

ORAL SUSPENSION FORMULATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to pharmaceutical liquid suspension formulations suitable for oral administration, more particularly to liquid suspensions that remain homogeneous during prolonged storage.

2. Description of Related Art

The most convenient and commonly employed oral drug formats are solids such as tablets and capsules. Many children and some adults however have difficulty swallowing solid dosage formats, and in this case, the drug is given in liquid form, either as syrup or suspension.

Drugs are formulated as suspensions for different reasons, but the most common one is poor drug solubility. Suspensions may also be used to mask the poor taste resulting from the dissolved drug in solution. A suspension, however, unlike syrup in which the drug is fully dissolved, requires adequate shaking of the container to resuspend the drug uniformly before dosing. Difficult redispersion of the drug from a sediment, or in the worst case, from caking, will result in under- and overdosing. This problem of variable dosing is also encountered when the patient or the caregiver forgets to shake the container before dosing. It is therefore desirable to produce a suspension that is able to maintain its homogeneity on prolonged storage without shaking.

Stoke's law defines the sedimentation rate of a sphere in a fluid as:

$$v = \frac{D^2(\rho_P - \rho_L)g}{18\mu} \quad (1)$$

where

v=sedimentation rate

D=mean particle diameter

ρ_P =particle density

ρ_L =liquid density

g=acceleration due to gravity

μ =viscosity of the liquid phase

The above equation indicates that the rate of sedimentation can be reduced by minimizing the density difference between the suspended particles and the liquid phase, reducing the particle size, and increasing the viscosity of the liquid phase.

If the densities of the suspended particle and the liquid phase are the same, sedimentation will not occur. In practice, precise matching of the densities is not always possible. The drug density may be too high, or the amount of density increasing ingredients may be too great.

Reducing the particle size is another way of slowing sedimentation. However, small particles tend to cake more severely because of the increased surface energy from the larger surface area, making redispersion much more difficult and sometimes impossible.

Small particle size is desirable for reasons other than slowing the rate of sedimentation. For drugs that are not very soluble, smaller particles generally dissolve faster due to the increase in the total surface area, which can in turn enhance bioavailability. Also, smaller drug particles are less likely to cause grittiness, which improves the palatability of the finished product. There is therefore a need for a suspension containing fine particles, hereafter referring to an average

particle size less than about 20 μm , which will not cake on storage, but in addition is able to maintain its homogeneity on prolonged storage without shaking.

The most popular approach to slowing the sedimentation rate is by increasing the viscosity through the addition of a suspending agent. Excessive viscosity is undesirable, however, if it interferes with pouring and redispersion of settled particles.

As described in the book *Pharmaceutical Dosage Forms: Disperse Systems Volume 2*, Second Edition, New York, 1989, pages 234-236, yield value is an important mechanism of permanent suspensions. The theoretical yield value (Y) must balance or exceed the force of gravity on the settling particles. For spherical particles:

$$Y = \frac{2}{3\pi}(\rho_P - \rho_L)Dg \quad (2)$$

Other than providing a general guideline of introducing a yield value to the dispersion medium, this prior art is unclear on what combinations of particle size, yield value, and density difference will produce a suspension of fine particles that maintains its homogeneity for prolonged period.

The prior art has shown extensive use of combinations of suspending agents to promote redispersability. U.S. Pat. No. 4,975,465 discloses a tastemasked ibuprofen suspension comprising a suspending base of xanthan gum, microcrystalline cellulose, sodium carboxymethylcellulose and polysorbate 80. U.S. Pat. Nos. 5,272,137 and 5,409,907 teach the use of xanthan gum and microcrystalline cellulose to minimize sedimentation. U.S. Pat. Nos. 5,374,659 and 5,621,005 provide easily redispersable pharmaceutical suspensions using xanthan gum, pregelatinized starch and polyoxyethylene sorbitan monooleate. U.S. Pat. No. 5,658,919 discloses the use of xanthan gum, a mixture of microcrystalline cellulose and sodium carboxymethylcellulose, and an auxiliary suspending agent selected from hydroxyethylcellulose and a salt of carboxymethylcellulose to minimize sedimentation of paracetamol suspensions. U.S. Pat. No. 5,712,310 provides easily redispersable suspension base comprising a water-soluble modified starch, a water-soluble hydrocolloid polysaccharide, and a water-soluble wetting agent. U.S. Pat. No. 5,759,579 provides a liquid suspension base comprising xanthan gum and hydroxypropyl methylcellulose. None of these patents discloses a storage stable suspension that remains homogeneous for prolonged period of time without shaking.

U.S. Pat. No. 5,112,604 assigned to Riker laboratories discloses an aqueous pharmaceutical suspension containing large particles of coated sustained-release theophylline, wherein the drug is maintained in suspension for prolonged period. The suspending base comprises a hydrocolloid gum, colloidal silicon dioxide, a carbohydrate, and a wetting agent. This prior art does not teach how particle size, density difference, and yield value can be combined to produce a suspension of fine particles that maintains its homogeneity for prolonged period.

SUMMARY OF THE INVENTION

The present invention provides an aqueous pharmaceutical suspension for oral administration comprising at least one particulate drug with a density of from about 0.9 to about 1.6 g/ml and an average particle size of less than about 20 μm ; at least one suspending polymer exhibiting plastic