COMPARATIVE SUSTAINED RELEASE MATRIX CAPACITIES OF SOME POLYMER MATRICES IN THEOPHYLLINE HYDRATE TABLETS

S.I. Ofoefule, *MPharm,*
C. Amanambu, *BPharm,*
Department of Pharm. Techn. and Industrial Pharmacy,
University of Nigeria, Nsukka

ABSTRACT

Sustained release matrix capacities of three polymeric materials in theophylline hydrate tablets were studied. The polymers (Carbopol) 941, Eudragit L-100-55 and Ethylcellulose) were used at 0, 20 and 30% w/w concentration levels. Dicalcium phosphate dihydrate and stearic acid were used as filler and lubricant respectively. Theophylline hydrate tablets were formulated using the direct compression method. In vitro drug release studies on the tablets were monitored over 8 hrs in 0.1 N HCl, simulated gastric fluid without pepsin (SGF) and simulated intestinal fluid without pancreation (SIF).

There was prolonged release of theophylline from 20 and 30% w/w of either Carbopol 941 (CP 941) or Eudragit L-100-55 (EDL) or Ethylcellulose (EC). Release rate of theophylline from CP 941 and EC was slowest in SIF while the release rate from EDL was fastest in this media. The comparative matrix capacities of this polymers were in the order of CP 941>EDL>EC.

Keywords: Sustained release, matrix capacity
Theophylline Hydrate

INTRODUCTION

Since the last decade, theophylline has been the subject of numerous publications on sustained release (1-4). Its short half-live, small dose, uniform absorption in the gastrointestinal tract and use in the treatment of chronic conditions (5) has made it amenable for sustained release formulations. Theophylline is an effective bronchodilator used both as a prophylactic drug and to prevent acute exacerbation of asthma. Plasma concentration of theophylline above 15, ug/ml may produce moderate to severe toxic effects (5-8). Steady-state plateau theophylline concentration from 5-20 ug/ml produces effective brochodilation in asthma (9). Under a severe life threatening acute attack of asthma, a patient may find it difficult to take oral medication repeatedly. A sustained release formulation of theophylline will not only reduce dose frequency, but will also minimise the possible incidence of toxicity.

Various inert hydrophilic and hydrophobic polymer matrices have been employed in sustained release formulations. Biswanath Sa *et al* (10) have evaluated Ethylcellulose micropellets as a controlled release dosage form for theophylline. Sustained release theophylline from carbopol matrix device has been reported (11). In sustained release formulations, it is important to maintain a steady rate of drug release so that, the desired constant blood level of drugs in the body might be achieved (12). The nature and type of polymer matrix employed may play a major role in the maintenance of steady rate of drug release.

The present study evaluated the matrix capacities of two hydrophobic and one hydrophilic polymer in sustained release theophylline hydrate tablets. The *in vitro* release studies were evaluated in 0.1 N HCl, simulated gastric fluid without pepsin (SGF) and simulated intestinal fluid without pancreatin (SIF).

MATERIALS

The following materials were used as procured from their manufacturers - Theophylline hydrate (Merck), Ethylcellulose (Fluka), unmilled dicalcium phosphate dihydrate (Stauffer Chem. USA), Stearic acid (Baker Co. USA), Carbopol 941 (B.F Goodrich Chem. Co. USA), Eudragit L-100-55 (GMBH), Sodium chloride (Vicker's Lab.), Sodium hydroxide, potassium ortho-phosphate, Hydrochloric acid (M & B Eng.).

METHOD

Batches of theophylline hydrate tablets were prepared using the formula in table 1.

Table 1: Formula for the preparation of theophylline hydrate tablets

	Batches		
	I	II	III
Theophylline hydrate (mg)	100	100	100
Polymer (% w/w)	0	20	30
Stearic acid (% w/w)	2	2	2
Ditab ® (% w/w)	194	140	110

Weighed quantities of all excipients to yield 120 tablets per batch were weighed in each case. Weighed quantities of theophylline hydrate, Ditab and either Ethylcellulose (EC) or Eudragit L-100-55 (EDL) or Carbopol 941 (CP 941) were mixed thoroughly in a geometric dilution method for 10 minutes. Weighed quantity of stearic acid previously screened through a 0.250mm stainless steel sieve was incorporated into the powder mix and mixing was continued for a further 5 mins. The powder mix was directly compressed into tablets using a single punch F-3 Manesty machine fitted with 9.5mm punches to a target weight of 300 ± 10mg. The pressure adjustment of the machine was maintained constant to achieve a constant compressional pressure as much as possible.

