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FORMULATION AND RELEASE KINETICS OF SUSTAINED RELEASE PHENYLPROPANOLAMINE HYDROCHLORIDE GRANULES AND TABLETS

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ABSTRACT

Sustained release phenylpropanolamine hydrochloride (PPH) granules and tablets were prepared using HPMC, HPMC and SCMC, Eudragit RS, Eudragit RS+L or HPMC + Eudragit RS matrices. The release pattern of PPH from the prepared granules and tablets was found to be in the following order HPMC > HPMC + SCMC > RS > RS+L > HPMC + RS. The results revealed that, although the drug concentration was kept constant in all the prepared granules and tablets, the drug release from these formulations was clearly different and depends mainly on the type of matrix used. The presence of Eudragit L with Eudragit RS and Eudragit RS with HPMC resulted in a marked decrease in the drug release compared with that obtained from the matrix containing HPMC or Eudragit RS alone. The release data of PPH from the prepared granules and tablets were treated mathematically according to zero order, first order, Langenbucher, modified Langenbucher and Higuchi models. The results revealed that no one model was able adequately to describe the drug release profiles from these formulations. In-vivo studies in human volunteers showed that, the peak urinary excretion of PPH occurred over a sustained period from 2 to 6.5 hr in case of HPMC + SCMC tablets and from 2 to 10 hr in case of either RS + L or HPMC + RS tablets.

INTRODUCTION

Although the intensity of a pharmacological effect is related to the drug concentration at the site of act-

ion, which is in turn generally related to the plasma drug concentration, an ideal situation is obtained when the concentration in the body is continuously maintained between the minimal effective and maximal safe values. However, when the drug has a relatively short elimination half-life, it is difficult to maintain the concentration within the therapeutic range without frequent dosing or the use of sustained release formulations.

Among sympathomimetic drugs, phenylpropanolamine hydrochloride is readily and completely absorbed from the gastrointestinal tract after oral administration, followed by relatively rapid elimination from the plasma in humans (1). The plasma half-life in humans however is short (about 4 hours) requiring that the drug be administered three or four times daily (1,2). It is therefore important and desirable to prolong the effective plasma level in order to maintain the clinical efficacy of the drug. A method of adequately maintaining a prolonged plasma drug level is to incorporate the drug in sustained release waxy matrices (3-6). The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceutical dosage forms. Different types of polymers were used as hydrophilic matrices (7-10) and their modelling aspects were reviewed (11-13). Ranga Rao et al. (14) had used hydroxypropylmethylcellulose alone or in a mixture with sodium carboxymethylcellulose for extending the release of 23 medicaments of various solubilities. Also, acrylic resins have been widely employed for preparing controlled-or slow released drug formulations (15,16).

The aim of this work was to formulate phenylpropanol- amine hydrochloride (PPH) in the form of sustained-release granules using different types of hydrophilic polymers (HPMC and SCMC) or acrylic polymers

(Eudragit RS and Euragit L) or mixture of both. PPH was selected as an example of freely soluble sympathomimetic amine hydrochloride which has a short half life. The prepared granules can be further processed into single unit dosage forms by incorporating suitable excipients and then filling into capsules or compressing into tablets. The release kinetics of PPH from the prepared granules and tablets were discussed. In-vivo evaluation of these formulations was also investigated.

EXPERIMENTAL

Materials and Methods:

Phenylpropanolamine hydrochloride (PPH), kindly supplied by Elkahera Pharm. Co., Cairo, Egypt. Hydroxypropylmethyl- cellulose (HPMC), Sigma Chemical Co., USA. Sodium carboxy- methylcellulose (SCMC), Dow Chem., USA. Eudragit retard RS and Eudragit L (Rohm and Haas, GmbH, Germany). Emcompress (Edward Mendell Co., Yonkers, USA).

Preparation of granules:

All types of granules were prepared by solvent evaporation technique according to the component ratios illustrated in Table 1.

1- Preparation of HPMC-SCMC granules:

The drug and HPMC or the mixture of HPMC and SCMC were dissolved in hydroalcoholic solution (ethanol: water 1:1). The solvent was evaporated at 50°C under reduced pressure, in a rotary evaporator until slurry of a suitable toughness was obtained. To facilitate the granulation, an equivalent amount of emcompress was added and the resulted mass was forced through a 1.6 mm sieve. The resulted granules were dried in hot air oven at 50°C, until free from solvents (constant weight).

Table 1: Formulations use for preparing PPH granules.

