DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(14-16), 2681-2693 (1989)

IN-VITRO RELEASE AND IN-VIVO AVAILABILITY OF CHLOROQUINE PHOSPHATE FORMULATED SUPPOSITORIES

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ABSTRACT

Chloroquine phosphate suppositories were formulated using witepsol H15 as a model base. The physicomechanical properties of the prepared suppositories were studied. In-vitro drug release as well as in-vivo availability were determined and compared with those from commercial tablets containing the same dose of the drug (250 mg). In addition, the effect of pH of the different segments of GIT on the partition coefficient of the drug was tested.

Results revealed that formulated suppositories exhibit good mechanical properties as well as high release characteristics. Volunteers received suppositories showed urine peak level after 2 hrs while with those administered the tablets the peak was reached after 3 hrs. The total amounts released were 60% and 48% from the administered dose in case of suppositories

and tablets respectively. The higher bioavailability of the medicament after rectal therapy is explained on the basis of the partition coefficient data. The obtained values were 0.667, 0.941 and 5.333 at pH 1.2, 6.8 and 7.4 respectively. Volunteers used the formulated suppositories did not suffer from any GI irritation which is accompanying the oral administration of the drug. The proposed formula had no irritating effect on the rectum.

INTRODUCTION

Chloroquine phosphate is one of the most potent drugs which is preferable in the treatment of malaria and hepatic amoebiasis (1). The drug is available in the form of injections and tablets. Oral administration of chloroquine phosphate is accompanied with gastrointestinal disorders such as nausea, vomiting and diarrhea which may be attributed to its extremely bitter taste (2). There is no information in the literature regarding the formulation of chloroquine phosphate suppositories. However, suppositories represent a special dosage form from the pharmaceutical point of view which is suitable for several medicinal substances such as analgesics, antispasmodics, antiemetics, non-steroidal antiinflammatory drugs as well as local anaesthetics (3-5).

Rectal route for drug administration was proved to be advantageous over other routes because of the reduced side effects such as gastrointestinal irritation and the avoidance of both disagreable taste and first-pass effects (6). Suppositories are a convenient dosage form for children and bed-ridden patients (7).

In addition, absorption of drugs from the rectal mucosa directly into the venous circulation may bring about faster onset of action than that observed after oral administration (8).

The aim of this work was to formulate chloroquine phosphate suppositories suitable for either children or adults so as to avoid the side effects arising from the oral administration of the drug, and to compare the in-vitro release as well as the bioavailability of the formulated suppositories with the commercial tablets containing the same dose of the drug.

EXPERIMENTAL

Materials:

Chloroquine phosphate (Sigma Chemical Co., St. Louis, MO, USA), Witepsol H15 (Dynamit Nobel A.G. Chemische Witten, G.F.R. W. Germany), Cellophane membrane, Spectrapor; M.W. Cutoff 12000-14000 (Fisher. Sci. Co. USA), n-octanol (BDH Chemicals, Ltd, Poole, UK).

All other chemicals and solvents were of analytical and reagent grade quality and used without further purification.

Methods:

Preparation of Suppositories:

Chloroquine phosphate suppositories, each containing 250 mg medicament and weighing 1 g±3%, were prepared by the fusion method (9), the powdered drug (passed through à 100 mesh sieve) was suspended in the

molten base at 40°C, the suspension was homogenized and then poured into stainless steel moulds (ERBO Prazisions-Formenbau GmbH, D-7470, West Germany) at 28°C. Suppositories were cooled at 10°C and kept at 4°C until used, Witepsol H15 was used as a model base.

2- Evaluation of the formulated suppositories:

The drug content uniformity as well as weight variation were determined according to BPC 1973 and BP 1980 respectively. The hardness test was determined using Erweka apparatus model SBT (West Germany). Deformation time was determined using Erweka apparatus SSP.

