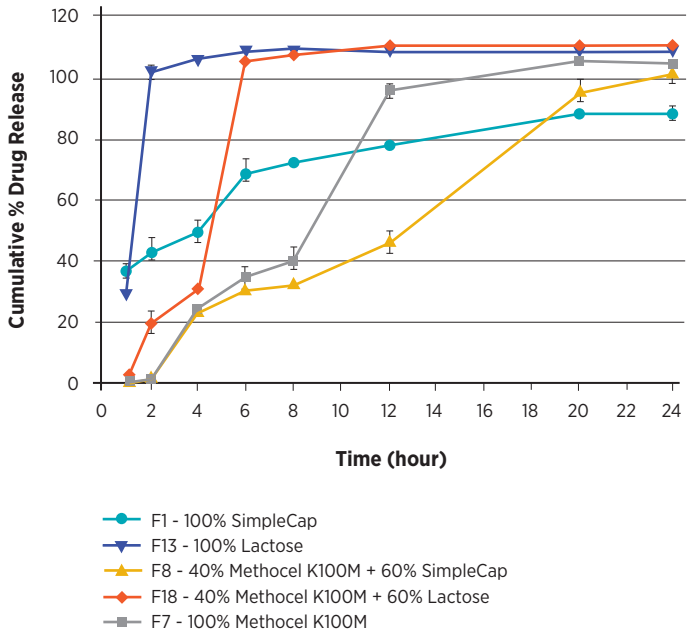


FIGURE 6. A COMPARISON OF TWO DIFFERENT FORMULATIONS UTILIZING 40% METHOCEL K100M.



slope shifted to the right, indicating a slower release rate in general. Interestingly, when SimpleCap (60%) was combined with 40% Methocel E4M (as in F3), 80% of the drug release over a 24-hour period remained the same as seen with SimpleCap alone, while exhibiting *Linear Probability* release kinetics. The reduction of the percentage of Methocel E4M from 40% to 30% (as in F4) increased the total release from 80% to 100% within a 12-hour duration with a *Zero Order* kinetic release profile. Overall, the formulation with lower percentateg of Methocel E4M (i.e., F4 with 30% Methocel E4M+ 70% SimpleCap) exhibited a higher percentage of drug release within 8 to 12 hours as compared to F1, F2, F3, and F6. A formulation with the highest percentage (90%) of Methocel E4M (F6), released only 70% of the drug content within 12 hours while displaying *Three Seconds Root of Mass* slow-release release kinetics. F6 and F3 showed a similar profile within the initial 7 hours, where 50% of the drug content was released from both formulations.

The release profiles of formulations containing various percentages of Methocel K100M and SimpleCap are shown in Figure 2 (Note: For simplicity, only selective, more informative plots have been shown.). When T3 was formulated with 100% Methocel K100M, the percentage of drug release within the initial 2 hours was neglegible, and only 40% release occured within 8 hours; yet, the majority of the release took place between 8 to 12 hours, with a release plateu of 100% after 12 hours. In general, the release patterns with Methocel K100M seemed to be much slower within the initial 8 hours; by increasing percentage of the Methocel K100M, the release-rate slope was shifed to the right indicating a slower release. When SimpleCap was combined with 30% Methocel K100M as exhibited in F9, the *Linear Probability* slow-release kinetics was observed, where 70% of the drug was released within 12 hours; a slower release pattern than that of formulation F4 (30% Methocel E4M+70% SimpleCap), and reached a 90% release within 24 hours. Formulations F8 (40% Methocel K100M+60% SimpleCap) and F12 (90% Methocel K100M+10% SimpleCap) exhibited similar release profiles with respect to time; both formulations released 50% of the drug in 12 hours and 100% after 24 hours.

The kinetic profiles of formulations containing a substitute of Lactose for SimpleCap were also explored for all formulations shown in Table 1, with only selective results displayed in Figures 3 through 6. As expected, the formulation containing solely 100% lactose (F13) was an IR formulation, where 100% of the release occured over the initial 2 hours (Figure 3). F15 (30% Methocel E4M+ 70% lactose) exhibited a *Higuchi*

TABLE 3. SUMMARY OF THE RESULTS OF KINETIC ANALYSIS FOR FORMULATIONS (1 THROUGH 21).

