Research Article

Preparation and *In Vitro* Evaluation of Extended Release Matrix Tablets of Propylthiouracil

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ABSTRACT

The objective of this work was to prepare and evaluate the effects of various concentrations of hydrophilic (Carbopol® 974 P) and hydrophobic (Eudragit® RL PO, Eudragit® RS PO) polymers on *in-vitro* dissolution profiles and sustained-release characteristics of propylthiouracil (PTU) from matrix tablets, to reduce the number of administrations of PTU required to treat hyperthyroidism. Matrix tablets containing 300 mg of PTU along with various amounts of the aforementioned polymers were prepared using the wet granulation technique. All matrix tablets were evaluated for physical characteristics, *in-vitro* drug release, kinetic models and mechanisms. Mean dissolution time is used to indicate the drug release retarding efficiency of polymer. Drug dissolution profiles were different from those polymers which were attributed to natural and characteristics of polymer used. Drug-polymer interaction was studied using fourier transform infrared spectrophotometer and differential scanning calorimeter. All matrices prepared had no initial burst release. This can be due to slight water solubility and weak acidity of the drug (PTU). A hydrophilic matrix tablets that contain 40% of Carbopol® 974 P revealed the best control over drug release and could sustain for approximately 16 h. Kinetic models indicated that both Carbopol® 974 P and Eudragit® RL, RS PO-formulations conformed best to Hixson-Crowell and Zero-order kinetics. According to Korsmeyer-Peppas equation, the value of release exponent (*n*) to the Carbopol 974® P, Eudragit® RL PO and Eudragit® RS PO – matrices was ranged from (*n*=0.76-0.87); (*n*=0.68-0.80), indicating that drug release from this matrices was mainly governed by diffusion and erosion. These results suggest that the developed sustained-release tablets of PTU by using hydrophilic polymers (Carbopol 974® P) were the best showed the most optimal dissolution patterns and could perform therapeutically, increase efficacy and patient compliance much better than conventional tablets.

Keywords: Propylthiouracil, Matrix tablets, Sustained release, Release kinetics.

INTRODUCTION

Propylthiouracil (PTU) is one of the oldest members of the thionamides group that used to treat and control hyperthyroidism by inhibiting the intra- and extra-thyroid hormonal synthesis[1, 2]. PTU is a weak acid [3], and has an aqueous solubility of 1g/900ml (20°C). The pK_a of this drug is 8.3(20°C) and its lipophilic hydrophilic balance (octanol-water partition coefficient) = 1.0.[4] Moreover, PTU is rapidly absorbed from the gastrointestinal tract (GIT) with a 50 to 75% bioavailability and a peak plasma concentration occurring about 2 hours after an oral dose[5]. Conventional tablets are mainly commercialized as 50 mg tablets and are usually administered 3 times daily in doses of 100 mg [6]. Some authors have suggested that hyperthyroid patients can be treated satisfactorily with a single daily dose of 300 mg [7], but others reported that a single daily dose was less satisfactory than dividing the dose over 3 administrations[8]. This observation might be related to saturation of the uptake mechanism of PTU in the thyroid gland at higher plasma concentration [9].

To be able to reduce the number of administrations in view of the risk of agranulocytosis, it might thus be interesting to develop an extended-release preparation, providing lower but more sustained plasma concentrations [6].

Some attempts have been made to prepare and develop controlling-release dosage forms of PTU such as matrix tablets including HPMC polymers [6, 10], and microspheres made of Eudragit RL 100 and cellulose acetate butyrate polymers[11] administered orally in treatment of hyperthyroidism.

In the present work, an attempt has been made to formulate extended-release (ER) matrix tablets of PTU and evaluate the effect of two groups of polymers, i.e. hydrophilic polymer (Carbopol®974 P) and hydrophobic polymers Eudragit® RL PO and Eudragit® RS PO on release behavior and kinetics of the drug.

MATERIALS AND METHODS

Materials

Propylthiouracil (Asia Talent Enterprise Shenzhen Co., Ltd., China), Propylthiouracil as a reference sample standard (Hangzhou Dayangchem Co., Ltd., China), Carbopol® 974 P (B.F. Goodrich, UK), Eudragit RL PO, RS PO (Evonik Röhm-Pharma GmbH, Germany), Polyvinylpyrolidone (Kollidon K30, BASF, Germany), Microcrystalline cellulose PH 101 (Avicel PH101, FMC International, Ireland), Magnesium stearate (MgSt) (Nitika, India), Aerosil 200 (BASF, Germany) and all other solvents and chemicals used in the study were of analytical grade.