3- Partition coefficient study:

Partition coefficient of chloroquine phosphate was determined using the presaturated n-octanol/phosphate buffer system. Five ml of n-octanol, 20 ml buffers of either pH 1.2, 6.8 or 7.4 as well as 20 ml drug were placed in 100 ml glass bottle. The bottles were tightly closed and rotated at 50 rpm for 24 hr in a water bath at 37±0.2°C. The bottles were removed, left to cool at room temperature. The oily phase was separated using a separating funnel while the aqueous one was clarified by filtration through a 0.2 μm Millipore filter. The amount of chloroquine phosphate in the aqueous phase was determined spectrophotometrically at 329 nm and the partition coefficient of the drug was computed (10). A control experiment was preformed under the same conditions but without the drug. The average of four determinations was reported.

4- Release rate study from the formulated suppositories:

The modified Krowcziniski method (11) was adopted. One suppository was added to 10 ml distilled water contained in a glass tube opened from both ends (150 mm length and 38 mm internal diameter). The tube was firmly tied on its end with a cellophane membrane, and vertically suspended in 250 ml beaker containing 100 ml distilled water so as that the membrane was just below the surface of water. The system was maintained at 37±0.2°C. One ml samples were withdrawn at predetermined time intervals and then replaced by the same volume of distilled water at the same temperature. The amount of drug released was measured spectrophotometrically. The average of six determinations was taken.

5- Dissolution rate studies of the commercial tablets:

The dissolution rate of tablets was determined using the modified USP rotating basket (Erweka Type DT) provided with 500 ml distilled water at 37±0.2°C. The speed of rotation was adjusted to 60 rpm. Samples were withdrawn at the depth of the basket and immediately replaced by fresh media. The amount of drug dissolved was determined spectrophotometrically. Five parallel experiments were performed and the average was calculated.

6- Bioavailability study:

Six healthy male volunteers aged 30-41 years (mean age: 36 years) and weighing 53-69 kg (mean body weight: 59 kg) were chosen for the experiments. All volunteers gave their consent after receiving full

verbal and written information about the purpose of the study. The selected subjects were allowed to administer both the formulated suppositories and the commercial tablets. The interval between the two administrations was at least 2 weeks in all volunteers. None was on any medication during the course of the experiment, and all volunteers were fasted 8 h prior to the experiment and 2 h postdosing.

Urine samples were collected quantitatively before and at 0.5, 1, 2, 3, 4, 6, 12 and 24 h after either rectal or oral administration of the formulated suppositories and commercial tablets respectively.

7- Determination of the drug in urine:

The method described by Vogel and Konigk (12) was used to determine the amount of drug excreted in urine. Two ml urine were shaken for 30 min with an equal volume of 1 N sodium hydroxide and 30 ml heptane. Twenty ml of the orgnaic layer was transferred to an another flask containing 3 ml 0.1N hydrochloric acid. The solution was shaken for 5 min and then centrifuged at 3000 rpm for 10 min. The heptan layer was removed by aspiration. Two ml of the aqueous layer was transferred to a cuvette containing 0.5 ml 0.4N sodium hydroxide and 0.5 ml 3M borate buffer (pH 9.5). The fluorescence was measured on spectrophotofluorometer (MINCO-BOWMAN, American Inst. Col USA) with an excitation wavelength of 340 nm and an emission wavelength of 385 nm.

RESULTS AND DISCUSSION

The weight of each suppository was found to deviate by not more than 5% from the average. Drug content in each suppository ranged between 243.91 and 252.32 mg, while in commercial tablets it was 239-245 mg. Chloroquine phosphate formulated suppositories exhibit good mechanical characteristics where hardness and deformation time were 2.3±0.2 kg and 292±20 sec respectively.

Partition coefficient of the medicament was determined using n-octanol/phosphate buffer at different pH values 1.2, 6.8 and 7.4 which represent the pH of different segments of the gastrointestinal tract.

The obtained results were presented in Table 1. It is obvious that, partition coefficient of the drug is markedly affected with the pH, where it showed the lowest value at the acidic pH (1.2). Slight increase (1.5 fold) in partition coefficient was obtained at pH 6.8. A marked increase in partition coefficient (9 folds) was shown at pH 7.4.

Release rate studies:

Figure 1 shows the release profiles of chloroquine phosphate from the formulated suppositories and the commercial tablets. About 86% drug was released from the commercial tablets within 30 min compared to 40% from the formulated suppositories. After 60 min, 90% and 70% drug were released from both the tablets and suppositories respectively.

