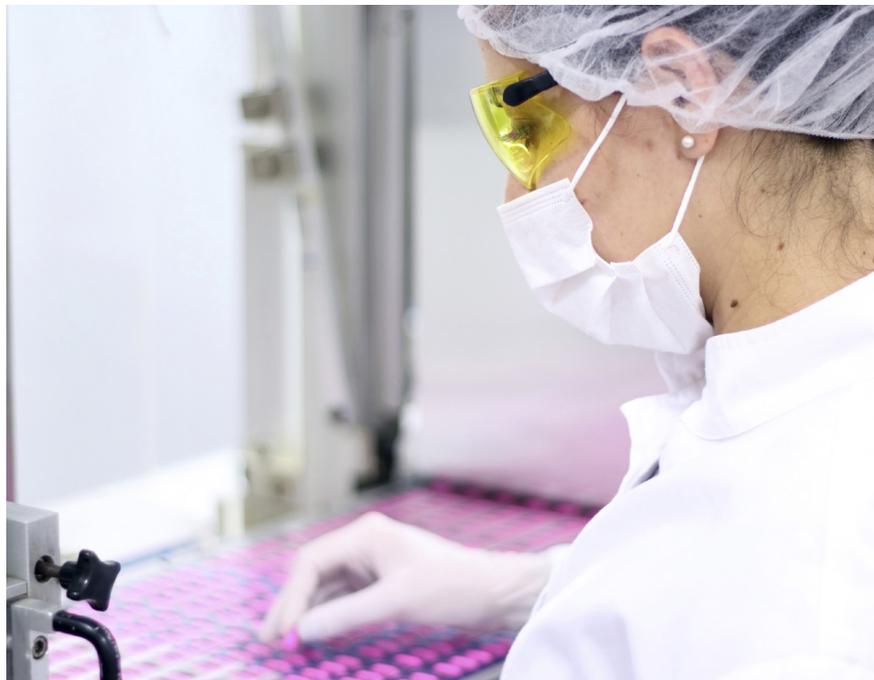




ANGUS[®]
LIFE SCIENCES



Key Performance Advantages

Provides chemical stabilization in aqueous formulations

Mild alkalinity for buffering at physiological pH

Exhibits minimal salt effects

angus.com

TRIS AMINO™

For use as an excipient in pharmaceutical applications

TRIS AMINO™ (tromethamine; 2-amino-2-hydroxymethyl-1,3-propanediol) is a four-carbon compound containing both hydroxyl and amine functional groups. The most notable uses of tromethamine are in the pH buffering of enzymes for both biotechnology and industrial applications, and in the purification of biological molecules, such as monoclonal antibodies, recombinant proteins and insulin for medical applications. In finished dosage forms, tromethamine is commonly found as an excipient in biologics and small molecule drugs formulated as parenteral drug products. It has also been included in ophthalmic solutions and topical drug products, mainly for its buffering and neutralization action.

Tromethamine is described in monographs of all major pharmacopoeial references, including the USP, EP, JPC and BP. Other common synonyms of tromethamine include Tris, trometamol and THAM. TRIS AMINO™ ULTRA PURE (USP/EP/JP) is the pharmaceutical grade of tromethamine produced by ANGUS Chemical Company (ANGUS). This multi-compendial grade of material simultaneously fulfills all the requirements contained in the monographs of the USP, EP and JPC, which fulfills the broad needs of any pharmaceutical formulator.

Chemistry of tromethamine

Tromethamine is a low molecular weight amine that possesses water, alcohol and glycol solubility. This can be attributed to the 3 hydroxyl groups and a primary amine group in the molecule (Figure 1). The primary amine is weakly basic with a pK_a value of 8.05 at 20°C. When combined with its hydrochloride salt at a molar ratio of 1:3, tromethamine functions effectively as a physiological buffer, with pH between 7.3–7.5. Tromethamine exists as solid white crystals under ambient conditions and is virtually non-hygroscopic and non-volatile. In contrast, other low molecular weight amines either exist as volatile liquids due to their low melting points, or are supplied in concentrated forms due to their extreme hygroscopicity. As a result, tromethamine exhibits better physical stability on storage/handling and is a versatile excipient suitable for solid, semi-solid and liquid dosage forms.