Methods

Drug-polymer interaction study

In this study, FT-IR spectrum was taken by scanning the samples of pure PTU and physical mixture of PTU with polymers individually over a wave number 400 to4000 cm^{-1} using fourier transform infrared spectrophotometer (FT-IR Spectroscopy, Bruker Vector 22, Germany). Changes in spectra of the drug in the presence of polymer were observed to investigate indicates any physical or chemical interaction of drug molecules with the polymer used. Differential scanning calorimeter (DSC) thermograms of the samples that contain PTU powder and physical mixture of PTU and the polymers individually were studied using a DSC apparatus (METTLER TOLEDO, OH, USA) at a scanning speed of 10°C/min in the temperature range of 25-300°C in crimped aluminum pans under nitrogen gas flow. The T onsets, T endsets, T peaks (°C) and enthalpy fusion of melting points of samples were automatically calculated by the instrument.

Preparation of PTU matrix tablets

Sixteen matrix tablet formulations, each containing 300 mg PTU, were prepared by the wet granulation technique. All powders were passed through a 250µm sieve before using. The oversize powder (retained on 250 µm sieve) was kept aside. The composition of various formulations of the tablets with their codes is listed in Table 1. Matrix prepared with Carbopol 974 p coded as 'A' series, with Eudragit RS PO coded as 'B' series, and with Eudragit RL PO coded as 'C' series. Calculated amount of the drug, polymer was mixed thoroughly and then granulated using 5% (w/v) ethanolic solution of PVP-K30. The wet mass passed through a 2 mm sieve. The wet granules were dried at 30°C for 3 hours and pass through 1mm sieve. Microcrystalline cellulose (Avicel PH101), as filler, was added after granulation and blended for 15 min. Finally, the granules mixture was blended for 5 min. with (0.5% wt/wt) of each magnesium stearate (Lubricant) and aerosil 200 (Anti-adherent) then the appropriate amount of mixture was compressed using a single-punch tableting machine (ERWEKA GmbH AR 402.Type EK0, D-63150 Heusenstamm, Germany) with concave-faced punch and 14.0 mm diameter.

Table 1: Composition of various trial formulations for the ER matrix tablet containing 300 mg PTU

Series	Ingredients (mg/tablet)					
	PTU	Retarding polymer	MCC (Filler)	Magnesium stearate (Lubricant)	Aerosil 200 (Anti-adherent)	Total
Retarding polymer: Carbopol® 974 p						
A1	300	60 (10%)	240	3	3	606
A2	300	120 (20%)	180	3	3	606
A3	300	180 (30%)	120	3	3	606
A4	300	240 (40%)	60	3	3	606
Retarding polymer: Eudragit® RS PO						
B1	300	60 (10%)	240	3	3	606
B2	300	120 (20%)	180	3	3	606
B3	300	180 (30%)	120	3	3	606
B4	300	240 (40%)	60	3	3	606
Retarding polymer: Eudragit® RL PO						
C1	300	60 (10%)	240	3	3	606
C2	300	120 (20%)	180	3	3	606
C3	300	180 (30%)	120	3	3	606
C4	300	240 (40%)	60	3	3	606

Evaluation of Physical parameters of matrix tablets

The prepared matrix tablets were evaluated as per standard procedure for hardness and diameter (n=6), friability (n=11) and weight uniformity (n=20) [12]. Hardness of the tablets was determined using hardness tester (ERWEKA TBH 300S, GmbH, Germany) and friability was conducted using an ERWEKA Friabilator (ERWEKA TAR20-GmbH Roche, Germany) at speed of 25 rpm for 4 min. Weight variation was evaluated by using an electronic balance Precisa XB 220A (Precisa, Switzerland). Means and standard deviations were calculated for each formulation.

Assay of PTU in matrix tablets (Content uniformity)

Twenty tablets, randomly chosen, from each formulation were thinly powdered in a mortar and a portion of the resulting powder equal to the weight of the respective tablet was transferred to 600 ml volumetric flask and was solubilized in 60 ml methanol and sonicated for 5 min. The solution was diluted with water to specific volume, mixed and filtered. 5 ml of the last solution was transferred to 100 ml volumetric flask and was diluted with water to specific volume to make a solution of 50 µg of PTU per ml. Several aliquots were assayed UV/VIS spectrophotometrically at 274 nm. Each measurement was carried out in triplicate and the results were

averaged. A blank solution containing all the components, except for the drug, was also prepared. Corresponding concentrations were calculated from the standard curve. No other assay methods were considered necessary, since no interference was observed at 274 nm. Means and standard deviations of the content were calculated for each formulation.