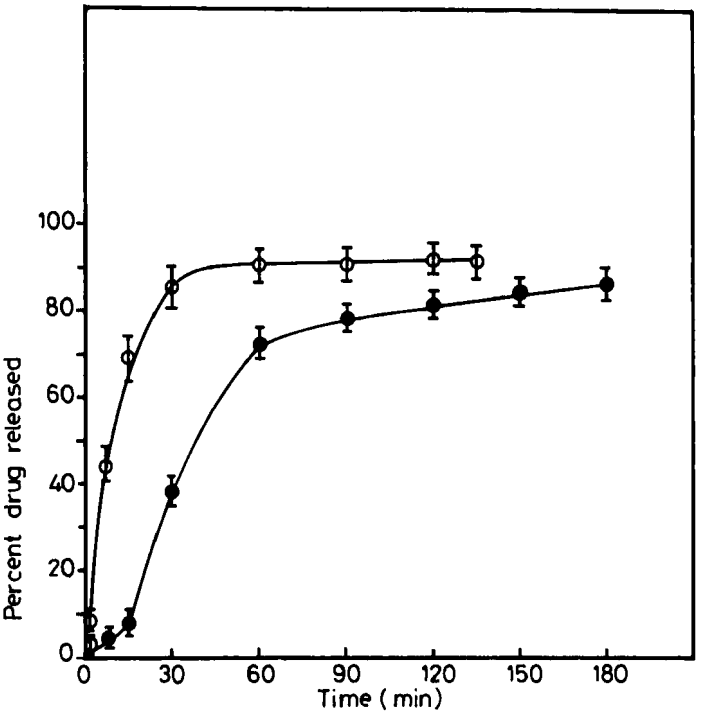

FIGURE 1
Release profiles of chloroquine phosphate from the fromulated suppositories and the commercial tablets.
Key: ● Formulated suppositories.
o Commercial tablets.

Theoretical analysis of the release profiles data revealed that first order kinetics (13) could be applied to describe the drug release from both formulated suppositories, and tablets (Figure 2).

The drug release rates from suppositories were slow compared with the dissolution rates from the commercial tablets. It is possible that the dissolution fluid in the case of tablets had the ability to penetrate the tablet structure forming fluid channels with the consequent disintegration and dissolution of drug

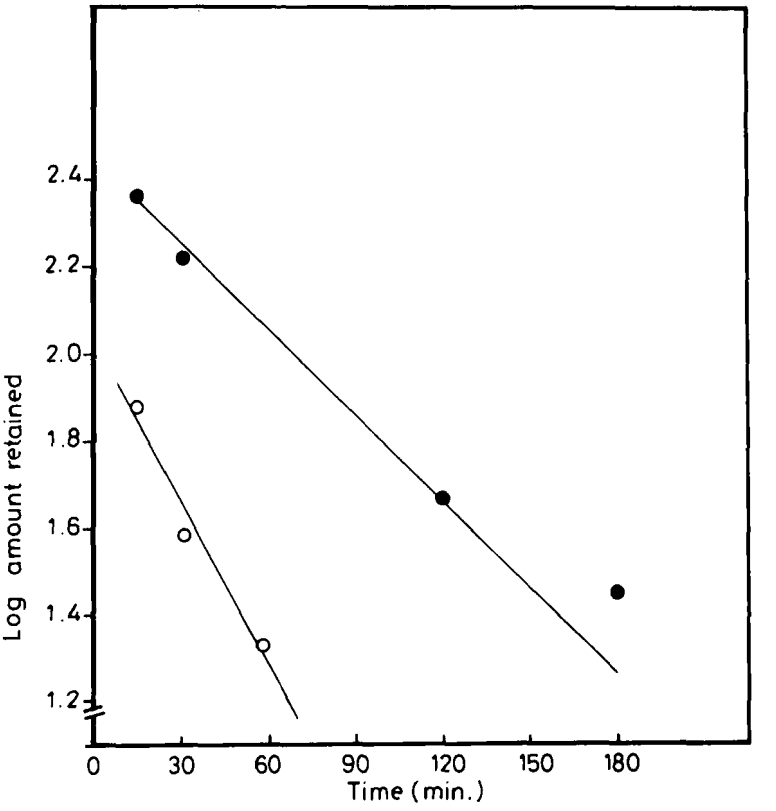

FIGURE 2
Relation between time and log the amount retained in the formulated suppositories and tablets.
Key : ● Formulated suppositories.
o Commercial tablets.

particles, while in case of suppositories the release pattern depends mainly on the melting range of the base (14) which takes comparatively longer time.