	BEST FIT MODEL	MAX RSQ	MPE	K	N
F1	Peppas	0.998	0.457	0.368	0.205
F2	Peppas- Zero Order	0.999	2.210	0.087	1.036
F3	Wagner Linear	0.999	1.831	0.184	-
F4	Zero Order	0.990	3.992	0.072	-
F5	Square Root of Mass	0.998	1.110	-	-
F6	Three seconds root of mass	0.997	2.285	-	-
F7	Hixon-Crowell	0.956	41.936	-	-
F8	Peppas-Higuchi	0.992	1.825	0.103	0.584
F9	Wagner Linear	0.987	9.053	0.1223	-
F10	Peppas-Higuchi	0.992	1.825	0.103	0.584
F12	Peppas	0.983	5.807	0.101	0.620
F13	-	-	-	-	-
F14	Hixon-Crowell	0.986	4.02	-	-
F15	Peppas-Higuchi	1	0	0.2300	0.502
F16	Peppas	0.978	8.89	0.0945	0.818
F17	Zero Order	0.994	5.35	0.0446	-
F18	Higuchi	0.994	12.03	0.318	-
F19	Peppas	1	0	0.1740	0.278
F20	Peppas-Zero Order	0.959	10.94	0.0834	0.973
F21	Peppas	0.972	2.05	0.3777	0.221

slow-release kinetic pattern similar to F4 (30% Methocel E4M+ 70% SimpleCap), where 100% of the drug was released within 12 hours; yet, F15 exhibited a much higher percentage of drug release within the initial 2 to 8 hours as compared to the respective times of F4; although both formulations exhibited slow-release kintetic patterns of *Higuchi* and *Zero order*, respectively (Figure 3).

Figure 4 shows the release profiles of formulations containing either SimpleCap or lactose with 40% Methocel E4M. Similar to Figure 3, F14 (40% Methocel E4M+ 60% lactose) had a higher percentage of drug release observed within 1 to 8 hrs as compared to F3 (40% Methocel E4M+ 60% SimpleCap), although both formulations exhibited slow-release kinetic patterns of *Hixon-Crowell* and *Wagner Linear,* respectively.

In Figures 5 and 6, the kinetic profiles of either SimpleCap or lactose with 30% and 40% Methocel K100M are depicted. Both F9 (30% Methocel K100M+ 70% SimpleCap) and F19 (30% Methocel K100M+ 70% lactose) released only 20% of the drug within the initial 2 hours, but the release rate was much faster afterwards with the lactose containing formulations where 100% of the drug was released within 4 hours. A 10% increase in the amount of Methocel K100 M as in F8 and F18 (Figure 6) exhibited a similar release pattern with a (more) slower initial release of the drug.

Interestingly, both formulations F8 (40% Methocel K100M+ 60% SimpleCap) and F18 (40 % Methocel K100M+ 60% lactose) exhibited *Higuchi* slow-release kinetics.

DISCUSSION

Despite available hormone replacement therapy strategies, still a significant percentage of patients with hypothyroidism and thyroid dysfunctionality remain symptomatic.[2-6] Compounding pharmacists have often been requested to compound (T3) SR capsules for the treatment of hypothyroidism since T3 mono- and/or with T4 combination therapy is not available commercially. Currently, the only commercially available dosage form of T3 is an immediate-release form (5-, 25-, 50-µg tablets). In addition, it has been shown that a slow-release (T3) or a blend of T4 with SR (T3) may improve patients' quality of life.[7,12] Hence, compounding optimal customized levels of T3 and T4 enables the clinician to achieve targeted serum levels of free T4 and T3 while minimizing the adverse side effects.[4,7,12] Customized dosage forms of T3 and T4 allow dose adjustments in order to achieve a desirable balance of necessary T3 and T4, which in turn leads to achieve an optimal health and resolution of the symptoms.[7]

In this investigation, several slow-release capsules of T3 (7.5 µg) were formulated and evaluated *in vitro*. Varying compositions of Methocel E4M or Methocel K100M with SimpleCap or lactose were examined as the primary slow-release excipients (Table 1). Methocel is a water soluble polymer which functions by decreasing the rate of drug release via the continuous hydration and formation of a gel barrier. The polymer level should be sufficient to form a uniform gel barrier to a desirable degree. This barrier protects the drug to be released immediately into the dissolution media. The mechanisms by which drug release is controlled is determined by diffusion (if soluble) through the gel and/or by the rate of erosion.[18,25] Higher aqueous solubility of the drug (T3 is highly soluble in an alkaline environment) generally leads to a higher diffusion driving force and a faster release profile, as was observed in the formulation of T3 and lactose (100%).