In-vitro drug release studies

Drug release studies for the prepared matrix tablets were performed using USP-34 dissolution apparatus 2, type (ERWEKA GmbH DT 800, Germany), at speed rotation of 75 rpm, temperature 37±0.5°C. According to USP pharmacopeial dissolution procedure for oral modified release formulation[12], the dissolution media used were 900 ml of hydrochloric acid buffer (pH1.2) for the first 2 hours, phosphate buffer (pH 4.5) for the second 2 hours followed by phosphate buffers solutions (pH 7.5) from 4 to 24 hours. Sink conditions were maintained for the whole experiment. As the tablets have floating tendency, metallic sinker was used to keep tablets immersed into the media. This process was continued for 24 h. At 1 to 16 and 24 intervals samples of 5 ml were withdrawn from the dissolution media and replaced with fresh dissolution media to keep volume constant. The samples withdrawn were filtered through a 0.45 µm membrane filter and suitably diluted. After that, drug content in each sample was analyzed by UV spectrophotometer (Cary 500 UV/ VIS Spectrophotometer, USA) at 274 nm. The amount of drug released were calculated using the calibration curves constructed in the three dissolution media and means of three determinations were used for data analysis. The percentage drug release was plotted against time to determine the release profile.

Drug release kinetics studies

The mechanisms of drug release from matrix tablets containing hydrophilic or hydrophobic retarding polymers are complex and involve different processes so that mathematical models are good tools for understanding and predicting drug release in matrix systems. Both empirical and mechanistic models are available, the latter being those most widely used owing to their correlation with real-life processes that occur in the system[13]. Many models have been developed to describe the process of drug release from matrices. To study the release kinetics of PTU from matrix tablets, the release data were fitted to five kinetic models including the zero-order [1][14], first – order [2][15], Higuchi [3][16], Hixson-Crowell [4] [17] and korsmeyer-Peppas[5] [18] release equations to find the equation with the best fit according to higher value of correlation coefficient (R^2).

$$Q_t = k_0.t \quad [1]$$

$$\ln (100- Q_t) = \ln 100 – k_1.t \quad [2]$$

$$Q_t = k_H.t^{1/2} \quad [3]$$

$$Q_0^{1/3} – Q_t^{1/3} = k_{HC}.t \quad [4]$$

Where Q_t is the amount of drug release at time t, Q_0 is the initial amount of the drug in tablet and k_0, k_1, k_H and k_{HC} are the rate constants of zero-order, first-order, Higuchi and Hixson-Crowell model, respectively. Later, in order to better characterize the drug release mechanisms for the polymeric matrix studied, the Korsmeyer-Peppas semi-empirical model was applied:

$$Q_t/Q_\infty = K_{kp}.t^n \quad [5]$$

Where Q_t/Q_∞ is the fraction of drug released at time t, K_{kp} a constant compromising the structural and geometric characteristics of the device (characteristic of the drug/polymer system), and n, the release exponent, which is indicative of the mechanism of the drug release. For the case of cylindrical geometries such as tablets, n=0.45 indicates a classical Fickian diffusion controlling drug release (Case I), n=0.89 indicates a zero order (Case II and swelling of the polymer is controlling the drug release) release kinetics, n> 0.89 indicates a super Case II transport and 0.45<n<0.89 indicates a non-Fickian (anomalous transport) release kinetics which as both phenomena (drug diffusion and polymer swelling in the matrix) [19,20]. All these models are currently the best way to approach and predict drug release kinetics, with which it is possible to estimate most of the technological factors, such as the optimal composition, geometry, dimensions and manufacturing methods, necessary to obtain the desired release profiles [21]. The constant *K* gives a measure of the velocity of drug release. Since *K* has the dimension time^{-n}, release constant of different kinetics cannot be compared directly. To characterize the drug release rate, the mean dissolution time (*MDT*) is applied [22]. *MDT* is determined as the sum of the individual periods of time during which a specific fraction of the total dose is released [23]. *MDT* can be calculated according to the following equation [24,25]:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad [6]$$

Where *j* is the sample number, *n* is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} (easily calculated with the expression $(t_j + t_{j-1})/2$ and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1} . A higher value of *MDT* parameter indicates a higher drug retarding ability of the polymer in formulation and vice-versa [26].

Statistical analysis of the drug release profile

All the results were expressed as mean values ± standard deviation (SD). The difference between percents (fractions) of PTU release after every 2 h from its various formulations (The chosen response for analysis) were statistically evaluated by using one ways ANOVA. All data analysis were performed using the SPSS® 10.0 statistical software (SPSS Inc., Chicago, IL, USA). A confidence limit of p<0.05 was fixed for interpretation of the results.

