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IN-VITRO EVALUATION OF SUSTAINED-RELEASE DYPHYLLINE TABLETS

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ABSTRACT

Dyphylline tablets were prepared by direct compression of mixtures of the drug, emcompress and different ratios of hydroxypropyl methylcellulose (HPMC) or cellulose acetate phthalate (CAP). Physical properties of the prepared tablets and the drug release in 0.1 N HCl and phosphate buffer, pH 7.4 were investigated.

All tablets were found to satisfy the USP requirements regarding content, weight uniformity and friability. Hardness was greatly enhanced and thickness was slightly increased by increasing the polymer ratio in tablet formulations. Disintegration time of the dyphylline tablets was delayed by the presence of either HPMC or CAP and there was a direct relationship between the polymer ratio and the disintegration time. Considerable retardation in the rate and extent of drug release from the prepared tablets in both dissolution liquids was observed. As the polymer ratio increased in the tablet formulations, the drug release was significantly inhibited.

INTRODUCTION

Dyphylline is a theophylline derivative (dihydroxypropyl theophylline) used for releif of bronchial asthma and for reversible bronchospasm associated with chronic bronchitis and emphysema. However the drug casuses gastrointestinal irritation, resulting in nausea, vomiting

epigastric pain and abnormal cramps[1] . The drug has a short plasma half-life, 2.1 hours in humans[2] .

Prolonged release dosage forms have been developed to avoid the problems associated with plasma level fluctuations and to increase the intervals between dosage regimens. Such Pharmaceuticals were formulated by employing various resins, plastics and polymers and applying different techniques . Sustained-release tablets may be prepared by compressing mixtures of inert,insoluble plastic materials and drugs. On exposing such tablets to gastrointestinal fluids, a slow release of the drug by leaching was observed[3].

High viscosity cellulosic substances(methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and hydroxypropyl methylcellulose) were used in different concentrations to prepare prolonged-action tablets by compressing their mixtrues with drugs [4-6]. When such tablets were tested for dissolution in aqueous fluids, delayed release of drugs were reported. Hydration and gelation of cellulosic gums at the tablet-liquid interface to form a viscous gel barrier occured so that the drug released at a slow rate that apparently depended on diffusion from and/or attrition of the gel barrier[6]. Baun and Walker[7] prepared tablets of atropine sulfate and carminophen hydrochloride by mixing different quantities of carbopol 934 with the tablet matrix. The authors reported that the carboxyvinyl polymer may be useful in preparing prolonged action dosage forms. Also Sawayangi et al[8] examined the applicability of chitosan as a vehicle for sustained-release preparations of water soluble drugs.

TABLE 1

Formulations of Dyphylline Tablets

Materials(g)	A	B	C	D	E	F	G
Dyphylline	40	40	40	40	40	40	40
Emcompress	55	45	35	5	45	35	5
HPMC	-	10	20	50	-	-	-
CAP	-	-	-	-	10	20	50
Starch	5	5	5	5	5	5	5

HPMC = Hydroxypropyl methylcellulose.

CAP = Cellulose acetate phthalate.

The aim of this work was to prepare prolonged-release dyphylline tablets by the direct compression. Mixtures of the drug, emcompress and either HPMC or CAP in different ratios were compressed into tablets. It was also desirable to prepare the tablets without special treatment for the drug and avoiding the use of organic solvents.

EXPERIMENTAL

Materials and Methods

Dyphylline (Cid. Pharm. Co., Cairo, Egypt). Hydroxypropyl methylcellulose (HPMC) and cellulose acetate phthalate (CAP) (Prolabo-France), Emcompress (Mendell, UK), Strach and Magnesium stearate (EL-Nasr Pham. Chem. Co., Cairo, Egypt).

Preparation of Tablets

Tablet formulations were prepared as shown in Table 1. All ingredients were kept at 50°C for 48 hours and passed through a set of standard seives. The fraction which has the particle size of 100-250 um from each ingredient was used. Powders were mixed well and directly compressed in a single punch tablet machine (Erweka Press, Type EKO No. 11144, West Germany) fitted with a 12 mm flate punch. The machine was adjusted to produce tablets without polymer (formulation A)having proper hardness and then kept constant during the compression of all tablet formulations. Each tablet was weighed (0.5 g) before compression.