Formulations	Drug-Polymer ratio
HPMC	1:2
HPMC + SCMC	1:1:1
Eudragit RS	1:2
Eudragit RS + L	1:1:1
HPMC + Eudragit RS	1:1:1

2- Preparation of Eudragit RS-L granules:

The drug and Eudragit RS or the mixture of Eudragit RS and L were dissolved in a mixture of acetone and ethanol (1:1). The granulation procedure was identical to that used in case of method 1.

3- Preparation HPMC-Eudragit RS granules:

The drug, HPMC and Eudragit RS were dissolved in a mixture of methanol, acetone and methylene chloride (1:1:1) and the granules were prepared as mentioned before in method 1.

The prepared granules of different formulations were sieved and the size fraction of 800-1000 μm were selected for further studies.

Drug content in the granules:

Triplicate samples of 300 mg of PPH granules were placed in 100 ml volumetric flasks containing hot ethanol/acetone mixture in case of granules containing Eudragits or ethanol/water mixture in case of granules

prepared with hydrophilic polymers (HPMC and SCMC). The suspension was shaken vigorously for 3 hours and then centrifuged for 10 min. Aliquots were filtered and assayed spectrophotometri- cally for PPH at 257 nm.

Preparation of tablets:

Each type of the prepared granules was mixed with 1% magnesium stearate and compressed into tablets (300 mg each) using a flat-faced punch (10 mm diameter) in a single puch Erweka tablet press (EKO, Germany). In each case considerable efforts were made to ensure uniform tablet weight and hardness to avoid variations in porosity.

Release studies:

The release of PPH from the prepared granules and tablets was determined over 8 hours, using the USP paddle method at 60 rpm. 500 ml of 0.2 M phosphate buffer (pH 7.4) at 37°±0.5°C was used as a dissolution medium. One tablets or an equivalent amount of granules containing 50 mg of PPH was employed for each dissolution study. At predetermined time intervals, 3 ml samples were withdrawn and replaced with an equal volume of fresh dissolution medium to maintain the original volume. The concentration of drug in each sample was measured spectrophotometrically at 257 nm. Triplicate runs were carried out for each study.

In-vivo study:

PPH tablets prepared from HPMC+SCMC, RS+L or HPMC+-RS granules were selected for this study on the basis of their reasonable sustained-release characteristics.

Six healthy male volunteers (age 35-42 years and weight 72-85 kg) were participated in this study in

cross-over manner with at least 10-days intervals between each drug administration. Following an overnight fast, each subject was instructed to void his bladder and took 50 mg of untreated PPH in hard gelatin capsule or one from the tested tablets, previously weighed together with 200 ml water. No food was allowed for at least 3 hr. Cumulative urine samples were collected at 1, 3, 5, 8, 12, 24 and 36 hr post-dosing. PPH in the urine samples was determined according to the method adopted by Heimlich et al. (17).

Results and Discussion

The percent of drug entrapped in the prepared granules and tablets was found to be from 92-96%, indicating the efficiency of the technique used for preparing these formulations. The release profiles of PPH from the prepared granules are illustrated in Figure 1. The results showed that, the release pattern of PPH was found to be in the following order: HPMC >HPMC + SCMC > RS > RS + L > HPMC + RS. These results revealed that HPMC + RS granules showed the slowest rate of drug release, where the $T_{50\%}$ was attained after 4 hr, while granules prepared with HPMC alone showed the highest rate of drug release ($T_{50\%}$ less than one hour). Although the drug concentration was kept constant in all the prepared granules, the drug release from these granules was clearly differnt and depends on the type of matrix used. In addition, the presence of SCMC or Eduragit RS with HPMC matrix and Eudragit L with RS matrix resulted in a marked decrease in the drug release compared with that from the matrix containing HPMC or RS alone. This effect could be explained on the basis, PPH is a cationic drug (pKa 9.4) may interact with anionic SCMC or Eudragit L at pH 7.4, so that the diffusion of the drug from these matrices (HPMC or RS) was inhibited or retarded.A similar explanation