RESULTS AND DISCUSSION

Interaction histogram analysis

Fourier Transform Infrared Spectroscopy (FTIR)

The FT-IR spectrum of the physical mixture (1:1) of PTU with polymers individually: Carbopol® 974 P, Eudragit® RL PO, and Eudragit® RS PO was compared respectively with FT-IR spectrum of pure PTU drug. FT-IR studies revealed that PTU showed a principal peak at 3120 cm^{-1} due to N-H stretching imide (Keto form), at 3041.29-2930.02 cm^{-1} due to CH,CH_2,CH_3 stretching, at 2360.66 cm^{-1} due to S-H stretching (Weak since the keto form predominates), at 1655.58 cm^{-1} due to C=O imide carbonyls (Keto form), at 1627.83 cm^{-1} due to C=C stretching aromatic (Enol form), at 1560.39 cm^{-1} due to N-H bending (Keto form), at 1242.91-1164.97 cm^{-1} due to C-N vibration (Aromatic secondary amine-Enol form) and at 1193.63 cm^{-1} assigned to C=S stretching (Keto form) [4,27] as shown in Figure 1.1 .

The FT-IR spectrum of the physical mixtures of PTU/ Carbopol® 974 P is shown in Figure 1.2. The broad peak assigned and reduction in intensity to C=O stretching absorption appeared at 1656 cm^{-1} and the broad peak assigned to O-H vibration absorption appeared at 3116 cm^{-1}. This may be due to an inter-molecular hydrogen bonding taking place between a carbonyl group of the PTU drug and hydroxyl group of the Carbopol® 974 P polymer.

The FT-IR spectra of the physical mixtures of PTU/ Eudragit® RL PO and PTU/ Eudragit® RS PO are shown in Figure 1.2. There is no appearance or disappearance of any characteristics peaks of PTU drug. This shows that there is no chemical interaction between drug and Eudragit polymers used within the formulations.

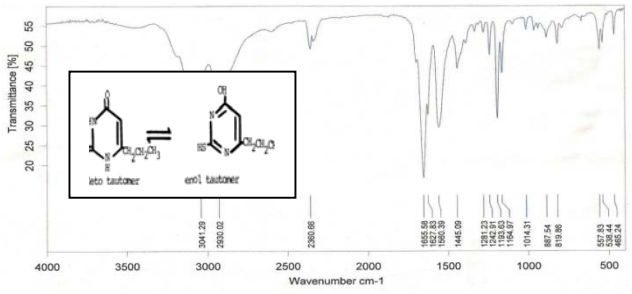

Figure 1.1: FT-IR spectra of Pure PTU drug.

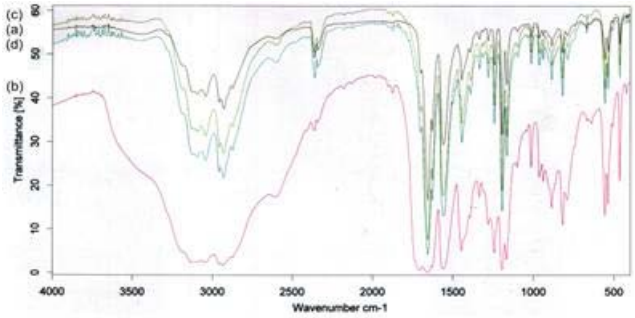

Figure 1.2: FT-IR spectra of Pure PTU (a), Physical mixture: PTU/Carbopol® 974 P (b), Physical mixture: PTU/Eudragit® RL PO (c), Physical mixture: PTU/Eudragit® RS PO (d).

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure PTU showed a crystal nature of the drug and exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the drug (Figure 2. d), (T_{onset} = 214.08, T_{peak} = 217.70, T_{endset} = 224.08 °C and ΔH fusion = -155.38 J/g). Carbopol® 974 P, Eudragit® RL and Eudragit® RS polymers showed an endothermic peak at 75.86, 64.24 and 63.54 °C, respectively, representing the glass transition (amorphous state) of these polymers used (Figure 2. a,b,c).

The thermogram of binary PTU–Carbopol® 974 P physical mixture (1:1) showed two endothermic peaks (Figure 2. e), the first peak corresponding to glass transition point of Carbopol® 974 P at 67.89 °C and another peak at (T_{onset} = 201.02, T_{peak} = 219.47, T_{endset} = 223.88 °C and ΔH fusion = -64.65 J/g), which is close to the PTU melting point. The result above indicates that there is a solid–state interaction between drug-polymer and it is in agreement with FTIR analysis result. The thermograms of binary PTU and Eudragit polymers physical mixtures (1:1) showed an endothermic peaks at 62.92, 64.26 °C, which is close to the Eudragit® RL and Eudragit® RS glass transition point, respectively [28], while the endothermic peak of PTU broadened, shifted to a lower value (209.65, 214.14 °C), reduced in enthalpy (ΔH fusion = -64.81,-71.69 J/g) and lost its sharp distinct appearance (Figure 2. f, g). This was probably due to interactions between drug-polymer in molten mixture under high temperature effect, but no significant interactions in physical mixture were appeared (Figure 2. f, g).

