Formulation of Taste Masked Oral Suspension of Quinine Sulphate by Complexation

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Quinine sulphate is an antimalarial drug and is very much effective against resistant strains of *Plasmodium falciparum*, where other antimalarials like chloroquine, sulphadoxine-pyrimethamine are ineffective. But, it is a very bitter drug and taste should be masked to formulate it in a palatable form. So in the work undertaken, an attempt was made to mask the taste, by complexation technique using ion-exchange resins and to formulate into a suspension. The products were evaluated for bitterness, drug content, particle size, viscosity, sedimentation time and volume, redispersibility and drug release and also subjected to stability studies. Of the different resins, Indion 234 was found to be the most suitable one. The release studies showed complete drug release within 20 min. Stability studies indicated no appreciable changes in the above mentioned parameters for 3 months.

Taste masking of bitter drugs has been found to improve the quality of treatment, especially in paediatrics. Various techniques are available[1] to mask the bitter taste or to improve the taste, such as, by using polymeric coatings, complexation with cyclodextrins and ion exchange resins, salt formation and use of excipients like flavours and sweeteners. Ion exchange resins have been increasingly used for this purpose. Indion 234 has been successfully used to mask the bitter taste of chloroquine phosphate[2]. Indion 204 was successfully used to mask the bitter taste of norfloxacin[3]. Quinine sulphate is a very bitter drug and taste masking becomes an important consideration in the formulation of its oral suspension. So the present work was chosen with objective of studying complexation of quinine sulphate with certain ion exchange resins such as cross linked polyacrylic copolymers (Tulsion 339, Tulsion 335), co polymers of acrylic acid and methacrylic acid (Indion 204, Indion 234), and to utilize the same in the formulation of taste masked suspension.

The formulation was carried out in three steps, i.e., forming the drug-resin complex, preparation of the base, and then the final suspension. The drug and the resin were taken in the ratios varying from 1:1 to 1:6. The slurry of the resin was made in 50 ml of demineralised water to yield a strength of 2-12% of resin and stirred for half an hour .The drug, as a solution in 0.1 N HCl was added slowly under stirred conditions to yield a concentration of 2%. Stirring was continued for 6-8 h. The mixtures were kept aside to allow the particles to sediment and filtered. The residue is washed with 0.1 N HCl. The concentration of the free drug in the filtrate is measured spectrophotometrically at 345 nm after suitable dilution. From the absorbance values, the amount of uncomplexed drug and then % amount complexed were calculated.

Bitterness evaluation was performed to compare bitterness of the drug-resin complex to that of quinine sulphate used in the formulation and to that of the standard quinine hydrochloride using a method prescribed by WHO[4], which was originally used to evaluate bitterness of medicinal plants. A series of concentrations of quinine sulphate, quinine hydrochloride and drug-resin complex were prepared and subjected to bitterness evaluation test and the bitterness threshold concentration was determined. Using this concentration, bitterness value was calculated.

Ingredients used for the bases were diglycero-digluco

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polyglyceride or sugar or sorbitol as sweetening agents, carbopol or xanthan gum or sodium carboxymethylcellulose as suspending agents, along with glycerin, menthol, aspartame as additional excipients for improving the taste with flavours like pineapple flavour, mixed fruit flavour, appropriate colours like erythrosine and tartrazine and preservatives like Nipagine and Nipasol.

Three different formulae were used for the base. The first formula contained diglycero digluco polyglyceride (30%) with carbopol (1.5%), honey and butterscotch flavour (q.s.). The second formula included sugar (70%) with zanthan gum (1.5%) and raspberry flavour (q.s.). The third contained sorbitol (15%), with sodium carboxymethylcellulose (1.5%) and mixed fruit flavour (q.s.). Glycerine (5%), menthol (0.4%), aspartame (0.5%) Nipagin (0.1%), Nipasol (0.2%) and colour were common ingredients in all the three formulae.

The final product was prepared by mixing the drug-resin complex in 500 ml of the base under constant stirring, for 1 h. pH was adjusted to a value between 7.5-8. Then the mixture was passed through a colloid mill to reduce particle size. Appropriate flavours were added. pH was checked. The strength of product formulated was 100 mg/5 ml.

The prepared suspensions were subjected to evaluation tests[5]. They were given to a group of 50 individuals and their response towards the taste was noted, as the initial qualitative evaluation of masked bitterness. Based on the results of this, the best two products were selected and taken up for further evaluation. Bitterness value was used to quantitatively express the extent of masking of bitterness. It was calculated based on bitterness threshold concentration, which was determined for the products in comparison with quinine sulphate and quinine hydrochloride, as per the method mentioned earlier[4].