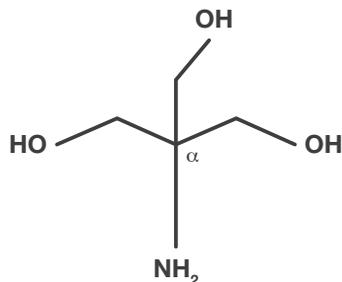


Figure 1. Molecular structure of tromethamine.

Tromethamine is a primary amine that has a fully substituted α -carbon. This confers it chemical stability.

Several chemical properties of tromethamine render it more favorable than other pharmaceutically acceptable amines. One critical feature of tromethamine is the full substitution of the α -carbon adjacent to the amine group. This prevents oxidation at that site, a reaction that would lead to degradation/fragmentation and color development. In most other organic amines, abstractable hydrogen atoms (lack of full substitution) often results in slow development of a yellow color in a formulated product.

The enhanced chemical and physical stability of TRIS AMINO make it amenable to steam sterilization. Due to its weak basicity, it is also less corrosive to manufacturing equipment and safer to handle when compared to the inorganic bases.

Multifunctional characteristics of TRIS AMINO in pharmaceutical products

The various functions of tromethamine in small molecule drug products include:

- Buffering agent in both small and large volume parenterals
- Neutralization of carbomer polymers in topical gels or creams
- Enhancement of antimicrobial action in contact lens solutions
- Emulsifier when combined in situ with fatty acids
- Formation of API salts to enhance solubility and bioavailability
- Stabilization of API in tablet formulations by inhibiting acid-catalyzed degradation

Tromethamine is an ideal neutralizer in carbomer gels that use low molecular weight alcohols as co-solvents for drug molecules (Table 1). Carbomer salts of tromethamine exhibit greater compatibility with alcohols compared to the inorganic bases. Tromethamine also contributes less to the overall ionic strength of the system—a factor known to disrupt gelling behavior.

PERFORMANCE ADVANTAGES OF TROMETHAMINE AS A NEUTRALIZER IN HYDRO-ALCOHOLIC CARBOMER GELS¹

Tromethamine	Inorganic bases (NaOH, KOH)
Viscous gels formed when up to 60% (w/w) of ethanol added	No gelling action, with precipitate formation, when ethanol content > 30-40% (w/w)
No incompatibility between cation and carbomer, gels exhibit higher viscosities	Incompatibility of cation (Na ⁺ and K ⁺) and carbomer, leading to lower gel viscosities
Excellent gel clarity up to 60% (w/w) ethanol and stable pH within 24h of gel preparation	Poor gel clarity and unstable pH within 24h of gel preparation, especially when incompatibilities are present
Buffering action in pH range of 7-9	No buffering action from cationic species

¹Carbomer studied was Carbopol® 940 and pH of gels were adjusted to approximately 7.0

Safety and tolerability of tromethamine

The widespread use of tromethamine in parenteral products is a testament to its excellent safety profile and tolerability. It is also compatible with different routes of administration/dosage forms, including the oral solid/solution, topical/transdermal gel and cream, nasal spray, nebuliser solution and mouth spray. A growing safety concern, originating from the cosmetic and food industries, is the potential toxicity of nitrosamines found in consumer products. Nitrosamine formation is mainly linked to secondary amines, regardless of their presence as an ingredient or as a trace impurity. The primary amine group, as well as the lack of abstractable hydrogen atoms on the α -carbon, are two important chemical features of tromethamine that allow formulators to avoid such concerns.

Manufacturing, traceability and supply of TRIS AMINO

ANGUS has more than 60 years of experience in the manufacturing of TRIS AMINO for both life sciences and industrial applications. TRIS AMINO is manufactured in ISO 9001:2008-certified facilities in the U.S. using cGMP-compliant manufacturing processes. As the world's only fully integrated manufacturer of TRIS AMINO, ANGUS provides customers with complete and transparent traceability from the starting raw materials to the final excipient, all from a single production site—a key requirement for manufacturers of pharmaceutical products. ANGUS is committed to maintaining a consistent global supply, both in quantity and quality, to pharmaceutical manufacturers.



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