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Application of Carbopol 971 as a sustained release matrix for theophyline hydrate tablets

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Abstract
An *in vitro study* on the application of Carbopol 971 (CP 971) as a matrix in the formulation of oral sustained release (SR) tablets of theophylline hydrate was carried out. Carbopol 971 was employed as matrix in the concentration range of 10 to 40 % w/w. The matrix tablets were prepared by the wet granulation method with 95% v/v ethanol as the dispersing fluid. Dissolution rate studies on the tablets were carried out over an 8 h period in three media of 0.1 N Hydrochloric acid (HCl, pH 1.2), simulated gastric fluid, (SGF, pH 1.3) without pepsin and simulated intestinal fluid (SIF, pH 7.2) without pancreatin. There was significant retardation of drug release in all three media as the polymer concentration increased. A burst release was achieved within 60 min (1 h), after which there was a gradual and sustained release of the drug over 7 h. Theophylline release was faster in the alkaline medium (SIF) than in the acidic media (0.1 N HCl and SGF). The mechanism of release of the formulations at all concentrations of the polymer matrix was dominantly diffusion controlled (Fickian or Case I).

1. Introduction

Carbopols are synthetic high molecular weight polymers of acrylic acid cross linked with allylsucrose and contain 56 to 68% of carboxylic acid groups (Florence and Juni, 1994). They have been used as matrices in extended release tablet formulations since 1957 (Brown, 1957). At concentrations of 5 – 40%, depending on the drug properties, co – excipients and processing parameters, carbopol polymers have been reported to achieve excellent control of the release of drugs from matrix tablet formulations (Okorie, 2004)(Alderman, 1984). Carbopol 971 and other carbopol resins which swell on hydration with a suitable solvent are known to be non toxic and have the capacity of accommodating a large quantity of an active drug without being affected by processing variables in drug release rates (Nerurker *et al,* 2005, Skong *et al,* 1993, Saha *et al* 1993, Yang *et al* 1996, Khurahashi *et al,* 1996).Carbopol polymers can be successfully included into a variety of different tablet forms including swallowable (peroral), chewable, buccal and sublingual tablets where they provide controlled release properties, bioadhesion and good binding properties. Chang (2004) reported the use of carbopol 971 polymer as a bioadhesive

and sustained release matrix in the formulation of doxycycline sublingual tablet. Carbopol polymers can also possess taste masking properties when reacted with certain amine drugs and this can be beneficial in formulating chewable tablets (Lubrizol, 2011). Theophylline hydrate is an anti-asthmatic which is used both as prophylactic and in treatment of chronic asthmatic attacks. It acts by inhibiting cyclic nucleotide phosphodiesterase. It has a narrow therapeutic index which requires regular monitoring of serum theophylline concentrations (Goodman and Gilman,1996). Conventional oral theophylline tablets are administered 3 to 4 times daily (Blake and Kelly, 2006) but its use is on the decline because of the incidence of high side effects which results from its high or rapid absorption. A sustained release formulation of theophylline would reduce the dosing frequency and minimize the possibility of incidences of toxicity (Chukwu *et al,* 1997). Although there have been reports of sustained release formulations involving oral theophylline using a number of polymeric materials, the present study is focused on the application of Carbopol 971 as matrix polymer in sustained release theophylline tablets.

1.1. Experimental

1.1.1. Materials

Theophylline hydrate, hydrochloric acid, ethanol (Sigma Chem. Coy, USA), lactose, sodium chloride (BDH, Poole, England), Carbopol 971 (G.F. Goodrich, Ohio), potassium dihydrogen orthophosphate (Aldreich, USA), talc and stearic acid (May and Baker, England).

