Excipient Nomenclature and Analytics

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Outlines

- Importance of Excipient Quality
- USP Standards and the Role in Law
- USP Excipient Strategies
- Simple and Complex Excipients
  - Definition
- Excipient Nomenclature Guideline
  - Excipients with Multiple Components (Complex Excipients)
    - Lipids
    - Synthetic Polymers
- Excipient General Chapters – Related to Analytics
- On Going Work with FDA
- Flexible Solutions
- Summary

Excipients – Important Components of Medicines

go.usp.org/l/323321/2024-04-25/92v5rf

What is an excipient?

Excipients can make up to about 90% of the total mass/volume of drug products and are required for:

- Enhancing therapeutic properties
- Bulking up solid formulations
- Modifying viscosity
- Enhancing solubility
- Long-term stabilization
- Drug delivery
- Drug release

Common excipients:

Glycerin
Propylene Glycol
Microcrystalline Cellulose
Magnesium Stearate
Polysorbate 80
Sodium Chloride

Risk factors affecting excipient quality

Source

Process

Adulteration

Why excipient quality matters

Fatal consequences linked to high-risk excipients

Pharmaceutical facility closure due to excipient quality/GMP violations

Product recalls and corporate reputational damage

How to ensure the quality of excipients

Supplier qualification

Evaluations are needed to assess a supplier's facilities, personnel, documentation, and quality control procedures.

General Chapters:

- *<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients*
- *<1195> Significant Change for Bulk Pharmaceutical Excipients*
- *<1197> Good Distribution Practices for Bulk Pharmaceutical Excipients*
- *<1080> Bulk Pharmaceutical Excipients—Certificate of Analysis*
- *<1083> Supplier Qualification*

Excipient standards and solutions

Excipient Monographs

Excipient Reference Standards

Ingredient Verification Program

- Good Manufacturing Practices (CGMP)
- Ingredient testing
- GMP Facility Audit

USP Standards – Quality and Performance

Over 530 Monograph (Documentary Standards (DSs)) on excipients in *USP–NF*
Over 25 General Chapters (DSs) on excipient in *USP–NF*

General Notices (GN) 4. MONOGRAPHS AND GENERAL CHAPTERS
4.10. Monographs
- *USP–NF* provide the appropriate, validated test procedures to establish the identity, quality and purity of excipients. **Subscribe to USPNF.com**

Over 338 excipient Reference Standards (across 13 functional categories) that have been approved as suitable for use as comparison standards in *USP* or *NF* tests and assays. Visit USP store

GN 5.80. USP Reference Standards
- USP Reference Standards are authentic specimens that have been approved as suitable for use in USP or NF tests and assays (see *USP Reference Standards* ⟨11⟩)

GN 4.20. General Chapters
……(e.g., Chromatography ⟨621⟩).
General chapters may contain the following:
……Descriptions of tests and procedures for application through individual monographs….
- General information for the interpretation of the compendial requirements…….
- **General guidance to manufacturers of official substances or official products.....**
- When a general chapter is referenced in a monograph, acceptance criteria may be presented after a colon.
- Some chapters may serve as introductory overviews of a test or of analytical techniques.
- They may reference other general chapters that contain techniques, details of the procedures, and, at times, acceptance criteria.

USP Excipient General Chapters (GCs) include:

- **GMP related**
  - **GC <1078>:** Complete revision in July 2022 *PF* (48(4)) and the updated version in *USP–NF* 2024 Issue 3
  - **GC <1195>:** Complete revision in Nov. 2019 *PF* (45(6)) and the updated version in *USP–NF* 2021 Issue 1
  - **GC <1197>:** New GC in Nov. 2011 *PF* (37(6)) and published in *USP*36–*NF*31 (2012)
  - **GC <1080>:** Complete revision in Sept. 2016 *PF* (42(5)) and the updated version in *USP*40–*NF* 35 2S (2017)
- **Performance**
  - **GC <1059>:** Complete revision in Sept. 2022 *PF* (48(5)) and the updated version in *USP–NF* 2024 Issue 1
- **Quality Test**
  - **GC <312>:** New GC in Nov. 2022 *PF* (48(6)) and published in *USP–NF* 2024 Issue 2
  - **GC <469>:** New GC in Sept. 2013 *PF* (39(4)) and published in *USP*37–*NF*32 2S (2014)

