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Investigation of Theophylline Release Kinetics from Carbopol 940P Sustained Release Matrix Tablets

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The hydrophilic matrix material, Carbopol 940P, has not been extensively investigated for drug release as the other polymers such as Carbopol 971P and 934P. The present study was aimed at investigating the release kinetics of a highly soluble drug, theophylline, from Carbopol 940P only without the addition of any other ingredient or excipient. Drug release from these matrices was analysed according to Higuchi, first order and zero order release kinetics. At low drug loading (20 %), release was mainly diffusion-controlled as the release pattern was best explained by square root of time kinetics (Higuchi mechanism). However, at higher drug loading (30 % and 40 %), constant release rates were obtained as shown by zero order kinetics explaining the release data best. Constant release rates are most desirable with controlled or sustained release devices. This ensures that constant drug levels in the blood/body are achieved. Carbopol 940P demonstrated that it is applicable in the fabrication of a controlled release matrix that is simple, easy to prepare and cost effective.

Key words: Carbopol 940P, Theophylline, Controlled Release, Zero Order

INTRODUCTION

Historically, the oral route is considered as the most popular route in the administration of drugs. The gastrointestinal physiology offers more flexibility in designing dosage forms than any other route. It has been estimated that approximately 50 % of all drug products available on the market are administered orally, tablets being the most widely used [1].

Orally administered tablets can be conventional (immediate release) or novel (controlled release). Of the novel oral tablets, matrix monolithic systems have become an area of intense research with some products already on the market [1, 2]. Matrix controlled release tablets are easy to manufacture, versatile, effective and have low cost in preparation [2].

They can be prepared from either hydrophobic or hydrophilic polymer materials. Hydrophilic polymer materials are at times termed hydrogels because on contact with the dissolution fluid, they swell/gel and then release the drug in a controlled manner over prolonged periods of time. Hydrogels can be classified as natural (e.g. gelatin, collagen, chitosan, xanthan gum, guar gum, locust bean gum); semi-synthetic (e.g. hydroxypropyl methylcellulose, hydroxyethyl cellulose, ethylcellulose) and synthetic (e.g. Carbopols, Eudragits, pyrrolidone).

In the present study, an investigation of the mechanism of drug release from Carbopol 940P matrices was carried out. This type of Carbopol has not been investigated that much as Carbopols 971P, 71G, 934P and 974P [3, 4]. Most drug release research on Carbopol 940P has been in combination with other polymers/excipients at low concentrations of Carbopol 940P [5 - 7]. The present study investigated the rate of drug release from high concentrations of Carbopol 940P without any additional excipients/ingredients. This was carried out so as to evaluate release from the Carbopol 940P without interference from other excipients such as lubricants.

Carbopols are acrylic acid polymers that are used largely in the pharmaceutical and cosmeceutical industries. The hydrogels formed by these polymers are widely used as vehicles and matrices for pharmaceutical preparations. Carbopols are compatible with

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many active pharmaceutical ingredients. They are often used in the formulation and preparation of controlled release hydrophilic matrix tablets as in the present study. Carbopol (Figure 1) has good compressibility characteristics which makes it a good candidate for direct compression as employed in the present study.

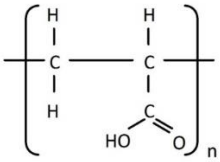

Figure 1: General Structure of Carbopol/Carbomer

Theophylline (Figure 2) was selected as the model drug to evaluate release from the Carbopol 940P matrix tablets. Theophylline is a medication mostly prescribed to patients with chronic obstructive pulmonary disease (COPD) and asthma. It is a xanthine derivative and is used as a bronchodilator in the long – term management of reversible airway obstruction caused by asthma or COPD. According to the Biopharmaceutical Classification System (BCS), theophylline is highly soluble and highly permeable (Class 1). All this makes it a suitable candidate for controlled release formulation.

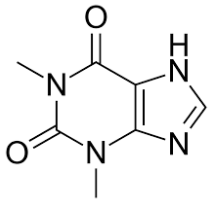

Figure 2: Chemical structure of Theophylline

MATERIALS AND METHODS

Materials

Theophylline was obtained from Sigma Chemical Company, St Louis, MO, USA while Carbopol 940P was procured from A. I. Davies, Workington, Harare, Zimbabwe.