Some *in vitro* Tablet properties

Crushing Strength

The crushing strength of ten tablets from each batch was determined individually with an Erweka hardness tester (Model TBH) 28). Mean of ten tablets were calculated.

Friability Test

Ten tablets from each batch were dusted and subjected to shock in the Erweka friabilator (TAR model) at 25 rpm for 4 mins. The per cent loss in weight was calculated as the friability.

Dissolution Studies

The release rates of theophylline from the tablets were determined over an 8-hr period using the fixed basket - magnetic stirrer assembly. The dissolution medium consisted 500ml of either 0. 1 N HCl or SGF or SIF all of which were without enzyme. The dissolution media were maintained at 37 ± 1°C at each instance and the magnetic stirrer was operated at a fixed speed of 100 ± 1 rpm. Samples were withdrawn at 30 mins interval. Withdrawn samples were analysed spectrophotometrically using a pye-unicam spectrophotometer at 271 nm. Per cent drug released was determined from the Beer's law plots previously constructed using 0. 1 N HCl, SGF and SIF.

RESULTS AND DISCUSSION

All the tablet batches, except the control batch were non-disintegrating in 0. 1 N HCl over 1 hr period. The control batch disintegrated within 32 mins. All the tablets exhibited friability values less than 1.5%. From table 2, tablets containing EDL increased in crushing strength with increase in concentration while those containing CP 941 decreased with increase in concentration. There was no significant increase in crushing strength in tablets containing EC with increase in concentration. In all the batches, friability loss decreased with increase in polymer concentration.

Table 2: Crushing strength and friability of Tablets polymer conc / w/w

	EC			EDL		CP 941	
	0	20	30	20	30	20	30
Crushing strength (N)	7.19	7.539	7.584	8.109	10.862	6.955	5.146
	(1.075)*	(1.093)	(0.769)	(1.276)	(0.837)	(1.216)	1.030)
Friability (%)	1.39	1.25	1.05	1.06	1.04	0.90	0.74

*Figures in bracket represent standard deviations.

Drug Release Pattern

The cumulative per cent release of theophylline from the two concentrations of the polymers as shown in figure 1 indicates differences in the amount of theophylline dissolved in 0. 1 N HCl from 0, 20 and 30% w/w of polymer matrix in each case. 30% w/w of EC exerted more sustained release than 20% w/w. Theophylline release from the two systems were about 100% for the latter within 6.5 hrs and about 70% for the former within the same period. For tablets containing EDL, marked differences in release rate of theophylline became apparent above 40% drug release. Steady state maximum release of theophylline occurred from 30% w/w of the polymer after 4 hrs at 50% drug release. Release of theophylline from tablets containing CP 941 reduced almost in proportion to the increase in the polymer concentration. At the two concentrations of the

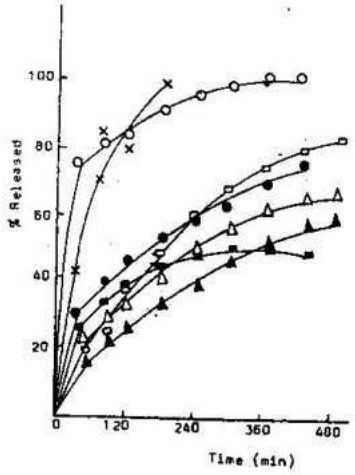

Fig 1: Dissolution profile of Theophylline Hydrate from matrices
O 20% Ethylcellulose ● 30% Ethylcellulose
□ 20% Eudragit L100-55 ■ 30% Eudragit L100-55
Δ 20% Carbopol 941 ▲ 30% Carbopol 941 **X control**

polymers, about 60 and 65% of drug were released over an 8hr period.