Optical microscopy was carried out to study the size and shape of the suspended particles. Viscosity studies were carried out using a Brookfield viscometer (model IDREQ 1-087) with spindle No. 2. Viscosity was measured at rpm ranging from 30-200, at room temperature.

Both the products were kept undisturbed in graduated cylinders and sedimentation time was observed. Sediment formed was shaken moderately to check redispersibility. The pH of final product was checked using a pH meter. Five millilitres of the suspension was treated with 100 ml of 0.1 N HCl and kept for 1 h shaking intermittently, to dissociate the drug from the complex. Then the solution was filtered and the drug concentration in the filtrate was measured spectrophotometrically.

Paddle type USP XXII dissolution test apparatus was used for studying the *in vitro* drug release. The rpm was set at 100. Medium used was 900 ml of 0.1 N HCl. Samples withdrawn were measured spectrophotometrically at 345 nm. The drug released was calculated, from the absorbance values.

Stability studies were carried out at three different temperatures 8°, room temperature, and 45°, for three months, to evaluate the stability under extremes of climatic temperature changes. During this period, both the products were evaluated for the above parameters at an interval of one month.

Results of evaluation revealed that ion exchange resin Indion-234 in drug to resin ratio of 1:4 and mixing time of 7 h was found to complex the drug to the maximum extent (99.1%). Bitterness value was also reduced by 100 times for the same. The complex with Indion-234 was hence selected for formulation into suspension and was incorporated into glyceride base, sugar base, and sorbitol base.

Among these products, the products formulated using glyceride base and sugar base were found to suppress the bitterness to the maximum extent as shown by results of qualitative evaluation i.e. in a group of 50 individuals, all 50 expressed no feeling of bitterness in product with glyceride base, where as 48 expressed no feeling of bitterness in product with sugar base, and hence these two products were subjected to further evaluation.

Results of evaluation of bitterness indicated complete masking of bitterness in the two products because, no bitterness was felt in both the products, and hence the bitterness threshold concentration was considered to be more than the concentration of drug in products. This implies that bitterness value is reduced by more then 100 times, when compared to standard quinine hydrochloride and pure quinine sulphate.

Drug content was found to be 104 mg/5 ml and 103 mg/5 ml for gleceride base and sugar base suspensions respectively, which lie within the limits specified by IP (95-105%) for quinine sulphate tablets. Particles were found to be irregular in shape and therefore approximate average particle size was determined which ranged between 130-140 mm and 125-135 mm for glyceride and sugar base products respectively. Complete settling occurred in 1 or 2 d with

sedimentation volumes of 0.54 and 0.42, the sediment formed being easily redispersible on moderate shaking. The viscosity for both the products was found to decrease, with increasing rpm as shown in fig. 1, indicating pseudoplasticity, which is desirable for a good suspension. The complexation of drug with ion exchange resin did not appreciably delay the drug release, as 100% drug release could be achieved in 20 min.

All the products, except the product with glyceride base, showed no considerable changes during storage at different temperatures for three months with respect to different parameters especially masked bitter taste. The product with glyceride base, showed decreased drug content and slower drug release, when stored at 8°. This may be due to increased viscosity and hence, incomplete redispersion, with moderate shaking, indicating that storage at about 8° is not recommendable for that suspension.

To conclude, complexing with the ion exchange resin Indion-234 and then, formulating into a suspension with sugar or glyceride base has shown promising results towards masking of bitter taste of quinine sulphate, without affecting its release after administration. This method being simple, reproducible, and safe without involving harmful organic solvents, requiring minimum excipients makes it very acceptable for the formulation of a cost effective product.

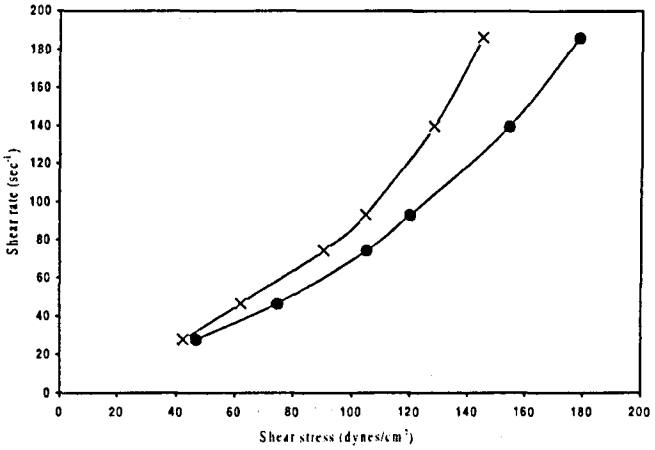

Fig. 1: Rheograms of selected suspensions.

Rheograms of selected suspensions, with gleceride base (-●-) and with sugar base (-x-) at rpm ranging from 30 to 200, at room temperature.

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