Role of USP Quality Standards in Law

- **Under FD&C Act**
  - **21 U.S.C. § 321 Section 201(g)(1)**

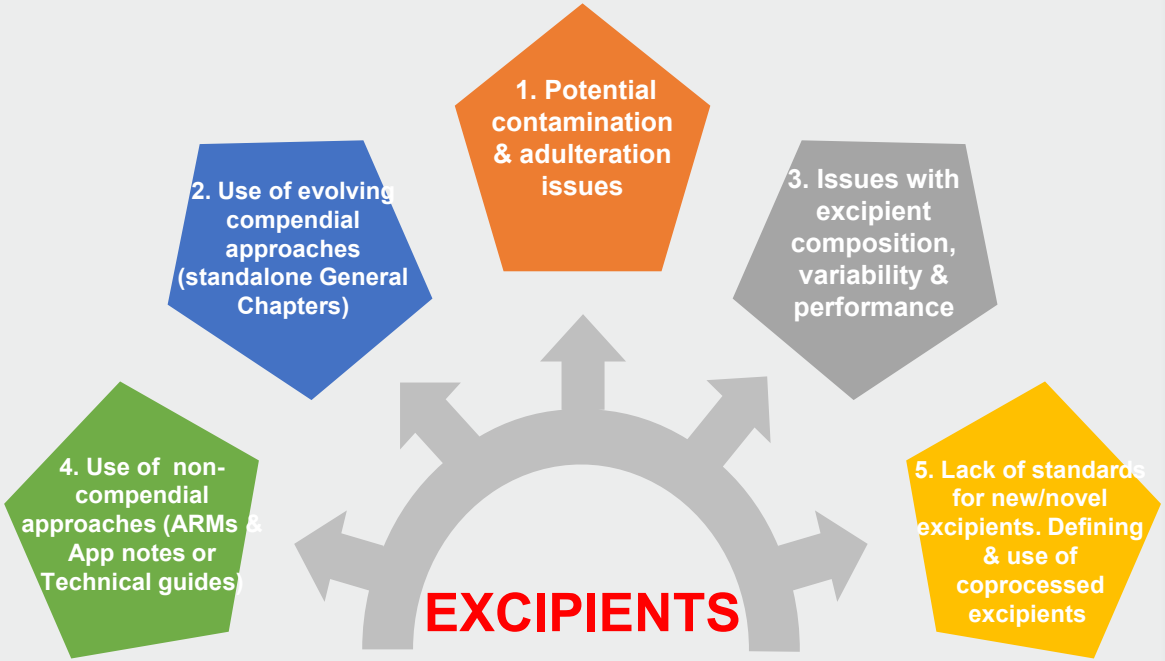
The term "drug" means articles:

- recognized in an official US compendium: United States Pharmacopeia, Homoeopathic Pharmacopoeia, or National Formulary
- intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
- (other than food) intended to affect the structure or any function of the body
- **intended for use as a COMPONENT of any article meeting the above criteria**

- **US FDCA § 501(b) and 502(e)(3)(b)) – Adulterated Drugs and Devices**
  - A drug with a name recognized in *USP-NF* must comply with compendial identity or be deemed adulterated, misbranded , or both. (501(b) & 502(e)(3)(b)). …..*Cannot label away from identity*!
  - Must also comply with compendial standards for strength, quality, and purity, unless labeled to show all differences (501(b) & 21 CFR 299.5).
  - To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs.
- **US FDCA § 502(g)**
  - In addition, to avoid being deemed misbranded, drugs recognized in ***USP–NF*** must also be packaged and labeled in compliance with compendial standards.
- **USP General Notices:** Enforcement of USP standards is the responsibility of FDA and other government authorities in the U.S. and elsewhere. USP has no role in enforcement.