1.1.2. Method

Table 1. *Formula for preparing theophylline hydrate tablets.*

Ingredient	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Theophylline hydrate (mg)	100.00	100.00	100.00	100.00	100.00
Carbopol 971(%w/w)	0.00	10.00	20.00	30.00	40.00
Talc (%w/w)	0.50	0.50	0.50	0.50	0.50
Stearic acid(%w/w)	1.00	1.00	1.00	1.00	1.00
Lactose qs (mg)	300.00	300.00	300.00	300.00	300.00

Lactose and theophylline hydrate as shown in Table 1 were weighed out in quantities enough to produce 100 tablets into a Wedgewood mortar and triturated using the geometric dilution method. The polymer Carbopol 971 was dispersed in 95% v/v ethanol and used in the wet massing of the powder mixtures. Wet massed granules were screened through a 1.7 mm stainless sieve, and were dried in an oven (Memmert® oven, GmbH, Germany) at 60˚C. The dried granules were further screened through a 1.0 mm stainless steel sieve. Prior to compression in a single punch tabletting machine (Manesty F – 3, England), stearic acid and talc were added extragranularly. The granules were compressed to a target weight of 300 ± 20 mg with a 9.5 mm biconcave set of punches fitted to the tableting machine and at a constant compressional force.

1.2. Evaluation of Granules

1.2.1. Flow rate and Angle of Repose

The fixed funnel and free standing cone method was used in the determination of angle of repose. A 10 g quantity of theophylline granule was poured into a glass funnel with orifice and base diameter of 1.10 cm and 5.50 cm respectively. The funnel was fixed at a height of 15.00 cm above a flat surface.

The time of flow of the granules, the diameter and height of the granules heap formed were determined. The flow rate and the tangent of the angle of the granule heap were calculated from Equations 1 and 2 (Shafar *et al,* 1956).

$$\text{Flow rate (F.R.)} = M / \text{F.T.(sec)} \quad (1)$$

$$\text{Angle of repose } (\theta) = \tan^{-1} (h / r) \quad (2)$$

Where M = mass of granules, F.T. = flow time of granules and h = height of granule heap and r = radius of granule heap.

1.2.2. Bulk and Tapped Densities

The bulk and tapped densities of theophylline granules were determined using a dry 100 mL glass measuring cylinder kept on a flat table surface. A 10 g quantity of theophylline granule was freely poured into the dry 100mL measuring cylinder and the volume, V_b noted. The cylinder was mechanically tapped on the flat surface until no further decrease in volume V_t was observed. The bulk and tapped densities were calculated as a ratio of the granule mass and the respective volumes from Equations 3 and 4 (Alderman, 1984).

$$\text{Bulk density } (D_b) = M / V_b \quad (3)$$

$$\text{Tapped density } (D_t) = M / V_t \quad (4)$$

Where M = mass of granules.

1.2.3. Hausner's quotient and Carr's Index

Hausner's quotient and Carr's index were calculated from equations 5 and 6 (Ganesh *et al,* 2006).

$$\text{Hausner's quotient (HQ)} = D_t / D_b \quad (5)$$

$$\text{Carr's index (CI)} = \{1 - D_b / D_t\} \times 100 \quad (6)$$

1.3. Evaluation of Tablets

The tablets were evaluated for uniformity of weight, hardness, and friability 24 h post compression.

1.3.1. Uniformity of Weight

Twenty tablets randomly selected from each batch of the theophylline hydrate were weighed together according to the British Pharmacopoeia, BP method (BP 2009). The

mean deviation and coefficient of variation were calculated. The acceptance criteria for each powder compact was dependent on the tablet weight as stipulated in the BP (BP 2009).

1.3.2. Crushing Strength

A Monsanto hardness tester was used to test ten tablets randomly selected from each tablet batch. The mean breaking strength and standard deviation were calculated for each batch.

