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MULTIPARTICULATE ENTERIC COATED FORMULATION OF CHLOROQUINE PHOSPHATE FOR BETTER PATIENT COMPLIANCE

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ABSTRACT

Chloroquine is an excellent antimalarial as well as an antiamoebic drug. It is the first drug of choice in the treatment of malaria. Chloroquine is a highly bitter drug and the oral marketed tablet has serious distressing side effects like gastrointestinal irritation leading to nausea, vomiting and diarrhea. In the present study, an enteric coated formulation of chloroquine phosphate was prepared using Acrycoat L-100. Pellets of chloroquine phosphate were prepared using different concentrations of Acrycoat L-100, the enteric coating polymer and dibutyl phthalate (DBP) as plasticizer. The prepared pellets were evaluated for their flow properties, friability, true density, bulk density, SEM studies, content uniformity and *in vitro* release studies. The physical parameters were observed to give excellent flow properties. The spherical shape and coating uniformity was indicated in the scanning electron micrographs. The *in vitro* dissolution studies revealed that formulation batch **A6** (10% Acrycoat L-100 and 30% of DBP) as the best batch out of **A1-A6** batches as it showed a release of less than 9 % in the acidic medium and more than 80 % in the basic medium in 45 min. resulting in improved bioavailability and patient compliance.

Key words: Chloroquine phosphate, Multiparticulate, Enteric.

INTRODUCTION

An enteric coating is a barrier applied to oral medication that controls the location in the digestive system, where it is absorbed. Enteric refers to the small intensine and therefore, enteric coating prevents release of medication before it reaches the small intestine[1-3]. Coated multiparticulates, often referred to as 'pellets' or 'beads' commonly form the basis for a

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wide range of delayed and modified release dosage forms[4,5]. Chloroquine phosphate still remains one of the main drugs of choice to treat malaria. Chloroquine phosphate belongs to the 4-aminoquinoline class of compounds. It is used both in control of acute attack of vivax malaria and for suppression against all plasmodium except *P. falaciparum*. However, the dosage forms of chloroquine phosphate have reported distressing side affects like gastrointestinal irritation leading to nausea, vomiting and diarrhea[6,7]. Several studies have reported formulations of chloroquine phosphate, which includes a bitterless syrup using methacrylic acid-methyl methacrylate copolymer; tablets coated with cellulose acetate phthalate[8]. Acrycoat L-100 is an anionic polymer synthesized from methacrylic acid methyl ester. Acrycoat L films are colorless and transparent and somewhat brittle. These films are soluble in solutions above pH 6 indicating solubility in gastrointestinal region of the intestine[9-11]. Pelletization can be carried out by various techniques like; by using coating pans, fluid bed machines, centrifugal equipments, spheronizers and high shear mixers[12-14]. The advantages of pelletization include maximizing drug absorption, reducing peak plasma fluctuations, minimizing the dose of the drug and thus, reducing side effects without lowering the drug bioavailability[15,16]. In the present study, enteric coated multiparticles of chloroquine phosphate were prepared using the pan coating method; Acrycoat L-100 as the enteric coating polymer and evaluated.

EXPERIMENTAL

Materials and methods

Chloroquine phosphate and non-pariel seeds for pelletization was provided by Zim Labs, Kalmeshwar. Acrycoat L-100 was procured from Corel Pharma, Ahmedabad. Dibutyl phthalate, isopropyl alcohol and tribasic sodium phosphate were obtained from Merck. All other reagents were of analytical grade.

Preparation of pellets

Drug layering onto non-pariel seed

200 g of non-pariel seeds, which are normally made of sugar, were placed in the coating pan rotating at 15-20 rpm. Layering of the drug powder was carried out by first wetting the non-pariel seeds with sugar syrup of 33.33% w/w. This was then followed by addition of drug powder in the vortex of the pan. The drug powder was layered gradually using 10 g in each addition. This procedure was repeated till the drug powder (400 g) has been used up. The drug loaded pellets were dried at 45°C for 12 hours. These pellets were then sieved through a 20 mesh sieve to remove fines.[13,17,18]

Enteric coating of pellets

The drug layered pellets were again loaded into the coating pan rotating at a speed of 25-30 rpm. The entire solution of Acrycoat L-100 in isopropyl alcohol was gradually applied. The time consumed for the above process was 2-3 hours. The coated pellets were then dried at 45^{o}C for 12 hours. These enteric coated pellets were then sieved through a 14 mesh sieve to remove the agglomerates[1-3]. Six formulation batches **(A1-A6)** (Table 1) with varying coating solution composition were prepared, which include dibutyl phthalate (as plasticizer) concentration in the range from 10-30 % and Acrycoat L-100 concentration in the range from 5-10 %.

