

HANDBOOK OF  
**PHARMACEUTICAL**  
**EXCIPIENTS**

THIRD EDITION



**APhA**  
American  
Pharmaceutical  
Association



EDITED BY

**ARTHUR H. KIBBE**

OUTDATED

Dr. Reddy's Laboratories, Ltd., et al.  
v.  
Helsinn Healthcare S.A., et al.  
U.S. Patent No. 8.729.094

RECEIVED  
AUG 07 2001

Enter your name

LDLK&M  
LIBRARY  
600 SOUTH AVE. WEST  
WESTFIELD, NJ 07090

Published by the American Pharmaceutical Association  
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA  
www.aphanet.org  
and the Pharmaceutical Press  
1 Lambeth High Street, London SE1 7JN, UK  
www.pharmpress.com

© 1986, 1994, 2000 American Pharmaceutical Association and Pharmaceutical Press

First edition 1986  
Second edition 1994  
Third edition 2000

Printed in the United States of America

ISBN: 0-85369-381-1 (UK)  
ISBN: 0-917330-96-X (USA)

**Library of Congress Cataloging-in-Publication Data**

Handbook of pharmaceutical excipients / edited by Arthur H. Kibbe.--3rd ed.  
p. ; cm.

Includes bibliographical references and index.

ISBN 0-917330-96-X

1. Excipients--Handbooks, manuals, etc. I. Kibbe, Arthur H. II. American  
Pharmaceutical Association.

[DNLM: 1. Excipients--Handbooks. QV 735 H236 2000]

RS201.E87 H36 2000

615'.19--dc21

99-044554

**A catalogue record for this book is available from the British Library.**

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder. The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

Managing Editor: Melanie Scgala  
Copyeditor: Paul Gottehrer  
Indexer: Lillian Rodberg  
Compositor: Roy Barnhill  
Cover Designer: Tim Kaage

---

# Handbook of PHARMACEUTICAL EXCIPIENTS

---

Third Edition

*Edited by*

**Arthur H. Kibbe, Ph.D.**

Professor and Chair  
Department of Pharmaceutical Sciences  
Wilkes University School of Pharmacy  
Wilkes-Barre, Pennsylvania



American Pharmaceutical Association  
Washington, D.C.



London, United Kingdom

# Citric Acid Monohydrate

## 1. Nonproprietary Names

BP: Citric acid monohydrate  
 JP: Citric acid  
 PhEur: Acidum citricum monohydricum  
 USP: Citric acid

## 2. Synonyms

2-Hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

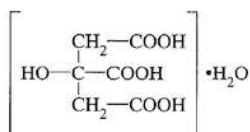
## 3. Chemical Name and CAS Registry Number

2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate  
 [5949-29-1]

## 4. Empirical Formula Molecular Weight

$C_6H_8O_7 \cdot H_2O$  210.14

## 5. Structural Formula



## 6. Functional Category

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer.

## 7. Applications in Pharmaceutical Formulation or Technology

Citric acid, as either the monohydrate or anhydrous material, is widely used in pharmaceutical formulations and food products primarily to adjust the pH of solutions. Citric acid monohydrate is used in the preparation of effervescent granules while anhydrous citric acid is widely used in the preparation of effervescent tablets.<sup>(1)</sup>

In food products, citric acid is used as a flavor enhancer, for its tart, acid taste. Citric acid monohydrate is also used as a sequestering agent and antioxidant synergist. It is a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

Use	Concentration (%)
Buffer solutions	0.1-2.0
Flavor enhancer for liquid formulations	0.3-2.0
Sequestering agent	0.3-2.0

## 8. Description

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. Crystal structure is orthorhombic.

## 9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Clarity and color of solution	—	+	—
Water			
(hydrous form)	—	7.5-9.0%	≤ 8.8%
(anhydrous form)	—	≤ 1.0%	≤ 0.5%
Bacterial endotoxins	—	+	—
Residue on ignition	—	—	≤ 0.05
Sulfated ash	≤ 0.1%	—	≤ 0.1%
Barium	—	+	—
Calcium	+	≤ 200 ppm	—
Aluminum	—	+	—
Oxalate	+	≤ 350 ppm	+
Sulfate	≤ 0.048%	≤ 150 ppm	+
Arsenic	≤ 1 ppm	—	≤ 3 ppm
Heavy metals	≤ 10 ppm	≤ 10 ppm	≤ 0.001%
Iron	—	≤ 50 ppm	—
Chloride	—	≤ 50 ppm	—
Readily carbonizable substances	+	+	+
Polycyclic aromatic hydrocarbon	+	—	—
Organic volatile impurities	—	—	+
Assay (anhydrous basis)	≥ 99.5%	99.5-101%	99.5-100.5%

## 10. Typical Properties

Acidity/alkalinity:

pH = 2.2 (1% w/v aqueous solution)

Dissociation constants:

$pK_{a1}$ : 3.128 at 25°C;

$pK_{a2}$ : 4.761 at 25°C;

$pK_{a3}$ : 6.396 at 25°C.

Density: 1.542 g/cm<sup>3</sup>

Heat of combustion:

-1972 kJ/mol (-471.4 kcal/mol)

Heat of solution:

-16.3 kJ/mol (-3.9 kcal/mol) at 25°C

**Hygroscopicity:** at relative humidities less than about 65% citric acid monohydrate effloresces at 25°C, the anhydrous acid being formed at relative humidities less than about 40%. At relative humidities between about 65-75%, citric acid monohydrate absorbs insignificant amounts of moisture but under more humid conditions substantial amounts of water are absorbed.

**Melting point:** ~ 100°C (softens at 75°C)

**Particle size distribution:** various grades of citric acid monohydrate with different particle sizes are commercially available.

**Solubility:** soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.

**Viscosity (dynamic):** 6.5 mPa s (6.5 cP) for a 50% w/v aqueous solution at 25°C

See also Section 18.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.