USP Strategies for Developing Quality Standards & Solutions

Focus on Excipients has changed



- Traditionally, excipient specifications were established with a **focus on intended use in the drug product** and less on excipient composition.
- Starting from 2005-2010 revision cycle, the Expert Committee's focus on expanded to include characterization, modernization of official methods, composition variability, performance and GMP's.
- Starting from 2020–2025 revision cycle introduced evolving compendial approaches (standalone chapters) and other solutions including the use of analytical reference materials (ARM's) and associated application notes.

Excipients – Simple and Complex

- In the 2018 *Stimuli* article, "*The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities*", *PF* 44(3) (https://www.uspnf.com/pharmacopeial-forum/pf-legacy-pdfs), the Excipient Expert Committees (EXC ECs) proposed the following definitions:
  - **Simple excipient**: An excipient composed of a single main substance with a well-defined chemical structure that can be characterized well analytically.
  - **Complex excipient**: Any excipient that does not fit the definition of a simple excipient.
- In the 2023 *Stimuli* article, "*Proposed Definitions of Excipient Components – Revisions to 2018 Definitions*", *PF* 49(5), the Excipient Composition and Impurities Joint Subcommittee (JS) kept the definitions for simple and complex excipients unchanged from the 2018 definitions and defined
  - Main component and minor component
  - Impurity

Excipient Nomenclature Guideline

Excipient Nomenclature Guideline

- Previously, there has not been a systematic approach to excipient nomenclature.
- Most often, a name in common usage has been adopted. However, there are instances where excipient nomenclature can lead to confusion, with similar nomenclature being adopted for somewhat different materials.
- The Nomenclature Guideline from USP provide definitions, examples, references, and general principles for naming drug substances and drug products, *but not excipients*.
- The Excipient Nomenclature Guideline was released to the public in 2023. It is the **first** USP nomenclature guideline for excipients.

Guideline: Key Sections and Highlights

Seven Sections

1. Introduction
2. Brief Overview of Excipient Nomenclature from 2016 to Date
3. Nomenclature of Single- versus Multi-component Excipients
4. Nomenclature of Natural, Synthetic, and Semi-synthetic Excipients
5. Nomenclature of Silicon-containing Excipients
6. Nomenclature for Co-processed Excipients
7. Conclusion

Excipient Component

Specific Monograph *vs*. Umbrella Monograph

Guideline-Defined “Excipient Component”

Excipient Component

(Page 13 of 48)

Generally, excipient component is intended to be included as part of an excipient and may be present in the excipient at an amount not less than (NLT) the specified NLT value and in some cases not exceeding the specified NMT (not more than) value.

- One specific example is that stearic acid is a component of NLT 40.0% and NMT 60.0% in Stearic Acid 50.
- Another specific example is that triglyceride is a component of NLT 5.0% and NMT 20.0% in Glyceryl Monooleate 40 and a component of NLT 2.0% and NMT 10.0% in Glyceryl Monooleate 60.
- Other specific examples are foeniculin is a component of NLT 0.10% in Star Anise Oil and Pseudoisoeugenyl 2-methylbutyrate is a component of NLT 0.30% in Anise Oil in which they are markers for identity

Guideline: Specific and Umbrella Monographs

- **Specific Monograph** (Page 3 of 48)

  A specific monograph represents an individual excipient product on the market

- **Umbrella Monograph**

  An umbrella monograph represents multiple types of the excipients in a single monograph

- **Examples of New Monograph Proposals in *PF***

  (November 2023 *PF* 49(6) and March 2024 *PF* 50(2))

  – Specific monographs
    - DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid
    - 1,2-Distearoyl-*sn*-Glycero-3-Phosphocholine
    - Mannose

  – Umbrella monographs
    - Locust Bean Gum
    - Sodium Oleate

Guideline: Lipids

- **Excipients with Multiple Components – for example, Lipids**
  - Follow the Excipient Nomenclature Guideline
    - 3.3. Excipients that are Mixtures with Multiple Simple Molecule Compounds

      Table 9 provides 12 monograph examples for lipids and lipid derived fatty acids and alcohols

Use the following three approaches to name excipients that are mixtures with multiple components which are simple molecules:

1. Use a combined term of two components, such as "Palmitostearate," "Cetostearyl," or "Caprylocaprate."
2. Indicate multiple components in the monograph title.
3. Use a number for a grade (or type) included in a monograph to indicate mixture type or multi-component nature of an excipient. The number usually represents the content of the named component expressed as a percentage.