Table 1: Composition of different formulation batches (A1 - A6) with % drug release in 2 hr

Formulation code	Conc. of acrycoat L-100 (%)	Conc. of dibutyl phthalate (%)	% Drug release
A1	5	10	32.34
A2	5	20	25.01
A3	5	30	19.31
A4	10	10	16.71
A5	10	20	12.87
A6	10	30	8.15

Table 2: Physical parameters of pellets

	Angle of repose (^{o})	Friability (%)	True density (g/cm^2)	Bulk density (g/cm^2)
Coated pellets	21.51	0.00	2.067	1.243
Uncoated pallets	19.50	0.147	2.090	0.798

Evaluation

Evaluation of physical parameters of pellets

Pellet samples for these studies were taken after they were dried at 45^{o}C for 12 hrs.

Angle of repose

The flow property, which is an essential factor in automated processes such as tabletting and capsule filling, was measured by the frictional forces or angle of repose. It has been reported that materials giving an angle of repose, less than 25^{o} showed excellent flow property[22].

The frictional force in a loose powder can be measured by the angle of repose. It is determined by the funnel method. Angle of repose was determined by the following formula:

$$\text{Angle of repose} = \tan \theta \; 2\, h/D \qquad \ldots(1)$$

Where d is the diameter of pile and h is the height of pile.

Hardness

The hardness of the pellets is related to its friability. The values of friability from 0.8 to 1 % are regarded as the upper limit of acceptability[23].

True density

The true density is indicative of the extent of densification or compactness of substances. The bulk density is indicative of the packing properties of particles. Most of the pellets were filled into hard gelatin capsules volumetrically. If the density of pellets varies significantly from batch to batch, the potency of the finished capsule will also vary. It has been stated that the bulk density values less than 1.25 g/cm^3 indicate good flow and the values greater than 1.50 g/cm^3 indicate poor flow[23].

Scanning electron microscopy

Sample of pellet formulation were mounted onto the stubs using double-sided adhesive tape and then coated with gold palladium alloy (150-200 Å) using fine coat ion sputter. The samples were subsequently analyzed under the scanning electron microscopy (SEM) for external morphology.

Estimation of drug content

In order to assess the drug content uniformity, ten capsule units were assayed by standard method given[20].

In vitro release study

The drug release was estimated by using USP XXXI NF XXVI apparatus II[19]. For

delayed release formulations, dissolution was carried out in 2 stages, the acid stage and the buffer stage. In acid stage, 750 mL of 0.1 N hydrochloric acid was used as dissolution media at a temperature of 37°C ± 0.5°C and dissolution was carried out for 2 hrs at 100 rpm and estimated spectrometrically at 343 nm. In buffer stage, 250 mL of 0.2 M tribasic sodium phosphate (pH - 6.8 ± 0.05) was used as dissolution media at a temperature of 37 ± 0.5°C. The dissolution was carried out for 45 min at 100 rpm and the amount of the drug released was estimated spectrophotometrically at 343 nm.

Dissolution profiles were also obtained for marketed uncoated tablet (Resochin) and uncoated (drug layered) pellets in 0.1 N hydrochloric acid for 45 min.

RESULTS AND DISCUSSION

Evaluation of pellets

Angles of repose of 21.5^{o} and 19.5^{o} (Table 2) were obtained for the coated and uncoated pellets, respectively, which indicated excellent flow property of pellets. The friability values of the pellets were found to be much below the upper limit (0.8-1 %), which showed that seeds possess the necessary cohesiveness and hardness. Bulk density values less than 1.25 g/cm^3 suggested good flow property of the pellets (Table 2).

Estimation of drug content

The assay procedure was carried out on 10 capsules. Drug content uniformity was found to be within the specified potency range of 85 to 115 %.