Calibration curve for theophylline

A series of theophylline concentrations ranging from 10 µg/ml to 100 µg/ml were prepared using distilled water. The absorbance values of the various concentrations were read off at the wavelength of maximum absorption for theophylline of 271 nm using a double beam UV-visible spectrophotometer (VWR UV-6300PC, 10037-442, VWR International, LLC, Radnor, PA, USA). Distilled water was used as the blank. A dilution factor of 1:10 was used to counteract the effect of high absorbance peaks associated with theophylline. The data obtained was used to plot the calibration curve for theophylline with the subsequent slope and intercept used to find corresponding drug concentrations in the dissolution studies. The equation for the calibration data obtained was:

$$y = 0.0074x + 0.1039$$

The correlation coefficient was 0.9854.

Formulation of tablets

Tablets contained either 20 %, 30 % or 40 % theophylline. Each tablet weighed approximately 500 mg. The appropriate quantity of theophylline was accurately weighed and then geometrically mixed with the appropriate quantity of Carbopol 940P (either 80 %, 70 % or 60 % respectively). 500 mg samples of the resulting theophylline-Carbopol 940P mixtures were weighed individually before manually directly compressing each sample using a flat faced punch Manesty tablet machine (Manesty Machines Ltd, Type 3, No. 13D180, Liverpool, England). Constant compaction force was used for all the tablets prepared. The three formulations prepared are shown below in Table 1. All the tablets prepared were 12 mm in diameter and 3 mm in thickness. The tablets were white with a smooth surface without any picking or lamination.

Table 1: Formulations Prepared

	F1 (mg/tablet)	F2 (mg/tablet)	F3 (mg/tablet)
Theophylline	20 % (100 mg)	30 % (150 mg)	40 % (200 mg)
Carbopol 940P	80 % (400 mg)	70 % (350 mg)	60 % (300 mg)
Total	100 % (500 mg)	100 % (500 mg)	100 % (500 mg)

Tablet friability testing

Tablet friability determination was carried out according to the method outlined in the USP [8] using a Vankel Friabilator (Model 45-2200, Serial 4-1709-1198, Vankel, Cary, NC, USA). Fourteen (14) tablets were used at each drug concentration giving a total mass of approximately 7 g per each formulation. The drum was operated at 25 ± 1 rpm for 4 minutes. The friability was calculated as follows:

$$Friability\ (\%) = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the initial weight of the fourteen tablets and W_2 is the weight of the fourteen tablets post the friability test. A friability value of not more than 1.0 % was considered acceptable.

Tablet hardness testing

The hardness of the tablet for each formulation was carried out using a Pfizer hardness tester (Serial No. 1811, Chemical Division, Pfizer, Inc., Brooklyn, NY, USA). Each tablet was compressed between the holding anvil and the piston connected to a force-reading gauge. The force required to break the tablet in diametric compression was recorded in kg (1 kg = 9.807 Newtons). A total of 10 tablets for each of the formulations F1-F3 were used in the test.

Tablet uniformity of weight

The uniformity of weight of the tablets was carried out according to the method described in the USP [8]. Twenty tablets were weighed for each formulation and their average weight was determined. Then the tablets were weighed individually. The percentage deviation of each tablet from the average weight was determined. For tablets with an average weight of more than 324 mg (as is the case in the present study), not more than two of the individual tablet weights should deviate from the average weight by more than 5 % and none by more than 10 %.

Dissolution Studies

Dissolution studies on the theophylline-Carbopol 940P matrix tablets were carried out using the USP basket rotating method I (Vankel VK 7000, Model 10-1100, Cary, NC, USA), using 900 ml distilled water per each vessel at 37 ± 1 °C at 50 rpm. Six tablets per each formulation were assayed with dissolution studies carried out for 5 hours. Sampling was carried out every 30 minutes by withdrawing 5 ml of the dissolution solution and replacing it with pre-warmed distilled water. The absorbance was evaluated using a double beamed UV-visible spectrophotometer at 271 nm, after appropriate dilution with distilled water. Drug concentration at each time interval was calculated using the theophylline calibration curve. Since these were preliminary studies to ascertain controlled release properties of Carbopol 940P, dissolution was carried out using distilled water [9-10].

RESULTS AND DISCUSSION

All the three formulations, (F1-F3) passed the friability test as shown in Table 2 below. Formulation F1 containing 20 % drug failed the uniformity of weight test.