1.3.3. Friability Test

The friability of each tablet batch was determined using an Erweka® TAR 200 friabilator programmed to revolve at 25 revolutions per minute (rpm) for four min. Ten tablets randomly selected from each tablet batch were tested. The percentage loss in weight for each batch was calculated from the Equation 7.

$$B = 100\ (1 - W/\ W_o) \qquad (7)$$

Where B = Friability or % loss in weight, W_o = Initial tablet weight and W = Final tablet weight

1.3.4. Total Drug Content

This was determined using the BP method. Twenty tablets randomly selected from each tablet formulation were weighed collectively in an Adventurer® analytical balance. They were powdered together and a quantity equivalent to the average weight of the twenty tablets was dispersed in freshly prepared 0.1 N HCl, filtered and volume made up to 100 mL to obtain a stock solution of 1 mg / mL. Dilutions of the stocks were prepared and their theophylline content analyzed spectrophotometrically at 271 nm using a JENWAY® 6405 UV/Vis spectrophotometer.

1.3.5. Dissolution Profile Studies

The dissolution profiles of the different batches were determined using the BP paddle method. A 900 ml volume of 0.1 N HCl (pH 1.2) maintained at 37 ± 1˚C with a paddle speed of 100 ± 1 rpm was employed. Five (5) ml samples were withdrawn from the dissolution medium at 1 h intervals over an 8 h period. Withdrawn volume was replaced each time with 5 ml of 0.1 N HCl to maintain sink conditions. Withdrawn samples were filtered and analyzed spectrophotometrically at 271 nm. The dissolution tests were repeated in simulated intestinal fluid (SIF, pH 7.2) and simulated gastric fluid (SGF, pH 1.3) without enzymes. All the tests were done in two replicates. Release data were fitted into percentage released – time curve, and into different release kinetics. Mechanism of theophylline release was assessed using the Korsemeyer – Peppas release model (Peppas, 1985).

2. Results

Table 2 shows the micromeritic properties of the granules while the physical properties of the tablets are shown in Table 3.

Table 2. *Micromeritic properties of the theophylline hydrate granules*

Batch	Flow rate {SD ± (g/s)}*	Angle of repose SD ± (°)}*	Bulk density {SD ±	Tapped density (g/ml)}*	Hausner's quotient (±SD*)	Compressibility index { SD ±(%)}*
1	8.00 ± 0.10	29.40 ± 0.70	0.45 ± 0.00	0.52 ±0.00	1.15 ± 0.00	13.50 ± 0.00
2	8.33 ± 0.17	30.70 ± 0.59	0.43 ± 0.00	0.50 ±0.00	1.16 ± 0.00	14.00 ± 0.00
3	8.40 ± 0.20	30.34 ± 0.22	0.43 ± 0.00	0.52 ± 0.00	1.19 ± 0.00	16.63 ± 0.00
4	8.20 ± 0.06	30.36 ± 0.18	0.40 ± 0.00	0.49 ± 0.00	1.12 ± 0.00	10.84 ± 0.84
5	9.53 ± 0.22	31.70 ± 1.56	0.47 ± 0.00	0.50 ± 0.00	1.12 ± 0.00	11.04 ± 0.84

*n = 3 where n is the sampling size.

Table 3. *Uniformity of weight, hardness and friability of theophylline hydrate tablets*

Batch/ Concentration CP 971	Uniformity of weight (SD ± CV[mg %])*	Hardness SD ± (Kg/f)*	Friability SD ± (%)*
1 (control)	287.25 ± 2.45	8.90 ± 1.44	0.33 ± 0.00
2 (10% w/w)	290.20 ± 1.53	10.30 ± 1.94	0.34 ± 0.01
3 (20% w\w)	291.90 ± 1.73	12.00 ± 1.91	0.33 ± 0.00
4 (30% w/w)	294.40 ± 2.46	13.00 ± 1.41	0.03 ± 0.04
5 (40% w/w)	297.45 ± 2.72	14.30 ± 1.78	0.00 ± 0.00

*n = 3, where n represents the number of samples, CV = coefficient of variation and SD = standard variation.

