Trissel's™ Stability of Compounded Formulations

5th Edition

Lawrence A. Trissel

American Pharmacists Association®
Improving medication use. Advancing patient care.
APhA

Ibuprofen

Properties

Ibuprofen is a white or nearly white crystalline powder or colorless crystals having a slight characteristic odor.[2,3]

Solubility

Ibuprofen is practically insoluble in water; with a solubility of less than 0.01 mg/mL, but is very soluble in ethanol.[2,3,7] It will dissolve in dilute aqueous solutions of alkali hydroxides and carbonates.[3]

pH

Ibuprofen oral suspension has a pH between 3.6 and 4.6.[4]

pK_a

Ibuprofen has a pK_a of 4.43.[7]

General Stability Considerations

Ibuprofen products should be packaged in well-closed, light-resistant containers and stored at controlled room temperature.[2,4,7]

Using accelerated degradation at 70°C and 75% relative humidity for three weeks, Cory et al.[1621] found that the degradation of ibuprofen in commercial tablets was accelerated when polyethylene glycol or polysorbate 80 was included among the tablet excipients. If either of these excipients was not present in the formulation, ibuprofen degradation did not occur under these conditions.

Stability Reports of Compounded Preparations

Oral

STUDY 1: Devi and Rao[537] evaluated various formulation approaches to preparing an oral elixir of ibuprofen containing 100 mg/5 mL. Cosolvent formulations incorporating glycerol, D-sorbitol, propylene glycol, and ethanol in concentrations ranging from 20 to 100% were tested. Ibuprofen solubility increased in propylene glycol and ethanol as the concentrations increased up to about 80%. Glycerol solutions effected a much more modest improvement in solubility, as did D-sorbitol in the range of 20 to 40%. The authors prepared elixirs of ibuprofen using various combinations of cosolvents. Ibuprofen powder was triturated in a clean dry mortar and pestle with a small amount (0.1%) of polysorbate 80 (Tween 80) to aid in wetting the powder. Saccharin sodium 0.1%, sodium benzoate 0.2%, and tartrazine for color were dissolved in a small amount (unspecified) of water. Banana flavor was dissolved in a mixture of ethanol 15% and propylene glycol 60%, and the aqueous colored preservative solution was incorporated into it. The mixture was added to the mortar contents and triturated until a clear solution resulted. Sorbitol 70% could be substituted for water, also resulting in a clear solution.

Devi and Rao[537] found that other combinations of solvents also resulted in clear solutions. The following solvent concentrations, with the balance being sorbitol 70%, were all clear solutions:

Ethanol	Propylene Glycol
44%	30%
34%	40%
28%	44%
25%	50%

However, if chocolate flavor was substituted for banana flavor, a precipitate formed in the elixirs.

STUDY 2: Martin-Viana et al.[1420] evaluated the physical and chemical stability of an ibuprofen 20-mg/mL oral suspension for pediatric use. The oral suspension was prepared using ibuprofen powder with unspecified "auxiliary substances in common use in the pharmaceutical industry." Samples of the oral suspension were packaged in amber glass bottles and stored at room temperature of 28 to 32°C protected from exposure to light for 24 months and at elevated temperature of 40°C and 75% relative humidity for accelerated testing over

six months. The oral suspension was a white viscous liquid with a pH near 3.8. At both storage conditions no physical changes were observed and the pH remained essentially unchanged. HPLC analysis of the ibuprofen concentration using the USP HPLC method found no ibuprofen loss in six months at elevated temperature and less than 3% loss in 24 months at room temperature.

STUDY 3: Burgalassi et al.[1537] evaluated the sedimentation rates of several oral liquid suspension formulations of ibuprofen 10 mg/mL using four different suspending mediums: (1) hydroxypropyl methylcellulose 1%, (2) microcrystalline cellulose 1.5%, (3) carboxymethylcellulose 2.5%, and (4) carrageenan iota 1%. The best suspensions with the slowest sedimentation rates were obtained using microcrystalline cellulose 1.5% and carrageenan iota 1%. The chemical stability of ibuprofen was not tested.

Injection

Injections, like other sterile drugs, should be prepared in a suitable clean air environment using appropriate aseptic procedures. When prepared from nonsterile components, an appropriate and effective sterilization method must be employed.

STUDY 1: Jain and Jahagirdar[538] evaluated ibuprofen 40-mg/mL injections solubilized with concentrations of sodium benzoate ranging from 5 to 35% (wt/vol). Ibuprofen solubility was improved 68-fold at the 35% sodium benzoate concentration; 30 and 35% concentrations were chosen for further evaluation. The required amount of ibuprofen powder was weighed and added to 150 mL of each concentration of sodium benzoate vehicle in 250-mL flasks along with 0.1% sodium metabisulfite and 0.01% edetic acid (EDTA). The flasks were mechanically shaken for two hours to ensure complete dissolution, and the solutions were aseptically filtered into sterile 10-mL glass ampules that were pull sealed. Sample ampules were stored at 8, 37, and 45°C. About 7% ibuprofen loss occurred in 28 days at 8°C. At the elevated temperatures, unacceptable losses were found after storage for 15 to 22 days. Physical stability of the solutions was good, with no color change or particulate matter observed. Both formulations produced analgesia in mice after 10-fold dilution in sterile water and an intraperitoneal dose of 100 mg/kg.

STUDY 2: Devi and Rao[537] also speculated that an ibuprofen injection might be possible using cosolvents. Ibuprofen solubility was 140 mg/mL in a mixture of ethanol 50%, propylene glycol 20%, and water. Ibuprofen solubility went up to 300 mg/mL in a mixture of ethanol 50%, propylene glycol 30%, and water. However, actual preparation and testing of such injections was not reported.

STUDY 3: Cao et al.[996] reported the formulation of ibuprofen injection for veterinary use. The formulation contained polyethylene glycol, ethanol, sodium carbonate, EDTA sodium, and sodium bisulfite in water for injection. No color change and about 2% ibuprofen loss was found after storage for three years at room temperature.

STUDY 4: Yeh and Wang[1514] developed a nonaqueous injection formulation of ibuprofen 50 mg/mL. Ibuprofen powder was solubilized in a vehicle composed of an equal parts mixture of propylene glycol and N,N-dimethylacetamide and packaged in type I glass vials. The samples were stored at temperatures of 40, 50, and 60°C for 91 days. Visual examination found no color change or precipitation. HPLC analysis of ibuprofen decomposition at the elevated temperatures was used to calculate the time to 10% decomposition (t_{90}). The t_{90} at 25°C was calculated to be 1180 days or over three years. ■