Evaluation of Tablets

Weight variation, drug content, hardness (ERWEKA hardness tester, Model TBT, ERWEKA, D-Heusenstamm, W.Germany) thickness (micrometer) and friability (Roche-Type friabilator (100 revolutions within 4min).

Disintegration time was tested (according to USP specifications) in 0.1 N HCl and phosphate buffer, pH 7.4 using USP disintegration apparatus. The results were the average of 12 randomly selected tablets from each batch.

In-vitro Dissolution Study of Tablets

The dissolution rates of all tablets were determined by USP XVIII rotating basket method. The dissolution media were 0.1 N HCl or phosphate buffer, pH 7.4 for tablets having the formulations A,B,C and D. In case of the formulations E,F and G, dissolution was carried out for 3 hours in 0.1 N HCl followed by phosphate buffer to complete the test. A

single tablet was weighed and placed in the basket which stirred at 100 rpm in 500 ml dissolution medium kept at 37±0.5°C. Samples of 2 ml were withdrawn at various intervals, filtered through millipore filter (0.45 um), suitably diluted with 0.1 N HCl and measured spectrophotometrically at 273 nm. Samples were replaced by equal volumes of fresh dissolution liquid. The presence of either HPMC or CAP did not interfere with the quantitative determination of the drug. The dissolution results were the average of 4 determinations.

RESULTS AND DISCUSSIONS

Generally in formulation of sustained release tablets, it is desirable to avoid either the use of special apparatus as fluidized bed, coating pan and coating machine or techniques such as microcapsules and copreciptate on ground of convenience and expence.So in this study the tablet ingredients were mixed and directly compressed. The obtained tablets were elegant, with smooth surface and easily ejected from the tablet machine.

The actual amount of dyphylline present in tablets containing either HPMC or CAP ranged from 93.8 to 105.4% w/w of the dose (200 mg). Table 2 shows the physical properties of the dyphylline tablets containing either HPMC or CAP in their different ratios. All the formulations were found to satisfy the USP requirements for weight uniformity and friability . As the polymer ratio increased in the tablet formulation, the friability were markedly decreased. It is clear in table 2 that the presence of 10% w/w polymer

TABLE 2

Physical Properties of the Dyphylline Tablets

Physical properties	Tablet Formulations[2]						
	A	B	C	D	E	F	G
Weight (g)	0.5024 (0.0061)	0.4970 (0.0082)	0.4965 (0.0075)	0.5086 (0.0059)	0.4958 (0.0086)	0.5092 (0.0067)	0.5002 (0.0024)
Coefficient of variation(%)	1.214	1.650	1.510	1.160	1.734	1.335	0.480
Thickness (mm)	2.890 (0.032)	2.90 (0.015)	2.95 (0.061)	3.15 (0.090)	2.91 (0.042)	3.00 (0.078)	3.25 (0.083)
Hardness (Kg)	3.26 (0.09)	6.15 (0.13)	8.15 (0.88)	15	5.75 (0.345)	7.00 (0.85)	10.60 (0.95)
Friability (%)	0.864	0.462	0.284	0.086	0.501	0.342	0.124
Disintegration time (min)	1.2 (0.009)	22 (1.93)	45 (3.40)	125 (8.82)	180 (16.46)	210 (19.34)	250 (23.75)

1- Reported as average of measurements of 20 tablets except for disintegration time (average of 12 tablets) with ±SD in parentheses.

2-Tablet formulations A,B,C, and D. were tested for disintegration in 0.1 N HCl while E,F and G were tested in phosphate buffer, PH 7.4 after passing 2 hours in 0.1 N HCl.

in the tablet formulations (B and E) decreased the friability of the tablets nearly to its half value in comparison to formulation A . The hardness results confirmed those of friability, i.e as the hardness increased the friability decreased and vice versa. Table 2 also shows that the hardness was markedly increased while, tablet thickness was slightly increased by increasing the polymer ratio in the tablet formulation. On plotting the polymer ratio (% w/w) against hardness (Kg) of the prepared tablets (Fig. 1), a linear relationship was obtained and the slope of line varried with the different polymers. As shown in Fig. 1 and Table 2, HPMC posses a more pronounced effect on tablet hardness than CAP. The effect of both HPMC and CAP on the hardness of the prepared tablets might be due to the increased cohessiveness and compaction properties of the tablet mixtures. Similar results have been reported by Baun and Walker(7), who noticed an increase in tablet hardness by the increase of the carbopol 934 content in the tablet formulations.