This study showed that both SimpleCap (100%) and Methocel E4M (100%) exhibit slow-release kinetic profiles of *Peppas Power Law* and *Zero Order,* respectively. Additionally, with an increasing percentage of Methocel E4M, the release-rate slope shifted to the right indicating a slower release rate in general. When SimpleCap (70%) was combined with (30%) Methocel E4M, the total content of the drug (100%) was released within 12 hours with a *Zero Order* kinetic release profile as compared to 75% release within the same time period with 100% Methocel E4M.

On the other hand, when T3 was formulated with 100% Methocel K100M, the percentage of drug release within the initial 2 hours was negligible and only 40% release occured within 8 hours, which is not considered desirable if a patient's immediate need is to elevate the plasma levels of T3. In general, the release patterns of formulation containing Methocel K100M were much slower within the initial few hours. By increasing the percentage of Methocel K100M, the release-rate slope was shifted to the righ, indicating of a slower release. This can be due to a higher molecular weight of the polymer, which results in higher apparent viscosity of the hydrated gel barrier.

F15, a formulation with 30% Methocel E4M+ 70% lactose, exhibited a *Higuchi* slow-release kinetic pattern which was similar to F4 (30% Methocel E4M+ 70% SimpleCap) formulation, where, in both, 100% of the drug was released within a 12-hour duration. However, the former exhibited a much higher percentage of drug release within the initial 2 to 8 hours, although both formulations exhibited slow-release kintetic patterns of *Higuchi* and *Zero order*, respectively. Interestingly, both formulations of F3 (40% Methocel K100M+ 60% SimpleCap) and F14 (40 % Methocel K100M+ 60% lactose) exhibited *Higuchi* slow-release kinetics. It is worthwhile to note that for all other formulations the release pattern was fitted to one of the eleven equations of slow-release pattern (see Table 3 for more details).

For the patients, the optimal formulation will depend upon each individual's specific target plasma levels and symptoms. If the plasma level is low, formulations with Methocel K100M may not be desirable because the fast elevation of the T3 plasma levels will not be accomplished. On the other hand, because of the limited absorption window due to the capsule's residence time in the gastrointestinal track, it will be more desirable to retain the slow-release characterictics since 100% of the drug content is going to be released within the initial few hours. This is an especially useful tool in cases of (subclinical) hypothyroidism, elevated Thyroid Peroxidase Antibiodies (TPO), and elevated Reverse T-3.

In general, formulations which exhibit a slower-release rate may benefit the patients who have already achieved their optimal plasma T3 concentration and are in need of more of a long-term maintenance of T3 plasma levels only.

The next reasonable step in this investigation should involve the study of *in vivo* performance of extemporaneously compounded T3 SR capsules. This allows the establishment of an *in vitro-in vivo (IVIVC)* correlation to predict their *in vivo* performance and to optimize the development of T3 SR capsules based on their *in vitro* dissolution data.

CONCLUSIONS

The results of this study demonstrated the optimal composition of slow-release compounded capsules of T3. Several formulations were identified with *Zero Oder, Higuchi,* and *Peppas* release-kinetic patterns. Future studies are warranted to evaluate the *in vivo* performance of the optimal formulations and to establish an *IVIVC* correlation. These results provide an excellent tool to help the clinician decide which excipient combination(s) best suit the unique needs of their individual patients. In addition, they can serve as a reference methodology to help eliminate variations in the delicate act of compounding thyroid hormone capsules.