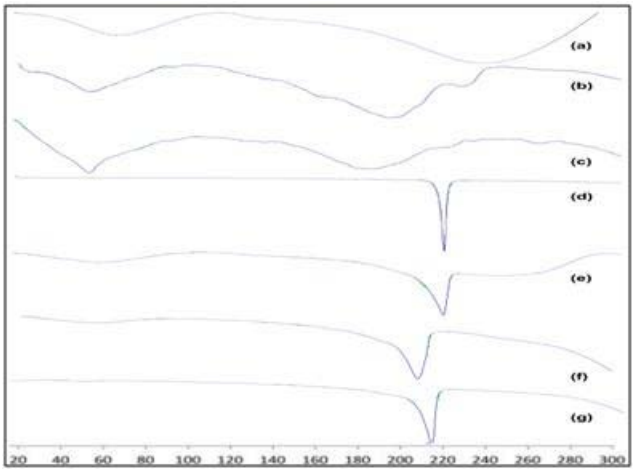

Figure 2: DSC thermograms of Pure Carbopol® 974 P (a), Pure Eudragit® RL PO (b), Pure Eudragit® RS PO (c) Pure PTU (d), Physical mixture: PTU/Carbopol® 974 P (e), Physical mixture: PTU/Eudragit® RL PO (f), Physical mixture: PTU/Eudragit® RS PO (g).

Physical parameters

The tablet hardness, diameter, friability, weight variation and content uniformity for each extended release (ER) formulation are showed in Table 2. In determinations of tablet weight and drug content, all formulations have weight and content of drug between 609.31 ± 1.16 to

616.42 ± 1.32 mg, 99.71 ± 1.42 to 103.39 ± 1.93%, respectively, so that the tablet weights were found to be within pharmacopoeial limits ± 5% and drug content uniformity indicated the presence of an acceptable amount of drug in the formulations[12]. Hardness within the range 12.10 ± 1.22 to 15.85 ± 1.12 kg/cm^2. However, hardness always remained within high values to give good handling properties without breakage or excessive friability problems, thus confirming the excellent compatibility properties of these polymers which allowed compression even in the absence of other excipients[29,30].

Table 2: Physical properties of the matrix tablets containing 300 mg PTU as ER formulation

Series	Weight Variation (mg)	Hardness (kg/cm^2)	Diameter (mm)	Friability (%)	Content Uniformity (%)
A1	615.31 ± 1.65[a]	13.90 ± 1.06[a]	15.48 ± 0.26[a]	0.25	102.76 ± 1.55[a]
A2	610.52 ± 1.8	12.10 ± 1.22	15.48 ± 0.21	0.19	100.04 ± 2.50
A3	609.86 ± 1.7	14.05 ± 2.36	15.51 ± 0.11	0.16	99.62 ± 1.97
A4	614.42 ± 1.32	15.70 ± 1.52	15.47 ± 0.09	0.11	102.89 ± 2.23
B1	610.31 ± 1.26	14.84 ± 1.26	15.47 ± 0.18	0.25	98.67 ± 1.69
B2	610.52 ± 1.81	15.12 ± 1.12	15.49 ± 0.22	0.14	100.64 ± 1.00
B3	612.86 ± 1.41	12.15 ± 1.15	15.50 ± 0.12	0.19	99.71 ± 1.42
B4	616.42 ± 1.32	14.69 ± 1.37	15.51 ± 0.14	0.21	103.39 ± 1.93
C1	609.31 ± 1.16	13.24 ± 1.34	15.43 ± 0.16	0.24	100.11 ± 1.24
C2	611.52 ± 1.57	15.85 ± 1.12	15.45 ± 0.13	0.32	100.36 ± 1.65
C3	614.86 ± 1.25	15.35 ± 1.11	15.45 ± 0.12	0.22	101.52 ± 1.73
C4	613.42 ± 1.39	14.19 ± 1.77	15.46 ± 0.17	0.21	102.27 ± 1.21

[a] Values represent mean ± SD.

In vitro dissolution studies

The studies were performed for 24 hours and cumulative drug release was calculated at several times. Figures 3, 4 and 5 show the effect of different concentrations of Carbopol® 974 P , Eudragit® RS, or Eudragit® RL (10%, 20%, 30%, and 40% wt/wt of drug) on release of PTU. All dissolution studies showed the extended release PTU formulations using phosphate buffer (pH7.5) as dissolution medium. The drug release was slower from tablets containing inert or hydrophobic polymer such as Eudragits in comparison with hydrophilic polymer such as Carbopol. Further increasing in the polymer concentrations resulted in a decrease in the drug release rate and a linearization of the drug release profile in specific when using Carbopol® 974 P polymer[31]. Statistical analysis revealed a significant difference ($P<0.05$) between matrix tablets containing either 10%, 20%, 30% or 40% of any polymer used within the PTU release rate study except for the first two hours, where there was no significant difference ($P<0.05$).