Scanning electron microscopy

Scanning electron micrographs of enteric coated pellets are shown in Fig. 1. The spherical shape and coating uniformity of pellet was observed.

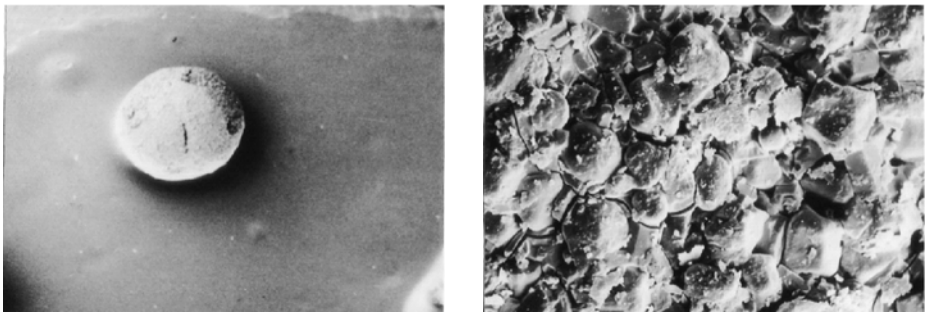

Fig. 1: Scanning electron micrograph of individual pellet and surface of pellet

In vitro release study

The dissolution studies in acid stage were carried out on all the formulation batches **(A1-A6)** prepared. The release of drug at the end of 2 hrs in 0.1 N hydrochloric acid for all the formulation batches **(A1-A6)** is shown in Fig. 2. Formulation batch **A6** (10 % of Acrycoat L-100 and 30 % of dibutyl phthalate) was selected as it fulfills the USP XXXI NF XXVI criteria for delayed release formulations, which states that not more than 10 % of the drug should be released at the end of 2 hours in 0.1N hydrochloric acid. The release pattern of this selected batch was further studied in buffer solution of pH 6.8 ± 0.05 and it was observed that 80.31 % of the drug is released in buffer at the end of 45 minutes (Fig. 3). This complies with the USP XXIII criteria, which states that more than 75 % of the drug should be released in the buffer solution of pH 6.8 within 45 minutes[19].

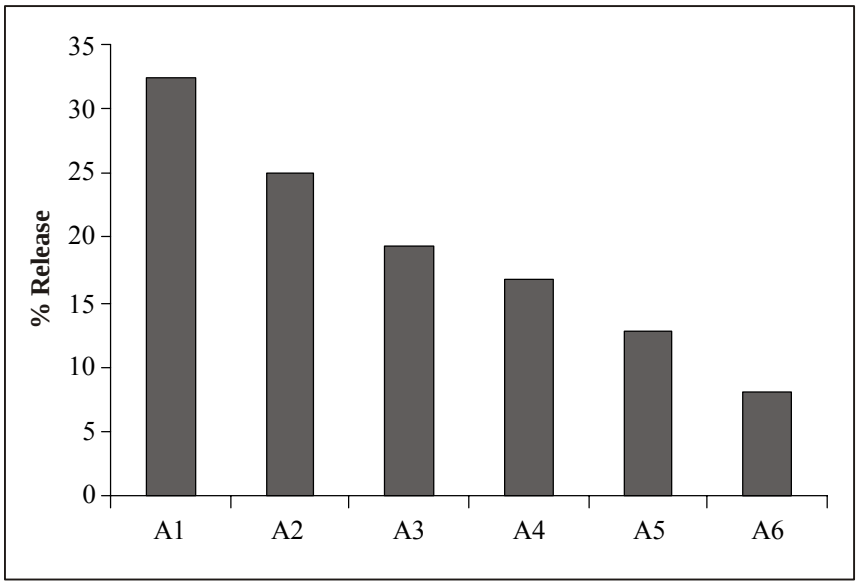

Fig. 2: % Drug release from formulation batches (A1 - A6) in 0.1 N HCl in 2 hr.