Interestingly, formulations F2 and F3 had the same tablet strength ($t = 0.438$; $p = 0.667$). This constant hardness irrespective of drug loading is desirable in formulations. However, F1 had significantly superior strength compared to F2 and F3 at the 5 % level ($t \geq 7.962$; $p \leq 0.001$). Sustained release tablets are supposed to have a hardness ranging from 10 to 20 kg [11] as obtained in the present study. Tablet hardness is not part of pharmacopoeial specification but one has to decide the lower and higher limit to produce a quality product. Hardness can impact disintegration, dissolution and bioavailability and is thus a good routine quality control test run.

The cumulative release data from theophylline-Carbopol 940P matrices was analysed according to the Zero order, Higuchi mechanism and First order kinetics. The resulting correlation coefficients and slopes obtained from the analysis are shown in Table 3 below. Student t-tests were carried out on the above correlation coefficients with the results statistically analysed at the 0.05 level.

Table 2: Hardness, Friability and Uniformity of Weight of Theophylline – Carbopol 940P Tablets

Formulation	Hardness (kg)	Friability (%)	Weight deviation	
			Within ± 5%	Within ± 10%
F1 (20 % Drug)	23.2±0.7	0.04	11	9
F2 (30 % Drug)	14.6 ± 3.3	0.11	19	1
F3 (40 % Drug)	14.1 ± 2.2	0.09	20	0

Table 3: Release Kinetics from the Carbopol 940P Matrices (n=6)

Release type		F1 (20 % Drug)	F2 (30 % Drug)	F3 (40 % Drug)
Zero Order, Q=kt	Slope (%/hr)	2.534 ± 0.200	13.113 ± 2.018	14.305 ± 0.653
	R	0.98046 ± 0.01079	0.99259 ± 0.00694	0.99492 ± 0.00460
Higuchi, $Q = kt^{0.5}$	Slope (%/√hr)	7.771 ± 0.575	38.739 ± 5.724	42.636 ± 2.013
	R	0.99521 ± 0.00213	0.97107 ± 0.01497	0.98124 ± 0.00768
First Order, Log(100%-Q)=kt	Slope (hr^{-1})	-0.0140 ± 0.0012	-0.1449 ± 0.0184	-0.1908 ± 0.0202
	R	0.98504 ± 0.00761	0.94677 ± 0.01800	0.96526 ± 0.00509

At 20 % drug loading (F1), release was best explained by the Higuchi mechanism ($t \geq 3.151$; $p \leq 0.0103$). This implies that at low drug loading the distance that the drug in the inner layers of the matrix has to travel to elute has a bearing on the release mechanism. Release in this instance was predominantly controlled by diffusion. This was also illustrated by the small Higuchi mechanism slope of 7.771 ± 0.575 $\%/hr^{0.5}$. In this formulation, the matrix content of 80 % could have also contributed to more sustained release than F2 and F3 which contained 70 % and 60 % of matrix, respectively.

At 30 % drug loading (F2), release was best explained by the zero-order mechanism ($t \geq 3.194$; $p \leq 0.0096$). This was possibly due to the fact that matrix erosion/de-aggregation and drug release were synchronised. The distance that the drug in the inner layers had to travel to elute into the medium was probably reduced by simultaneous matrix erosion/de-aggregation resulting in constant drug release rate. Such a controlled release device is highly desirable as it ensures that the release rate remains constant throughout the release period hence maintaining constant blood levels of the drug. Matrix level in F2 was 70 % which probably contributed to faster drug release than F1. This is confirmed by the larger slope in formulation F2 for both zero order and Higuchi kinetics.

Drug release from formulation F3 (40 % loading) was best explained by zero-order kinetics ($t \geq 3.745$; $p \leq 0.0038$), for the same reasons describe for formulation F2. In contrast, Kumar et al [7], prepared a matrix tablet containing about 17 % Carbopol 940P besides chitosan and poly(styrene-divinylbenzene) as additional polymers. Their model drug was ranitidine. Drug release from this matrix was best explained by square root of time kinetics (Higuchi mechanism), showing that diffusion was the dominant release mode. However, Newton et al [6], investigated amoxicillin trihydrate release from HPMC-Carbopol 940P matrices. Formulations containing 8 %, 12.5 % and 17 % Carbopol 940P had their release kinetics best explained by zero order kinetics as obtained in the present study. This may suggest that the type and quantity of auxiliary polymer added to the Carbopol 940P might have an effect on the mechanism of drug release. Zero order release slopes for the 30 % (F2) and 40 % (F3) matrices were not significantly different at the 5 % level ($t = 1.377$; $p = 0.1986$). This implies that the two formulations released drug in a similar fashion.