All matrices prepared had no initial burst release that could be attributed to the dissolution of the slightly water soluble, weakly acidic PTU from the surface of the tablets[3, 10]. Figure 6 shows the effect of changed pH dissolution medium to the drug release rate from the highest retardant and completed release for every series (A4, B2, C3). It was found that the drug release rate from Carbopol® 974 P matrix tablets was changed when mutating pH of the dissolution medium from 1.2, 4.5 to 7.5 . On the contrary, in Eudragit® SL PO and Eudragit® RL PO matrix tablets, the total percentage of drug release was kept the same corresponding to Eudragit® RS PO and Eudragit® RL PO polymer was inert and independent pH medium without dissolving compared with Carbopol® 974 P polymer [32].

Initially, PTU has pH-independent solubility between pH 1 and 8 [10]. Next, the effect of Carbopol® 974 P at 40% level on the release profile of PTU was investigated. As shown in Figure 6, a fast release of PTU was happened during at first 2 h then followed by a salient reduce in the release rate of the drug. Carbopol® 974 P form a gel at basic pH solution, therefore, the initial fast release is related to an acidic pH of the dissolution medium (i.e. pH 1.2) in which the Carbopol® 974 P polymer forms a weak gel not capable of controlling the drug release. However, in the next dissolution medium (phosphate buffer), Carbopol® 974 P forms a stronger gel because the ionization of the carboxylic acid groups causes maximum swelling when the pH medium increases, resulting in fewer and smaller regions of microviscosity (polymer fully hydrated in pH:7.3), which the drug could slowly diffuse out at uniform rate [33,34].

This result is in agreement with that observed by other researchers, they found that using Carbopol® 974 P was successful for controlling the release of slightly soluble drugs such as diclofenac and ibuprofen[29, 33]. Addition of suitable basic salts such as sodium bicarbonate to formulations containing carbopols may improve their

retarding effect in acidic media by making the matrices form a stronger polymer network [35].

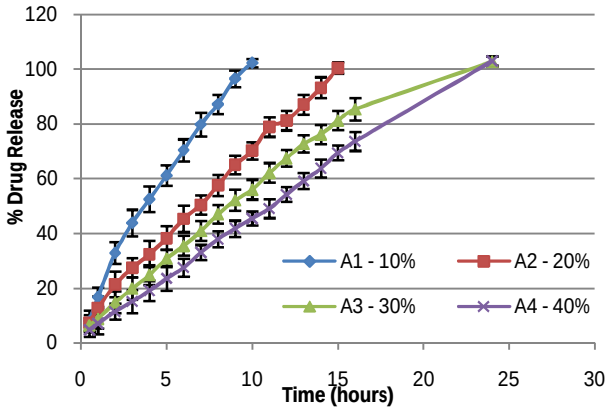

Figure 3: *In vitro* release profiles showing the effect of different concentration of Carbopol® 974 P on PTU release from matrix tablets. Data are represented as mean ± SD (n=3).

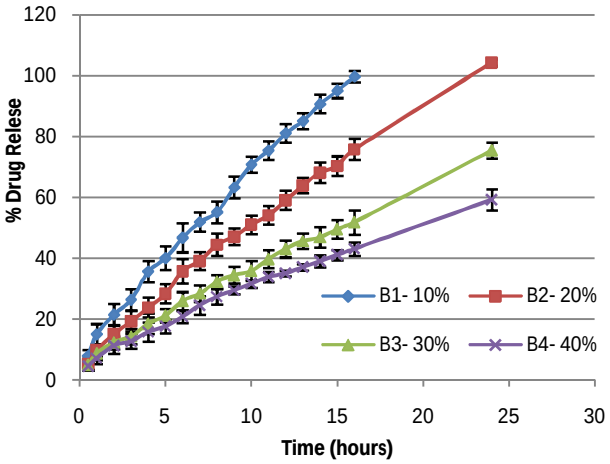

Figure 4: *In vitro* release profiles showing the effect of different concentration of Eudragit® RS on PTU release from matrix tablets. Data are represented as mean ± SD (n=3).