2.1. Total Drug Content

The results of tests for content of active ingredient for batches that contain 0% to 40% w/w CP 971 had values of 98.83 ± 0.65%, 96.00 ± 0.19%, 92.75 ± 2.45%, 99.81 ± 1.13% and 91.12 ± 0.86 % of theophylline hydrate.

2.1.1. Drug Release Profiles

Dissolution profiles of theophylline hydrate in 0.1 N HCl are shown in Fig. 1 while Fig.2 shows its release profile in media with varying pH (0.1 N HCl, SGF and SIF)

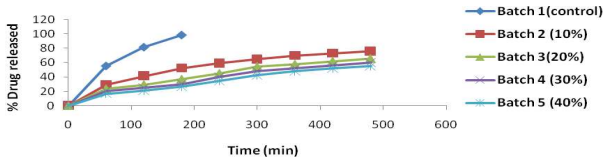

Fig. 1. *Dissolution profile of Theophylline hydrate tablets in 0.1 N HCl*

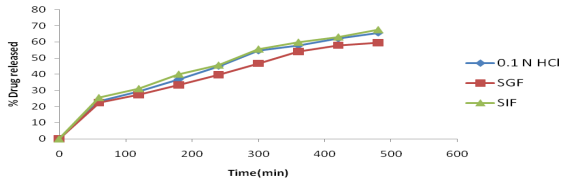

Fig. 2. *Dissolution Profile of theophylline tablets in 0.1 N HCL, SGF and SIF at 20 % w/w CP 971*

Table 4. *Kinetics and mechanism of release of theophylline hydrate tablets.*

Batch	Zero order	First order	Higuchi	Korsmeyer Peppas	square root	Model
0.1 N HCl	r^2	r^2	r^2	r^2	n	K
Batch 1(control)	0.9807	0.8883	0.9996	0.9982	0.5233	0.8178
Batch 2(10%w/w)	0.9754	0.9917	0.9927	0.9936	0.4707	0.6373
Batch 3(20%w/w)	0.9818	0.9863	0.9917	0.9807	0.5302	0.3962
Batch 4(30%w/w)	0.9888	0.9883	0.9841	0.9817	0.5439	0.3174
Batch 5 (40%w/w)	0.9820	0.9882	0.9742	0.9816	0.6185	0.0799
Batch 3(20%w/w)SGF	0.9820	0.9867	0.9786	0.9909	0.5409	0.3308
Batch 3(20%w/w) SIF	0.9467	0.9566	0.9703	0.9865	0.5188	0.3678

3. Discussion

3.1. Evaluation of the Granules

The micromeritic properties of the granules are shown in Table 2. Flow rates were between 8.00 ± 0.10 to 9.53 ± 0.22 g/s, angle of repose ranged from 29.40 ± 0.70 to 31.70 ± 1.38˚,bulk density 0.45 ± 0.00 to 0.47 ± 0.00, and tapped density 0.52 ± 0.00 to 0.50 ± 0.00 g/mL. Hausner's quotient values were < 1.2 and Compressibility index between 13.50 ± 0.00 to16.63 ± 0.00%. These flow indices indicate that the granules would flow well during tabletting operations. Flow properties generally increased with increased polymer concentrations.

3.2. Evaluation of the Tablets

The tablets on visual examination had no defects. They had uniformity of weight values that conformed to BP and USP acceptable standard requirements for uncoated tablets (BP 2009, USP 2009) (Hongtau, 2008). The crushing strength of the tablet batches were generally higher than 4 Kg/f. They are therefore considered adequate for handling and transportation (Ofoefule,2002, Osadebe and Akabuogu, 2004) . The crushing strength increased with increase in the polymer concentration. The friability of the tablet batches were less than 1.0% and at polymer concentration of 40%, the tablets were non friable. The results indicate that at all concentrations of the polymer, the tablet batches exhibited minimal loss of components. This is desirable for an uncoated tablet that is handled, packaged and transported(Banker and Anderson, 1991).