Table 2 shows the disintegration time of the prepared tablets in O.1 N HCl and phosphate buffer, pH 7.4 according to USP specifications. Tablets without polymer (formulation A) disintegrated rapidly (1.2 min) in O.1 N HCl, while those containing HPMC(formulations B,C. and D) disintegrated slowly in the same liquid. As HPMC content increased in the tablet formulation, the disintegration time was delayed. Formulations B and D disintegrated after 22 and 125 min, respectively in O.1 N HCl. This might be due to the suppression of the tablet porosity as a result of the increased hardness resulted by the presence of polymer in the tablet for-

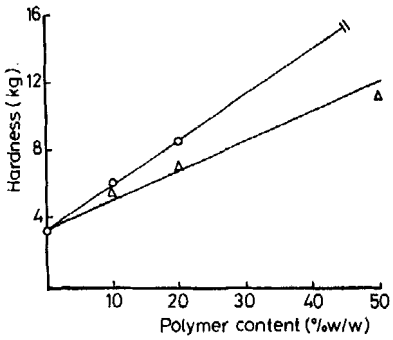

FIGURE 1.

Effect of polymer content on the hardness of dyphylline tablets.

Key : o Tablets containing HPMC.
Δ Tablets containing CAP.

mulations. On the other hand, tablets containing CAP(formulation E,F and G) retained their shape for 2 hours in 0.1 N HCl as a disintagration medium and deformation started after displacing the acidic medium by the alkaline one (phosphate buffer, pH 7.4). This attributed to the enteric behaviour of CAP[10]. As CAP content increased in the tablets, disintegration time was delayed. Tablet formulations, E,F and G disintegrated after 60,90 and 130 min respectively in alkaline medium after passing 2 hours in 0.1 N HCl. This might be attributed to the decrease in tablet porosity as a result of the increased hardness.

Fig 2 shows the dissolution profiles of dyphylline from the tablet formulation containing HPMC (B,C and D) in either 0.1 N HCl or phosphate buffer, pH 7.4. As the HPMC content inereased in the tablets, the drug release was retarded in both dissolution liquids. This might be due to the high hardness of the tablets (Table 2). Wiseman

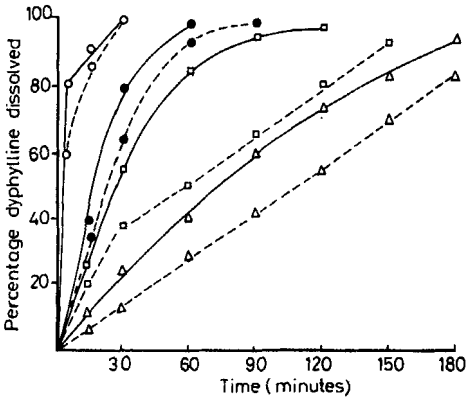

FIGURE 2.

Dissolution profile of dyphylline tablets containing varying concentrations of HPMC in either 0.1 N HCL(——) or phosphate buffer, PH 7.4 (---).

Key: o Tablets containing no HPMC.
● Tablets containing 10% w/w HPMC.
▫ Tablets containing 20% w/w HPMC.
△ Tablets containing 50% w/w HPMC.

and Federici[9] reported that the drug release from prolonged-action tablets was controlled by their hardness.

The rate of dyphylline release from tablets containing HPMC in phosphate buffer, pH 7.4 was slower than that in acidic pH (Fig 2). The time required for release 60% of the drug (t_{60}) were 21,33 and 95 min in 0.1 N HCl from tablets containing 10,20 and 50% w/w HPMC, respectively while t_{60} in phosphate buffer, pH 7.4 were 27,75 and 126 min for like cases. This was due to the retardation effect of the gel layer formed on the tablet surfaces in the alkaline medium . The hydrated zone (gel) of HPMC acted as a physical barrier between the drug and the dissolution medium. Part of the drug would be diffused through the hydr-

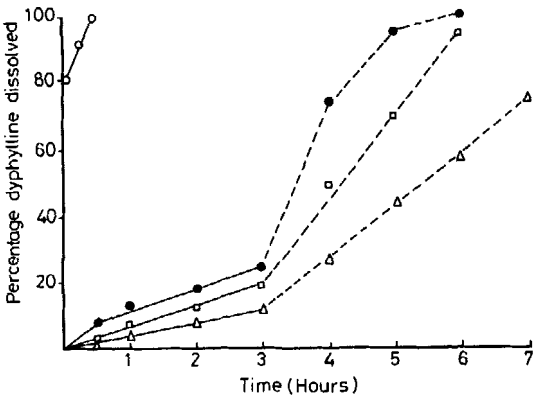

FIGURE 3.