The influence of dissolution media on theophylline release from solid dosage forms has been reported (13-15). An almost super-imposable release curve of theophylline release from micropellets in acidic and phosphate buffer was reported by Biswanath Sa *et al* (10). Earlier McGinity *et al* (16) have reported a similar observation. Theophylline release from tablet dosage forms has been shown to be pH dependent (17). In one of the above reports (14), it was shown that the release of theophylline is increased in alkaline medium, a behaviour which was attributed to the dissolution of cellulose acetate phthalate used at that pH. In another report, (18) release rate of theophylline in hydrochloric acid was faster than in phosphate buffer. This effect was attributed to ionization of the carboxyl group in carbopol and the expansion of the polymer molecules. These reported observations and the results obtained in the present study indicate that release of theophylline from solid dosage forms depends on a combination of the nature of excipient employed, pH of the dissolution medium and chemical nature of the drug. The influence of dissolution media on theophylline release from the three polymer matrices is shown in figures 2-4. There were slight differences in the release rate of theophylline from EC matrix in 0. 1 N HCl and SGF. The presence of sodium chloride in SGF is known to decrease the solubility of theophylline (18) hence a decrease in drug release is expected to occur in SGF. Release of theophylline in the two media appears to have been governed mainly by the solubility of EC other than the solubility of the drug. In SIF, the release of theophylline from EC matrix decreased appreciably with a little less than 50% drug release after 8 hrs. Dicalcium phosphate dihydrate (Ditab) used as a direct compression filler is slightly alkaline and, therefore, is

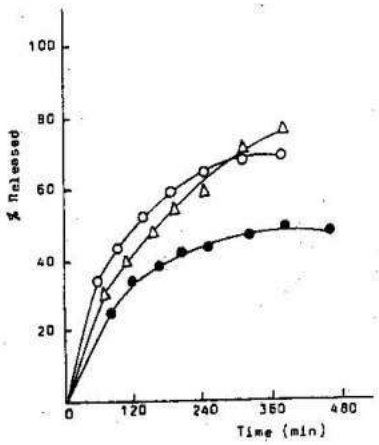

Fig 2: Effect of pH on the Dissolution profile of Theophylline Hydrate from 30% Ethylcellulose matrix
Δ0.1NHCL O SGF ●SIF

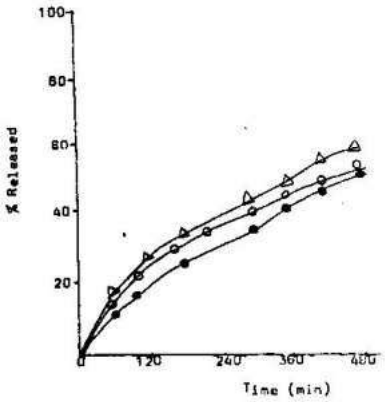

Fig.4: Effect of PH on the Dissolution profile of Theophylline Hydrate from 30% Carbopol 941 matrix
Δ0.1NHCL O SGF ●SIF

expected to be slightly soluble in acidic medium but insoluble in alkaline medium. This may have contributed to the decrease release obtained in SIF.

From figure 3, the release of theophylline from Dudragit L-100-55 in the three media is in the order of SIF SGF 0. 1 N HC1. EDL is a metacrylicacid polymer usually employed in enteric coating where it is expected to be unaffected by the acidic pH of the stomach but dissolving at higher pH with increase release of drug. Release of theophylline from carbopol 941 in the three media was in the reverse order of 0. 1 N HC1>SGF>SIF. CP 941 is supplied as a white powder in the acid form and exhibits its greatest viscosity

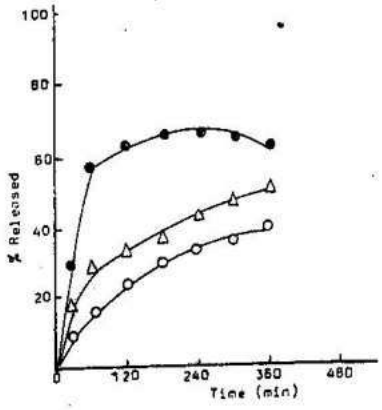

Fig. 3: Effect of pH on the Dissolution profile of Theophylline Hydrate from 30% Eudragit L100-55 matrix
Δ0.1NHCL O SGF ●SIF

Table 3: Effect of pH on the Release of Theophylline from Polymer Matrices Legend To Figures