Dissolution profiles for the marketed uncoated tablet (Resochin) and uncoated (drug layered) pellets (provided by ZIM Labs) are shown graphically in Fig. 4. The uncoated pellets released the drug at a faster rate than the marketed tablet. This is because pellets disperse rapidly and due to their large surface area, the release of the drug is faster than from the tablet, whereas the marketed tablet takes some time to disintegrate before drug release. The enteric coated pellets (batch **A6**) showed only 8.75 % release in acid stage and 80.31 % release in buffer stage indicating a delay in the release of the drug until it reaches intestine. This may be due to intact nature of coating film of enteric polymer in gastric fluids and in

environment with a higher pH gradient i.e. intestine, solubility gradient for the polymer develop across the film, which leads to dissolution of coating film[21].

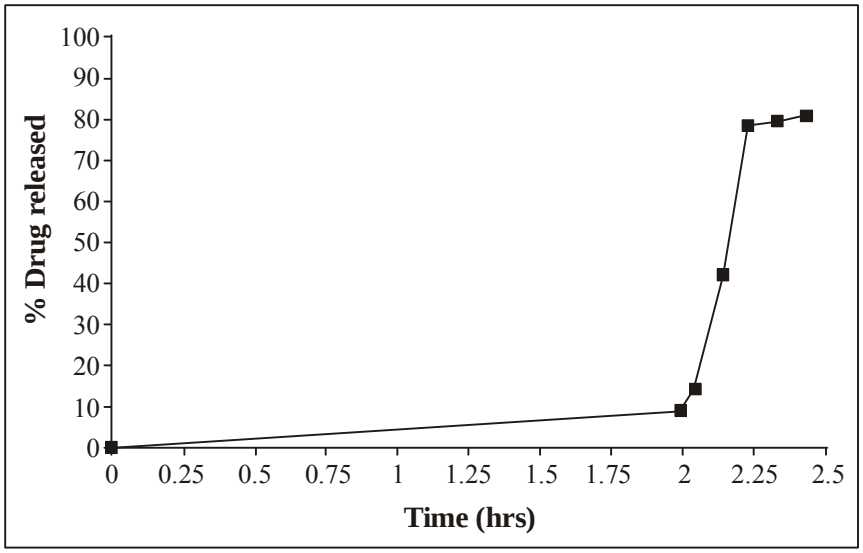

Fig 3: Dissolution profile of batch A6 in acid stage (0.1 N HCl) for 2 hr and in buffer stage (pH- 6.8 ± 0.05) for 45 min

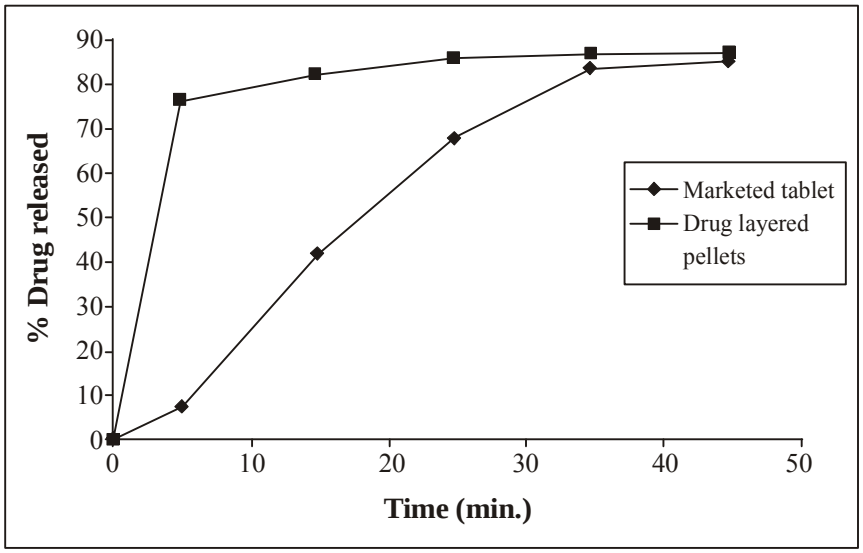

Fig 4: Dissolution profile of marketed uncoated tablet and uncoated drug layered pellets in 0.1 N HCl for 45 min

CONCLUSION

The enteric coated formulation batches **(A1-A6)** of chloroquine phosphate were prepared using different ratios of coating polymer and plasticizer. Batch **A6** complies well with the USP standards in terms of drug release (less than 10 % release in gastric fluids and more than 75 % in buffer stage). Pelletization proved to be beneficial as it leads to development of multiparticulate dosage form with increased patient compliance and improved bioavailability.

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