Dissolution profile of dyphylline tablets containing varying concentrations of CAP in 0.1 N HCL (—) and phosphate buffer pH 7.4 (---).

Key: o Tablets containing no CAP.
● Tablets containing 10% w/w CAP.
▫ Tablets containing 20% w/w CAP.
△ Tablets containing 50% w/w CAP.

ated zone and would be released to the medium, while the remainder liberated when the hydrated zone dissolved. The mechanism of drug release from the granules containing HPMC was reported [11&12]. The zero-order controlled release of the drug from the tablets containing high ratio of HPMC in phosphate buffer was attributed to the gel formation in the alkaline medium (Fig. 2). Kohri, et al[12], studied the sustained release of nifedipine from granules containing HPMC and discussed the mechanism of the drug release.

Fig. 3 shows the dissolution profiles of dyphylline tablets containing varying concentrations of CAP. The release was tested in 0.1 N HCl for 3 hours and continued for other 4 hours in phosphate buffer pH 7.4 using the same

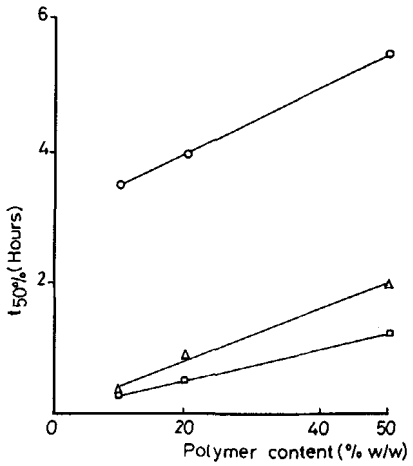

FIGURE 4.

Relationship between t_{50} (mean time required to dissolve 50% of dyphylline content) and the polymer content in the dyphylline tablets.

Key: o Tablets containing CAP.
Δ Tablets containing HPMC (dissolution medium is phosphate buffer, pH 7.4).
□ Tablets containing HPMC (dissolution medium is 0.1 N HCl).

tablet samples. It is clear from the figure that the release of the drug was very slow in 0.1 N HCl. As the tablets containing no polymer released all the drug content after 30 min, the amounts of drug released from the tablets containing 10,20 and 50% w/w CAP were 25,20 and 11%, respectively after 3 hours of dissolution in acidic medium. This may be related to the low porosity resulted from the high hardness of the tablets (9) . It may also attributed to the low permeation of the drug through the CAP matrix which resulted from insolubility of the polymer at acidic pH. Meanwhile the rate of release of the drug increased in phosphate buffer as shown in Fig. 3 by the sharp raise of the plots

for all tablet formulations containing CAP. In alkaline pH CAP starts to swell and dissolve simultaineously[10] producing a progressive decrease in the matrix thickness over the period between 4 and 7 hours. Also Fig.3 indicates that zero-order controlled release of dyphylline from tablets containing CAP was obtained in both acidic and alkaline liquids. Slight deviation observed in case of tablets containing 10% CAP in pH 7.4 may be due to the low polymer concentration and the higher solubility of CAP in alkaline pH.

The relationship between $t_{50\%}$ (mean time requried to release 50% of dyphylline content) and the polymer content in the dyphylline tablets is represented in Fig. 4. A linear relationship was obtained for the polymer content $>10\%$. This indicated that the action by which HPMC or CAP retarded release was most probably a physical phenomenon. Increasing the polymer content increased the thickness of the polymer matrix shielding the dyphylline particles and improved the tablet hardness. When the polymer content was low ($<10\%$), incomplete sheilding occured and hence less retardation in release and lower $t_{50\%}$ was obtained

It can be concluded from this investigation that, HPMC and CAP may be useful for preparing sustained release dyphylline tablets furthermore the gel property of HPMC may be of great importance in inhibiting the irritation of dyphylline to the gastro-intestinal tract.

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