Medium	EC			EDL			CP941		
	Min			Min			Min		
	T 20	T 40	T 50	T 20	T 40	T 50	T 20	T 40	T 50
0.1 N HCl	36	96	144	96	180	336	60	84	120
SGF	30	66	120	30	390	-	240	300	360
SIF	48	204	-	24	42	60	360	420	456

at a pH range of 5 to 10 (19). Schwarz *et al* (20) reported the loss of viscosity of carbopol and attributed it to the presence of trace metals. These, in addition to the ionization of the carboxyl group in alkaline pH (18), may have contributed to this release trend in the three media. The presence of sodium chloride in SGF may have exerted dual effect on the theophylline release from this medium - causing reduction in theophylline solubility and a possible reduction in the degree of ionization of the carboxyl group in carbopol. At alkaline pH, however, increase in viscosity and possible high viscosity gel-formation known to decrease drug release may have enhanced retardation of theophylline release in SIF (Fig.4).

Comparatively, the T_{20}, T_{40} and T_{50} values obtained with the three polymers in the different dissolution media show that CP 941 exerted more matrix capacity in the three dissolution medium than either EDL or EC. Their comparative matrix/sustained release capacities in 0. 1 N HC1, SGF and SIF is in the order of CP 941>EDL > EC.

CONCLUSION

Carbopol 941 and Eudragit L-100-55 could be employed and sustained release matrices in theophylline hydrate tablets in direct compression formulation from

concentration of 20% w/w. Ethylcellulose, on the other hand could be employed in similar formulation at concentrations above 20% w/w.

REFERENCES

1. Jonkman, J.H.G., Schoenmaker, R., Grimberg, N. and De Zeeuw, R.A. Int. J. Pharm. *8*, 153 (1981).
2. Taylor, J.B. and Simkpins, D.E. Pharm. J. *227*, 601 (1981).
3. El-yazigi, A. and Sawchuk, R. J. J. Pharm. Sci. *70*, 452 (1981).
4. Simons, K.J., Frith, E.M. and Simons, R.E. J. Pharm. Sci. *71*, 705 (1982).
5. Jenne, J.W., Wyze, E., Rood, B.S. and MacDonald, F.M. Clin. Pharmacol. Thera., *13*, 349 (1972).
6. Ogilvie, R.I., Fernadez, P.G. and Winsberg, F. Europ J. Clin. Pharm., *12*, 409 (1977).
7. Jocobs, M.H., Senior R.M. and Kesslerg, J. Am. Med Assoc. *235*, 1983 (1976).
8. Hendeless, L., Bighley, L., Richardson, R.H., Helper, C.C. and Carmichael. J. Drug Intell. Clin. Pharm. *11*, 12 (1977).
9. Mitenko, P.A. and Ogilvie, R.I. New Eng. J. Med. *289*, 600 (1973).
10. Biswanath Sa, Bandyopadhyay, A.K. and Gupta, B.K. Drug Dev. Ind. Pharmacy, 16 (7) 1153-1169 (1990).
11. Graf, E., Ghanem, A.A., Sakr. A. and Mahmoud, H. Pharm. Ind. *43*, 576 (1981).
12. Chukwu, I.K., Chukwu, A. and Udeala, O.K. Acta Pharm. *42*, 181-188 (1992).
13. Be-Hivan Chung and Chang-Koo Shim Int. J. Clin. Pharmacol. Res. *7*, 337-344 (1987).
14. Deltaan, P. and Lerk, C.F. Int. J. Pharm. *31*, 15-24 (1986).
15. Graf, E.I., Tsaktanu and Fawzy, A.A. Pharm. Ind. *48*. (6) 661-665 (1986).
16. McGinity, J.W., Cameron, C.G. and Cuff, G.W., Drug Dev. Ind. Pharm. *9* , 57 (1983).
17. Brockmeirer, D., Dengler, H.J. and Voegele, D. Europ. J. Clin. Pharmacol. *28*, 291-300 (1985).
18. Cohen, J.L. Analytical Drug profiles of Drug substances, Klaus F. ed. pp. 291-300. (1975).
19. Bates, T.R. (1970). "Liquid dosage forms containing insoluble matter". *In prescription pharmacy* Sprowls J.B. ed. 2nd edition. J.P. Lippincolt Comp. Philadelphia pp. 201-226.
20. Schwarz, T.W. and Levy, G. J. Am. Pharm. Assoc. (Sci) *47*, 695 (1958).