3.3. Content of Active Ingredient

All the batches of tablets complied to the United States Pharmacopoeia, USP 32 (2009) assay requirements for content of active ingredient for theophylline hydrate which states < 90 and > 110 % of the labeled amount(USP, 2009).

3.4. Dissolution Profile

There was a fast dissolution within the first 60 min from all the batches and this was followed by a gradual release over the next 7 h. This arose from the initial wetting of the tablets which resulted to dissolution of the drug at the tablet surface (Hongtau *et al,* 2008). Increased intake of the dissolution medium led to gelling of the polymer which slowed drug release (Taukder *et al,* 1996). The fastest release was exhibited by the batch that did not contain CP 971 (control batch). There was more than 50% theophylline release from all the batches within the 480 min (8 h) release period. The retarding effect of CP 971 on theophylline generally increased as the concentration of the CP 971 increased. This can be attributed not only to the gelation of the matrix after the initial wetting but also to subsequent formation of more viscous gel layers on the tablet which reduced the rate of elution of the dissolved drug from the tablet core (Parojcic *et al*, 2004)

Theophylline release was sustained for up to 480 min (8 h) in all three dissolution media. There was more than fifty percent (50 %) drug release within the 8 h release period. There was a faster release of the drug in the alkaline medium than the acidic media. Theophylline exists in the ionic form, a state in which it is more soluble at high pH (between pH 5 and 10). At low pH the drug exists as a free acid which is less soluble than the salt (Cohen, 1975). This effect is expected to enhance its greater release in SIF than in 0.1 N HCl and SGF. Theophylline solubility has been reported to be reduced in SGF due to the presence of sodium chloride (Cohen, 1975), hence a decreased release observed in the SGF.

3.5. Mechanism of Drug Release

The correlation coefficient (r^2) values of the plots of the release profiles show that theophylline hydrate tablets exhibited mixed order kinetics in 0.1N HCl. For the control batch and batches that contain 10 % and 20 % w/w CP 971, Higuchi square root kinetics was the dominant release kinetics and was closely followed by First order. At 30 and 40% w/w, First order was dominant and was followed by Higuchi square root kinetics. The mechanism of release was Fickian (diffusion controlled) for batches that contained 0% to 30% w/w of Carbopol 971 and Non Fickian (anomalous) for the batch that contained 40% w/w of the polymer. This indicates that theophylline hydrate release was by diffusion and erosion from the tablets containing 0% to 30% w/w of Carbopol 971 and a mixed mechanism at 40 % w/w of the polymer. The kinetics of release of theophylline hydrate in SGF and SIF showed a mixed order release involving all the three kinetic models (Table 4). This is similar to what was obtained in 0.1 N HCl. The mechanism of release was Fickian. Thus change in pH of dissolution medium did not affect the mechanism of theophylline release but however affected the kinetics.

3.6. Statistical Evaluation

Statistical analysis of theophylline hydrate tablets release using Graph Pad Prism® Version 5.04 software showed significant differences in the release ($p < 0.05$) at 60 min, 120 min, 180 min, 240 min, 300 min, 360 min, and 420 min in all three media (0.1 N HCl, SGF, and SIF). The release was insignificant at 480 min ($p > 0.05$). Thus pH of dissolution media significantly affected theophylline release in all three media up to 420 min. (Fig.2).

4. Conclusion

Drug release studies for theophylline hydrate show more than 50% drug release for all batches in the dissolution media of 0.1 N HCl, SGF and SIF. Order of release was mixed order with Higuchi square root kinetics being dominant for the control, 10% and 20% w/w batches First order was dominant at 30% and 40% w/w. Release mechanism was dominantly diffusion controlled (Case I or Fickian) and was not affected by change of pH of the dissolution media. There was a significant difference in theophylline hydrate release in all three media ($p < 0.05$) for the batch containing 20% w/w CP 971. The overall results indicate that a good sustained release of theophylline using Carbopol 971 as matrix could be formulated using the polymer in the concentration range of 20 % to 40 % w/w.

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