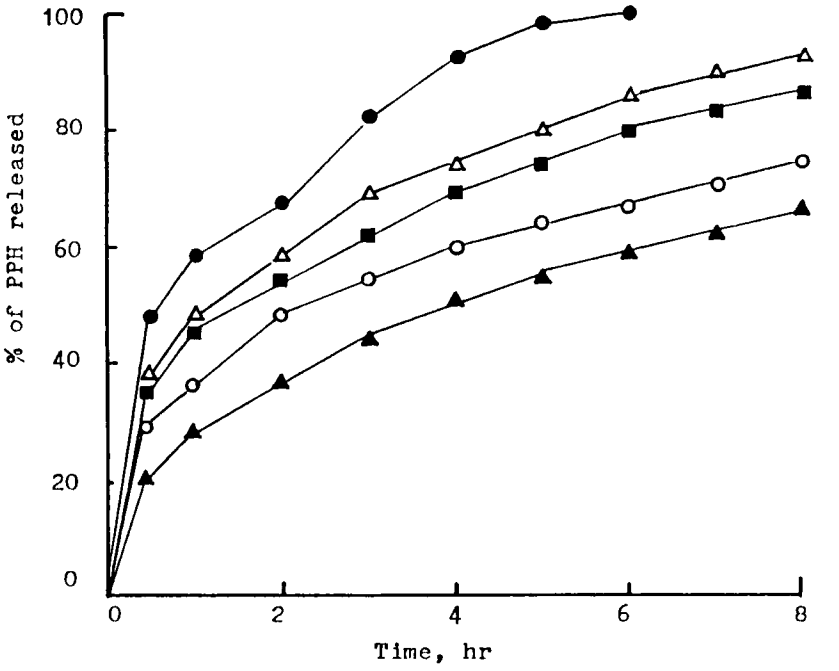

Fig. 1- Release profiles of PPH from granules .

Key; ● HPMC, △ HPMC+SCMC, ■ Eudragit RS,
○ Eudragit RS+L, ▲ HPMC+ Eudragit RS

was proposed and proved by Lapidus and Lordi (7) for the release of chlorpheniramine maleate from matrices containing SCMC. The authors attributed this response to a drug/polymer interaction. Baveja et al. (18) had used a combination of HPMC and SCMC for retarding the release of β-adrenergic blockers from tablets and attributed the retarding effect of this combination to the high degree of cross-linking between the nonionic HPMC and anionic SCMC leading to synergistic increase in gel viscosity at tablet periphery.

In order to varify and explain the possible interaction between PPH and the anionic polymers (SCMC and

Eudragit L) at pH 7.4, the release of the drug from these granules was tested in acidic medium (0.1 N HCl). The results obtained revealed that there was no significant change in the drug release from HPMC + SCMC and HPMC alone; from RS + L and RS alone. These results supporting the explanation of the presence drug-polymer interaction at pH 7.4. However at pH 1.2 SCMC and Eudragit L were present in the unionized form which is water insoluble, the electrostatic interaction was no longer be possible and the polymer was therefore behaves as an inert insoluble matrix. Similarly, Freely and Davis (19) reported that, no interaction occurred between sodium salicylate and SCMC at pH 7.0, since both were anionic at this pH.

As mentioned before, granules of HPMC + RS showed the lowest values of PPH release. HPMC is a hydrophilic swellable polymer when mixed with the water insoluble and pH independent Eudragit RS a synergistic retarding effect may be occurred. The drug diffusional path length was extended which might be due to the slower erosion of this matrix in the dissolution meidum. This was detected by examining the granules at the end of the release experiment, the granules were found to be hard and rigid i.e. don't swell over the period of 8 hr. This may be probably due to an interaction between the two polymers (HPMC + Eudragit RS) through the formation of hydrogen bonding between the carbonyl groups of Eudragit RS and the hydroxyl groups of HPMC, leading to stronger cross-linking between the two polymers.

Evaluation of the formulated tablets:

All the prepared tablets exhibited good physical and mechanical properties regarding their uniformity of weight, hardness, friability and disintegration time

Table 2: Physical characteristics of PPH tablets.

Types of Tablets	Weigh:(mg) Mean	C.V.%	Hardness Kg	Friability %	Disinteg. Time min.
HPMC	305.5	1.82	4.85	0.29	> 180
HPMC+SCMC	306.2	1.56	5.00	0.23	" "
Eudragit RS	302.4	1.82	4.60	0.47	" "
Eudragit RS+L	301.9	1.69	4.50	0.55	" "
HPMC+Eudragit RS	304.8	1.75	4.75	0.38	" "

(Table 2). The hardness of tablets was ranged from 4.5 to 5 kg (Erweka) and the friabilities were less than 0.55%. All tablets showed no evidence of disintegration for a period of 3 hr.

The release pattern of PPH from the prepared tablets was similar to that from the granules but with a lesser extent(Fig. 2). The $T_{50\%}$ was attained after about 8, 6.5, 3.5, 3.0 and 2.2 hr for HPMC + RS, RS + L, RS, HPMC + SCMC and HPMC tablets, respectively. This may be due to the limited and lower surface area of tablets than that of the corresponding granules. Tablets containing only the hydrophilic polymers swelled, maintaining their cylindrical shape, but underwent slow attrition in water. Tablets containing Eudragit RS or RS + L started deformation after 3 hr, while tablet containing HPMC + Eudragit RS retained their original shape during the release experiment (8 hr).