Bioavailability studies:

Figure 3 shows the mean cumulative urinary excretion of chloroquine phosphate after rectal and oral administration. It is clear that the total amount re-

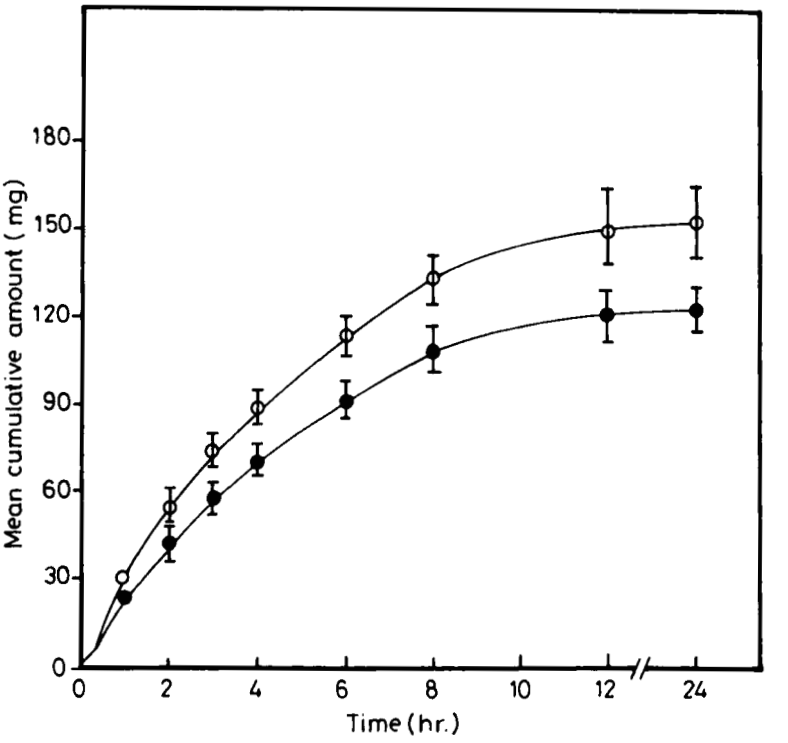

FIGURE 3
Mean cumulative urinary excretion of chloroquine phosphate after rectal and oral administration
Key : o Formulated suppositories.
● Commerical tablets.

leased from the formulated suppositories was about 60% of the administered dose while that amount was 48% from the administered dose in case of commercial tablets. It was observed that volunteers received suppositories showed urine peak level after 2 h while those administered the tablets showed peak after 3 h. This could be explained on the basis of the drug acidic nature, pK_a 8.3 and 10.2 (15) which retards its absorption from the stomach until the drug reachs the in-

TABLE 1

Effect of pH on the Partition Coefficient of Chloroquine Phosphate

pH	Partition Coefficient
1.2	0.667 ± 0.102
6.8	0.941 ± 0.131
7.9	5.333 ± 0.112

Average of four determinations

testine where complete absorption takes place gradually. In case of rectal administration absorption takes place directly from rectal mucosa to blood circulation.

In addition the partition coefficient study of the drug between organic and aqueous phases proved the higher absorbability of the drug at the pH of the rectum than at that of the stomach (Table 1).

Volunteers used the formulated suppositories did not suffer from any gastrointestinal irritation which was accompanying the oral administration of the drug.

The obtained findings indicate that the formulated suppositories could be considered as a suitable form for chloroquine phosphate administration especially in young patients suffering from malaria and hepatic amoebiasis.

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