Guideline: Lipids (Cont'd)

- **Excipients with Multiple Components**
  - **Approach 2:** Indicate multiple components in the monograph title

Table 1. Splitting of Three Umbrella Monographs

(Newly created monograph titles for *Mixture* types)

Original Monograph Title	Monograph Title for *Purified* Type	Monograph Title for *Mixture* Type
Glyceryl Monocaprylate	Glyceryl Monocaprylate	Glyceryl Mono and Dicaprylate
Glyceryl Monocaprylocaprate	Glyceryl Monocaprylocaprate	Glyceryl Mono and Dicaprylocaprate
Propylene Glycol Monocaprylate	Propylene Glycol Monocaprylate	Propylene Glycol Mono and Dicaprylate

Guideline: Lipids (Cont'd)

- **Excipients with Multiple Components**
  - *Purified* Type *vs*. *Mixture* Type
  - **Approach 3:** Use a number for a type included in a monograph to indicate mixture type or multi-component nature of an excipient. …
- Based upon the Excipient Nomenclature Guideline, new monograph titles for the following lipid-derived excipients (*Mixture* type) were approved by the Nomenclature and Labeling Expert Committee (NL EC)
  - Myristyl Lactate 75 (published in July 2024 *PF* 50(4))
  - Isostearic Acid 75 (published in November 2023 *PF* 49(6))
  - Glyceryl Monostearate 50 Type A (published in July 2024 *PF* 50(4))

Guideline: Lipids (Cont'd)

- Lipid-derived excipients are traditionally produced from vegetable and animal sourced materials
  - Lecithin *vs*. Egg Phospholipids

Lecithin (official)
(vegetable source from either Soybean, Sunflower or Canola Oil) (It contains multiple components including phosphatidylcholine (PC), PE, PI, PA, and etc.)

Egg Phospholipids (official)
(Egg Phospholipids is a mixture of naturally occurring phospholipids obtained from the yolk of hens' eggs that is suitable for use as an emulsifying agent in injectable emulsions. The content of phosphatidylcholine (PC), phosphatidylethanolamine (PE), lysophosphatidylcholine (LPC), and other related phospholipids is to be reported in the certificate of analysis. …)

- Innovative therapeutics require more purified, well characterized, and botanically specific lipids
  - Use of advanced and improved analytical technologies including chromatography with ELSD (Evaporative Light Scattering detection), CAD (Charge Aerosol detection) and MS (Mass Spectrometry) can help define lipid's identity, composition and profile, thus lead to an appropriate nomenclature
    - Soybean Phospholipids *vs*. Soybean Phosphatidylcholine

Soybean Phospholipids
March 2022 *PF* 48(2)
(A mixture of phosphatidylcholine, phosphatidylethanolamine, lysophosphatidylcholine, phosphatidic acid, phosphatidylinositol, and N-acylphosphatidylethanolamine obtained from the soybean source. It contains NLT 65.0% and NMT 89.9% of phosphatidylcholine, NLT 6.0% and NMT 11.0% of phosphatidylethanolamine, NMT 6.0% of lysophosphatidylcholine, NMT 3.0% of phosphatidic acid, NMT 1.5% of phosphatidylinositol, and NMT 6.0% of N-acylphosphatidylethanolamine, calculated on the anhydrous basis. The phospholipids are in l-isomer forms. …)

Soybean Phosphatidylcholine
May 2023 *PF* 49(3)
(Soybean Phosphatidylcholine contains NLT 90.0% and NMT 102.0% of phosphatidylcholine, calculated on the anhydrous basis, obtained from the soybean source. It is in an L-isomer form. It may contain a suitable stabilizer.)