Drug release profiles of the three formulations are shown in Figure 3 below. Drug release from the two higher drug loadings (30 % and 40 %) and lower polymer levels (70 % and 60 %, respectively), are similar while the lowest drug loading (20 %) and highest polymer level (80 %), is distinctly different. This is possibly due to the lower porosity and higher tortuosity in the matrix at this lower drug loading. This is also partly explained by the significantly higher tablet hardness at this lower drug loading and

higher polymer content. These results possibly suggest that for constant release rates to be obtained, the device must be loaded with at least 30 % of drug and have at most 70 % of Carbopol 940P.

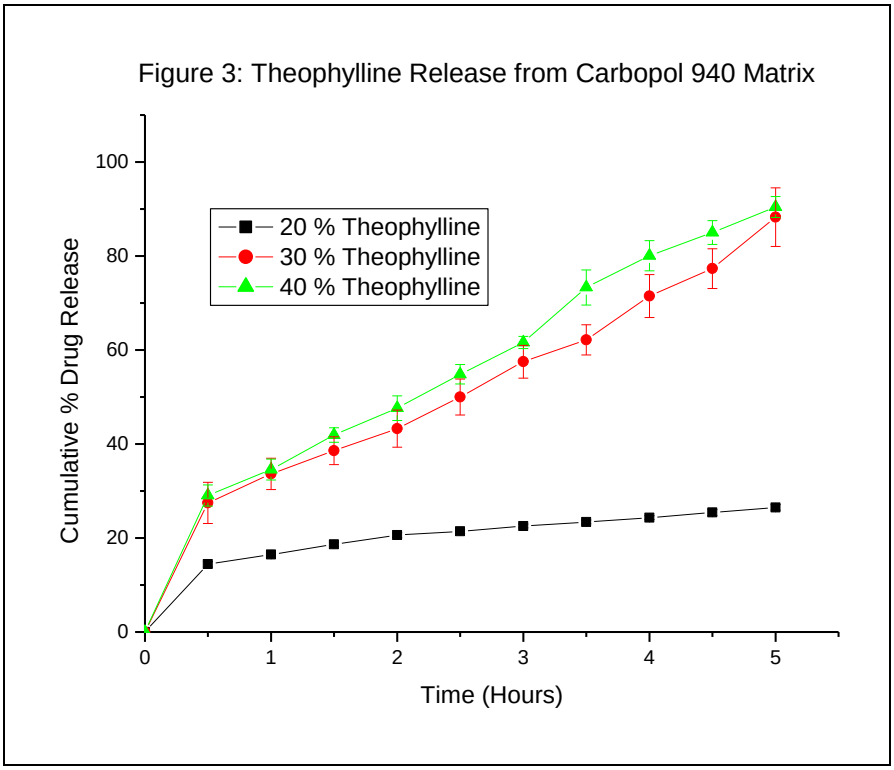

Figure 3: Drug release profiles from the Carbopol 940P matrix tablets

CONCLUSION

Carbopols have been extensively used as binders and rheology enhancing agents in pharmaceutical preparations. From this study, selection of Carbopol 940P as the sole excipient was highly beneficial leading to successful manufacture of controlled release tablets. Tablets containing higher drug loading (30 and 40 %) and lower polymer matrix levels (70 & 60 %) exhibited controlled and constant drug release compared to the formulation with a lower drug loading (20 %) and higher polymer matrix level (80 %). The former two formulations are highly desirable in making devices as this ensures constant drug levels in the body. Findings from this study confirmed that higher concentrations of Carbopol 940P can be used to manufacture controlled release tablets. Furthermore, the two higher drug loading formulations had similar hardness and passed the friability test. The formulation with a lower drug loading had significantly superior tablet strength compared to the other formulations and this possibly affected its release profile and kinetics. A similar experimental approach can be followed

in screening and ascertaining the application of new excipients in pharmaceutical formulation.

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