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REFERENCES

1. Wartofsky L. Combination L-T3 and L-T4 therapy for hypothyroidism. *Curr Opin Endocrinol Diabetes Obes* 2013; 20(5): 460–466.
2. College of Physicians and Surgeons of British Columbia. Hypothyroidism in adults: Levothyroxine if warranted by clinical and laboratory findings, not for simple TSH elevation. *Prescrire Int* 2015; 24(164): 241–244, 246.
3. Cho MK. Thyroid dysfunction and subfertility. *Clin Exp Reprod Med* 2015; 42(4): 131–135.
4. Jonklaas J. Update on the treatment of hypothyroidism. *Curr Opin Oncol* 2016; 28(1): 18.
5. Kraut E, Farahani P. A systematic review of Clinical Practice Guidelines' recommendations on levothyroxine therapy alone versus combination therapy (lt4 plus lt3) for hypothyroidism. *Clin Invest Med* 2015; 38(6): E305–E313.
6. Ng SM, Anand D, Weindling AM. High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism. *Cochrane Database Syst Rev* 2009; 1(1): CD006972.
7. Milner M. Hypothyroidism: Optimizing medication with slow-release compounded thyroid replacement. *IJPC* 2005; 9(4): 268–73.
8. Thomson Reuters Micromedex. Micromedex Healthcare Series; 2011.
9. Walsh JP, Shiels L, Lim EM et al. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: A randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab* 2003; 88(10): 4543–4550.
10. Bunevicius R, Prange AJ. Mental improvement after replacement therapy with thyroxine plus triiodothyronine: Relationship to cause of hypothyroidism. *Int J Neuropsychopharmacol* 2000; 3(2): 167–174.
11. Hennemann G, Docter R, Visser TJ et al. Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: Proof of principle. *Thyroid* 2004; 14(4): 271–275.
12. Timmons ED, Timmons SP. Custom-compounded micronized hormones in a slow-release capsule matrix. *IJPC* 2002; 6(5): 378–379.
13. Hasselström K, Siersbæk-Nielsen K, Lumholtz IB et al. The bioavailability of thyroxine and 3,5,3′-triiodothyronine in normal subjects and in hyper- and hypothyroid patients. *Acta Endocrinol* (Copenh) 1985; 110(4): 483–486.
14. Allen L, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems: Lippincott Williams & Wilkins; 2013.
15. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences. Alphen aan den Rijn, Netherlands: Wolters Kluwer; 2006: 508.
16. Bogner RH, Szwejkowski J, Houston A. Release of morphine sulfate from compounded slow-release capsules: The effect of formulation on release. *IJPC* 2001; 5(5): 401–405.
17. Webster KD, Al-Achi A, Greenwood R. *In vitro* studies on the release of morphine sulfate from compounded slow-release morphine-sulfate capsules. *IJPC* 1999; 3(5): 409–11.
18. Zur E. Compounding slow-release capsules: A comprehensive review and an Excel spreadsheet for faster calculations of excipients. *IJPC* 2013; 17(1): 10–22.
19. Allen LV Jr. Contemporary pharmaceutical compounding. *Ann Pharmacother* 2003; 37(10): 1526–1528.
20. Pinheiro VA, Kaneko TM, Velasco MV et al. Development and *in vitro* evaluation of extended-release theophylline matrix capsules. *Brazilian J Pharm Sci* 2007; 43(2): 253–261.
21. Dow T. Using methocel cellulose ethers for controlled release of drugs in hydrophilic matrix systems. Midland, MI: The Dow Chemical Company; 2000.
22. Khan F, Razzak SM, Khan ZR et al. Preparation and *in vitro* evaluation of theophylline loaded gastroretentive floating tablets of METHOCEL K4M. *Dhaka Univ J Pharm Sci* 2008; 7(1): 65–70.
23. Rowe RC, Sheskey PJ, Weller PJ, eds. *Handbook of Pharmaceutical Excipients*. London, UK: Pharmaceutical Press; 2006.
24. United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary*. Rockville, MD: US Pharmacopeial Convention, Inc.; Current Edition.
25. Glowiak DL, Green JL, Bowman BJ. *In vitro* evaluation of extemporaneously compounded slow-release capsules containing morphine sulfate or oxycodone hydrochloride. *IJPC* 2005; 9(2): 157–164.

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