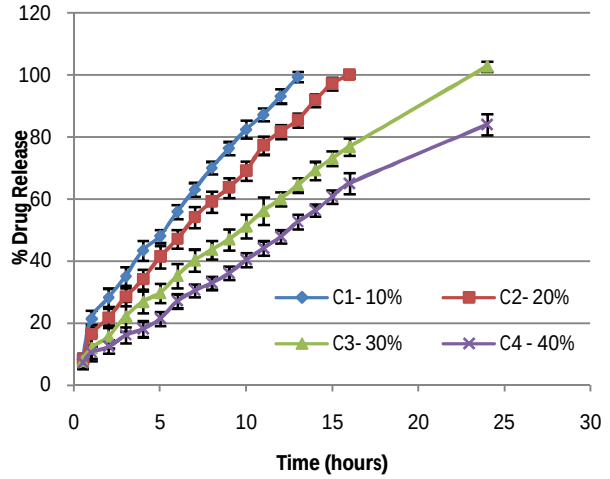

Figure 5: *In vitro* release profiles showing the effect of different concentration of Eudragit® RL on PTU release from matrix tablets. Data are represented as mean ± SD (n=3).

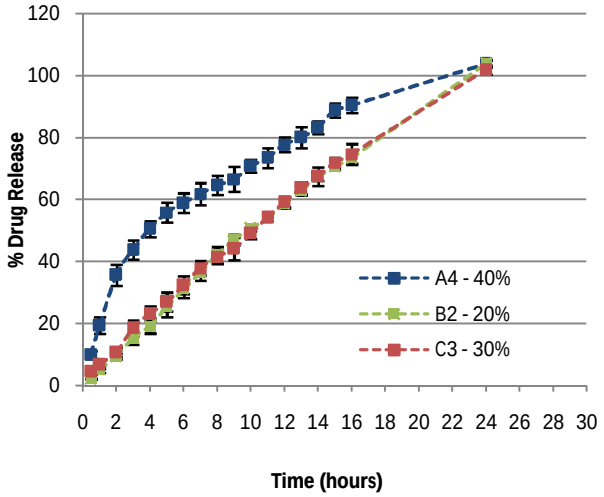

Figure 6: The effect of different pH medium (pH: 1.2, 4.5, 7.5) on PTU release from matrix tablets formulation (A4, B2, C3). Data are represented as mean ± SD (n=3).

Eventually, the effect of Eudragit® RS PO at 20% and Eudragit® RL PO at 30% levels on the release profile of PTU was explored. As shown in Figure 4, 5 and 6, the drug release rate and permeability were slower from tablets containing Eudragit® RS PO as compared with that from Eudragit® RL PO matrix tablets. As the latter contains less quaternary ammonium groups (ionizable groups) than Eudragit® RL PO, it is more hydrophobic and slightly permeable to water [32]. Consequently, the polymer chain mobility was lesser in Eudragit® RS PO than Eudragit® RL PO, resulting in decreased drug mobilities within the polymer network. Different authors reported identical data for other drugs [36, 37].

Release Kinetics

In order to describe the kinetics of drug release from controlled release matrix tablets and to analyze Correlation Coefficient (R^2) values of all series, it was found that all of the matrix tablets formulations showed a good fit into the zero-order (R^2 = 0.973-0.999), Hixson-Crowell (R^2 = 0.980-0.998), and Korsmeyer-Peppas (R^2 = 0.973-0.997) kinetic models (Table 3). The R^2 values for Hixson-Crowell model were slightly higher than the zero-order and other models. Applicability of the release profiles to Hixson-Crowell model indicated a change in surface area and diameter of the tablets, with a progressive dissolution of the matrix as a function of the time[38]. From Korsmeyer-Peppas model the values of release exponent (n) ranges from (0.68-0.87) and the (K) values ranges from (0.29-1.27) indicating anomalous or non-Fickian transport. Therefore, both diffusion and erosion mechanisms play a role in PTU (slightly soluble drug) release from all matrices [39] (Table 3). The values of (n) and (k) were found to vary with type and concentration of polymer [40].

Table 3: *In-vitro* release kinetic parameters of PTU from the matrix tablets.