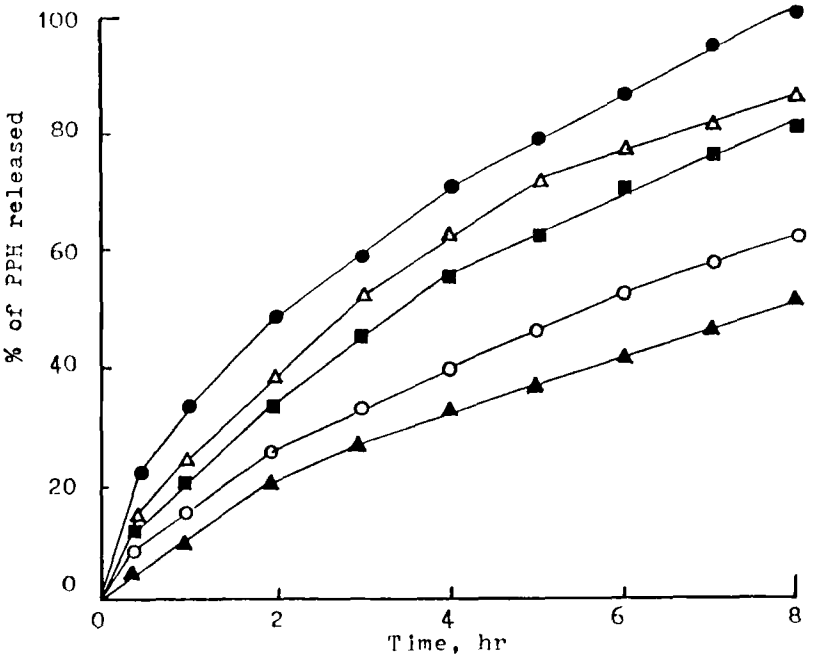

Fig. 2- Release profiles of PPH from the prepared tablets.

Key; As in Fig. 1.

The release data from the prepared granules and tablets were treated mathematically according to zero order, first order, Langenbucher, modified Langenbucher (20,21) and Higuchi models. The results obtained revealed that, no one model was able adequately to describe the drug release profiles. In case of granuels prepared with Eudragit RS, RS + L and HPMC + RS, the best linear relations and the highest linear correlation coefficients were obtained with Higuchi equation (r = 0.9888, 0.9853 and 0.9973, respectively). This was followed by first order (r = 0.9835, 0.9761 and 0.9796, respectively). In case of granules prepared using HPMC and HPMC + SCMC, the best linear correlations were obtained with first order equation (r = 0.9786 and 0.9870, respecti-

vely). In case of tablets, considering all points between 0 and 8 hr, the best linear correlations were obtained with first order (r = 0.9867 - 0.9991) followed by Higuchi model (r = 0.9837 - 0.9939) and zero order (r = 0.9677 - 0.9854). However, in case of tablets prepared with HPMC + SCMC, RS and HPMC + RS, zero order equation was valid with higher correlation coefficient up to 5 hr (r = 0.9897, 0.9871 and 0.9895 respectively). These results indicated that, different mechanisms of release were observed for the same drug according to the type of coating materials and the formulations used. In all cases, the three mechanisms may present but that one would predominate the others.

Bioavailability studies:

The mean urinary excretion of PPH over the period of 36 hr following the oral administration of the selected three formulations and the untreated drug are shown in Table 3 and Figure 3. From the results obtained, it was found that, the rate excretion of PPH from the tested preparations was in the following order: untreated drug > HPMC + SCMC tablets > RS + L tablets > HPMC + RS tablets. Accordingly, HPMC + SCMC tablets showed the highest relative bioavailability (91.89%) while, HPMC + RS tablets showed the lowest one (84.65). These results revealed that, PPH was absorbed from the tested formulations in the same order stated before. The peak urinary excretion of the drug from the selected tablets occurred over a sustained period from 2 to 6.5 hr in case of HPMC + SCMC tablets and from 2 to 10 hr in case of either RS + L or HPMC + RS tablets (Table 3 and Fig. 3). These results indicated that, the tested sustained release tablets gave slow increase in PPH plasma concentration and slow excretion of the drug in urine, along with an avoidance of transient high PPH concentration in plasma

Table 3. Mean urinary excretion and relative bioavailability of PPH sustained release tablets.

