Narcotic analgesic

PHARMACEUTICALS INDIA
ACTIVE PHARMACEUTICAL INGREDIENTS
TAJ GROUP

PRODUCT CODE- MPSTJ278

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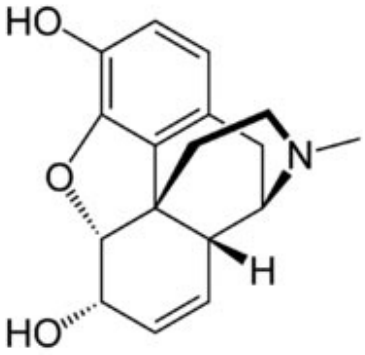
TAJ PHARMACEUTICALS LIMITED

MORPHINE SULPHATE

Formula C17H19NO3
Cas No. **64-31-3**

Systematic (IUPAC) name (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol



Morphine sulphate
Chemical data
Formula **C17H19NO3**
Mol. mass **285.34**
Pharmacokinetic data
Bioavailability **~25% (oral); 100% (IV);**
Protein binding **30–40%**
Metabolism Hepatic 90%
Half life **2–3 h**
Excretion Renal **90%, biliary 10%**

DRUG DESCRIPTION

Morphine sulphate Cas No. 64-31-3

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Morphine sulphate in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate

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Testing Frequency

According to ICH requirements, chemical and physical tests were performed on three batches after 3, 6, 9, 12, 18, 24, and 36 months for long-term studies (25°C) and after 3 and 6 months for accelerated studies (30° and 40°C). Water loss from two batches was determined after 3, 6, 12, 24, and 36 months of storage for long-term studies and after 3 and 6 months for accelerated studies. Sterility was tested at time 0 and after 6 and 36 months of storage.

Physical Stability Assessment

The physical stability of the samples was assessed by visual examination and by measuring the subvisible particle content with a light obscuration particle size counter (Model 9700, Hiac-Royco, Division of Pacific Scientific Company, Silver Spring, Maryland). The protocol used was that of the *United States Pharmacopoeia*

Materials

Three batches of 1-mg/mL morphine sulfate solution (Lots 01032100, 01032101, and 01112368) in PP bags (Polimoon Langeskov) were used for this study.

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Results and Discussion

Physical Stability Evaluation

All the test samples remained free of visible particles and practically colorless throughout the study. Electronic evaluation of the subvisible particles after 6 months of storage at 25°, 30°, and 40°C indicated that the total number of particles was below the pharmacopeial
specifications (Table 1).
There was no significant change in either pH or osmolality of the samples in the stability studies.
At the start and end of 36 months of
storage, the pH and the osmolality of the samples were within the
ranges 4.3 to 4.5 and 285 to 300 mOsm/kg, respectively.
The water losses were low at 25°C, 1.5% after 36 months of storage.
The water losses at 30°C were higher than those at 40°C; this
difference probably was due to the lower relative humidity at 30°C
(60% ± 5%) than at 40°C (75% ± 5%) (Table 2).

Chemical Stability Evaluation

Morphine

Little or no morphine loss occurred in any of the samples at any storage temperature throughout the study (Table 3). The increase in concentration of morphine due to vehicle evaporation was minimal even after 6 months of storage at the elevated temperatures of 30°C and 40°C.

Related Substances

The stability of morphine in aqueous solution has been investigated by Yeh et al.[23] They claimed that pseudomorphine and morphine-N-oxide are the main oxidation products and that these products probably degrade further. The determination of these degradation products is not required by *USP*.[22] No data are available concerning the activity or toxicity of morphine- N-oxide in man. Vermeire et al reported that a nontoxic level of morphine-N-oxide is 1.3%.[17] A reasonable specification for this product is not more than 1%. The concentration of morphine-Noxide was found to be about 0.14% of that of morphine sulfate after
36 months of storage at 25°C (Table 4). Similarly, no data are available concerning the activity or toxicity
of pseudomorphine in man. For intrathecal use, according to Caute et al[24] and Sitaram et al,[25] pseudomorphine is not toxic at a concentration of 1%. Vermeire et al reported a nontoxic level of 2% of
pseudomorphine.[17] For morphine in plastic syringes, Hung et al reported a nontoxic concentration of 5% of pseudomorphine after 33 weeks of storage.[26] **Based on these toxicology data, the limits for pseudomorphine were set to not more than 3%. The mean concentration of pseudomorphine in bags stored at 25°C after 36 months was 0.9% relative to that of morphine sulfate (Table 5)**

Microbiological Stability Evaluation

Results of all sterility tests were negative, demonstrating that the
product was sterile even after 36 months of storage.

Conclusion

Morphine sulfate solution at **1 mg/mL in a 100-mL PP bag can be produced for long-term storage by using terminal sterilization.** Three industrial batches stored for 36 months at 25°C showed excellent physical stability and practically no loss in morphine concentration. Levels of the degradation products morphine-N-oxide and pseudomorphine were well below the acceptable limits. Although morphine solution in aseptically **filled PVC bags could remain stable over the short term, long-term stability is not feasible because of problems associated with autoclaving and evaporation problems from PVC. This study reflects hospital pharmacists' interest in using newer packaging materials such as PP. Collaboration between a hospital pharmacy and a pharmaceutical manufacturer has led to development of a stable and safe productthat can be stored under normal conditions for at least 3 years for use with PCA pumps in both the operating theater and recovery room. The preparation has been used for 3 years in the surgical, obstetric, and pediatric departments of the University Hospitals of**
Geneva with complete acceptance by hospital workers. Their satisfaction probably results from reduction of manipulation and calculation errors (in stress situations), elimination of potential bacterial contamination, and diminished workload.

HPLC Parameters for Chemical Stability Analysis

Wavelength: 254 nm
Column: Nucleosil C_{18} AB (5 µm), stainless steel col
umn 250 x 4.6-mm internal diameter with
precolumn (Machery-Nagel, Oensingen,
Switzerland)
Mobile phase: A/B/C 375/15/610 mL
A: Acetonitrile for HPLC (Carlo Erba
Reagenti SRL, Val de Reuil, France)
B: Acetic acid glacial for analysis (Carlo
Erba Reagenti SRL)

C: 610 mL of distilled water containing 1.442 g of sodium dodecyl sulfate, purity ≥ 99% (Fluka Chemie GmbH, Buchs, Switzerland) and 6.166 g of ammonium acetate, purity ≥ 99% (Fluka Chemie)
Column temperature: 25°C
Flow rate: 1.0 mL/minute
Volume injected: 20 µL
Duration: 20 minute
Test solution: Dilute a quantity of the injection with suffi cient water for injection to produce a solution containing **0.1% w/v of anhydrous** morphine sulfate
Standard solution: **Aqueous solution of 0.1% w/v of morphine sulfate**
Resolution standard: Aqueous solution containing 1 mg/mL of morphine sulfate and 25 µg/mL of codeine phosphate hemihydrate

Stability of Morphine Sulfate in Polypropylene Infusion Bags for Use in Patient-Controlled Analgesia Pumps for Postoperative Pain Management

Storage Conditions

The three batches of 1-mg/mL morphine sulfate were stored according to International Conference on Harmonisation (ICH) Guidelines[21] **(i.e., 25° ± 2°C, 60% ± 5% relative humidity for longterm studies; 30° ± 2°C, 60% ± 5% relative humidity and 40° ± 2°C, 75% ± 5% relative humidity for accelerated studies).**

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91 022 30601000.
This leaflet was prepared by
Taj Pharmaceuticals Limited,
Mumbai (India).
MPSTJ278
Last revised: 29 August 2009