Series	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	K_0 (%min^{-1})	R^2	K_1 (min^{-1})	R^2	K_H (%min$^{1/2}$)	R^2	K_{HC} (%min^{-1})	R^2	K (%min^{-n})	n	R^2
A1	0.2189	**0.983**	0.0222	**0.832**	3.3429	**0.997**	0.0210	**0.994**	1.0779	0.7656	**0.997**
A2	0.1392	**0.991**	0.0157	**0.881**	2.5161	**0.992**	0.0149	**0.996**	1.0386	0.7995	**0.973**
A3	0.1063	**0.999**	0.0132	**0.936**	2.0800	**0.977**	0.0126	**0.998**	0.7492	0.7908	**0.983**
A4	0.0848	**0.998**	0.0119	**0.940**	1.6948	**0.967**	0.0116	**0.994**	0.2903	0.8784	**0.993**
B1	0.1403	**0.990**	0.0154	**0.886**	2.5682	**0.987**	0.0145	**0.995**	0.9783	0.7502	**0.997**
B2	0.0987	**0.993**	0.0128	**0.899**	1.9180	**0.976**	0.0123	**0.992**	0.7269	0.7811	**0.997**
B3	0.0761	**0.993**	0.0120	**0.905**	1.4215	**0.977**	0.0115	**0.991**	0.8802	0.7138	**0.995**
B4	0.0649	**0.986**	0.1134	**0.902**	1.1961	**0.977**	0.0110	**0.986**	0.6541	0.6815	**0.996**
C1	0.1802	**0.973**	0.0187	**0.802**	2.9547	**0.987**	0.0176	**0.987**	1.2717	0.7293	**0.996**
C2	0.1436	**0.991**	0.0155	**0.882**	2.6143	**0.983**	0.0146	**0.994**	1.0948	0.7379	**0.997**
C3	0.1081	**0.994**	0.0138	**0.928**	2.0059	**0.981**	0.0130	**0.995**	0.6951	0.7357	**0.996**
C4	0.0869	**0.984**	0.0129	**0.958**	1.5951	**0.945**	0.0122	**0.980**	0.6470	0.8024	**0.990**

Note: K_0, K_1, K_H, K_{HC} and K are the rate constants of zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas, respectively. n is the diffusion exponent and R^2 is the Correlation Coefficient.

Table 4: Dissolution parameters of extended PTU matrix tablets

Series	$t_{25\%}$ (hours)	$t_{50\%}$ (hours)	$t_{75\%}$ (hours)	$t_{90\%}$ (hours)	*MDT* (h)
A1	1.54	3.64	6.24	8.03	4.209
A2	2.82	6.68	10.78	13.36	6.834
A3	2.57	7.16	13.24	17.61	9.212
A4	5.01	10.81	17.37	21.66	10.632
B1	2.64	6.57	11.00	13.90	6.928
B2	4.01	9.59	16.42	21.12	10.124
B3	6.13	14.69	24.25	30.46	10.843
B4	7.47	19.16	33.98	44.37	10.219
C1	1.83	4.93	8.66	11.20	5.423
C2	2.53	6.38	10.73	13.58	6.818
C3	3.73	9.28	15.83	20.24	10.044
C4	5.40	12.40	20.03	24.90	10.470

The time taken to release 25% (t_{25}), 50% (t_{50}), 75% (t_{75}), and 90% (t_{90}) of drug from different tablets was determined. These values were significantly higher when matrix tablets prepared with Eudragit® RS PO. This indicated sustained release nature of Eudragits (Table 4).

Mean dissolution time (*MDT*) value is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of a polymer used within a formulation. Tablets prepared with Eudragit® RS PO (series B) showed highest *MDT* value in comparison to tablets prepared with Carbopol® 974 P and Eudragit® RL PO (series A and C) as shown in (Table 4 and Figure 7).

This finding can be attributed to the water- repelling property of Eudragits, which retarded drug release from the matrices[26].

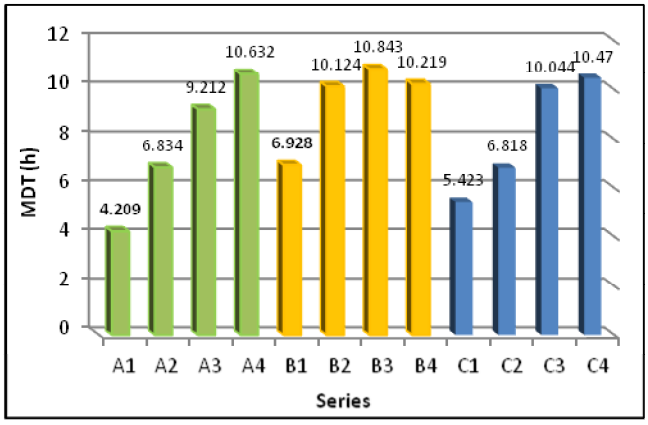

Figure 7: Maximal *MDT* values (Table 4)

CONCLUSION

Although all the polymers studied could slow down the release rate of PTU from the matrix tablets, Carbopol® 974 P showed the best results in the ability to effectively control drug release for 16 h which can be expected to decrease the frequency of administration of conventional PTU tablets. Increasing Carbopol® 974 P concentration in the tablets produced a significant reduce in the release rate and increased the linearity of the drug release profile. The matrix prepared using Carbopol® 974 P polymer, yet needs some further modifications to allow better controlled release rate. Preparation of matrices by different kinds of Carbopol® polymers may also be another solution.

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