Formulations	mg of PPH excreted after, hr							Total amount excreted	Relative Bioavailability
	1	3	5	8	12	24	36		
Untreated Drug ±(S.D)	7.9 (1.40)	14.10 (1.90)	9.10 (1.20	6.15 (0.95)	5.0 (1.05)	3.15 (0.65)	0.85 (0.15)	46.25	---
HPMC+SCMC tablets ±(S.D)	3.80 (1.15)	8.20 (1.65)	7.0 (1.37)	10.75 (1.77)	7.15 (1.05)	3.65 (0.92)	1.95 (0.33)	42.50	91.89
RS +L tablet ±(S.D)	2.20 (1.02)	6.40 (1.39)	6.05 (1.67)	8.35 (2.00)	8.80 (0.97)	6.85 (0.97)	2.25 (0.42)	40.90	88.43
HPMC +RS tablets ± (S.D)	1.80 (0.82)	5.00 (1.32)	5.40 (1.15)	7.35 (1.07)	9.40 (1.29)	7.60 (0.99)	2.60 (0.47)	39.15	84.65

SD : Standard deviation

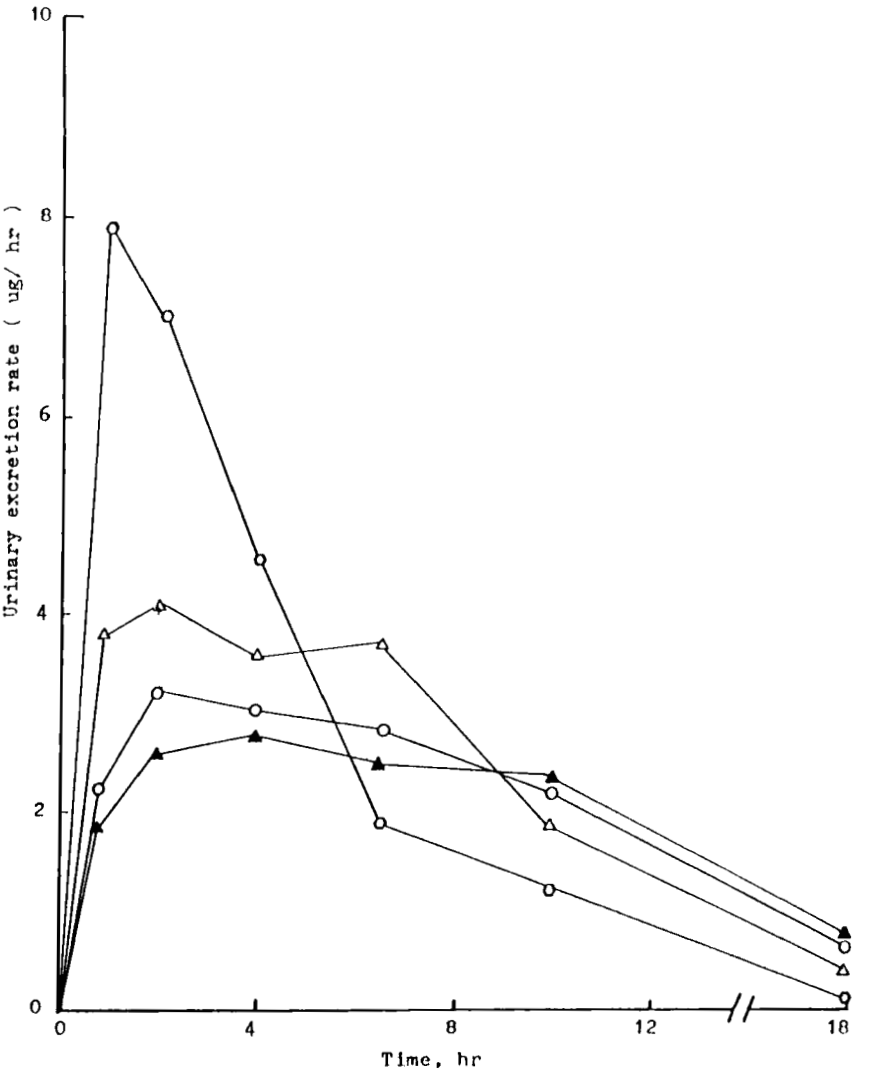

Fig. 3- Mean urinary excretion of FPH following the oral administration of untreated drug and sustained release tablets.

Key: As in Fig. 1.

(as in case of the untreated drug) and mentained its concentration for a long time.

The analysis of variance (ANOV) was applied to the cumulative amount of PPH excreted in urine from all the tested formulations. It was found that, significant differences ($P<0.05$) were existed between the untreated drug and all the tested tablets, while insignificant differences ($P>0.05$) were existed between RS + L tablets and HPMC + RS tablets at all time intervals. In addition, significant differences were existed between HPMC + SCMC and either RS + L tablets or HPMC + RS after 3, 5 and 8 hr.

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