Guideline: Lipids (Cont'd)

- Advanced and innovative approaches applied to manufacturing processes lead to the stereospecific excipients
  - 1,2-Distearoyl-*sn*-Glycero-3-Phosphocholine (DSPC), which is the first *NF* monograph that uses "*sn*"
    - Published in November 2023 *PF* 49(6)
  - Sodium N-(Carbonyl-Methoxypolyethylene Glycol 2000)-1,2-Distearoyl-*sn*-Glycero-3-Phosphoethanolamine (MPEG-2000-DSPE)
    - In development
    - Both DSPC and MPEG-2000-DSPE are frequently used in liposomal or lipid nanoparticle formulations or biologics/vaccines

Guideline: Synthetic Polymers

- **Polymeric Excipients – traditionally use an umbrella monograph approach**
  - Follow the Excipient Nomenclature Guideline
    - 4.4. Nomenclature of Synthetic Polymers

To describe more complex polymeric excipients and to accommodate quality tests using advanced analytical techniques, USP uses the terms “Homopolymer,” “Copolymer,” “Block Copolymer,” and “Graft Copolymer” in their names.

  - Specific monograph: Polyethylene Glycol 3350 *USP* (reflect its use as both an active and inactive ingredient)
    - The value 3350 represents weight-average molecular weight for the homopolymer

Guideline: Synthetic Polymers (Cont'd)

- **The following *elements* are included in specific *NF* monograph titles for synthetic polymeric excipients**

The monomer names, including any stereochemistry notation (D, L, or DL)

If there is only one monomer used, the term "Homopolymer" would be used. If more than one monomer is used, the term "Copolymer" would be used. These terms would appear after the name(s) of the monomers, before the names of the end groups

Monomer ratio in the case of a copolymer

Weight-average molecular weight or number of monomer repeating units

End group or terminating group

Guideline: Synthetic Polymers (Cont'd)

- **The following techniques are utilized in support of specific *NF* monograph titles for synthetic polymeric excipients**

NMR (and/or qNMR) – determine number-average molecular weight, number of monomer repeating units, monomer ratio, content of monomer, block length and block-length distribution, end group

HPLC or GPC with multiple directors including light scattering, refractive index, viscometer – determine weight-average molecular weight, molecular weight distribution, polydispersity, etc.

Bulk light scattering – determine weight-average molecular weight (M_w)

Membrane osmometry – determine number-average molecular weight (M_n)

Guideline: Synthetic Polymers (Cont'd)

- **More and more specific new *NF* monographs for polymeric excipients are being developed**

Specific Monograph Titles Approved for Polymeric Excipients after 2016
Polypropylene Glycol 11 Stearyl Ether
Methyl Acrylate, Methyl Methacrylate, and Methacrylic Acid (7:3:1) Copolymer 280000 Dispersion
Polyethylene Glycol 12 Cetostearyl Ether
Polyethylene Glycol 30 Dipolyhydroxystearate 5
Polyethylene Glycol 40 Castor Oil
Polyethylene Glycol 60 Hydrogenated Castor Oil
DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid
DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester
DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid

Guideline: Synthetic Polymers (Cont'd)

- **Lactide (or Lactic Acid) and Glycolide (or Glycolic Acid) (LG) Polymers**
  - Please visit USP web, LG Polymers and download our LG polymer flyer
  - Explore USP's suite of LG polymer solutions to ensure quality without compromise

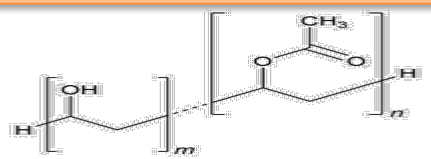
Monographs published in *Pharmacopeial Forum* (*PF*)	USP Reference Standards and Materials	General Chapters	*Stimuli* Article to Address Naming and Testing Challenges
DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid, *PF* 48(3)	USP DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid RS	<315> NMR Spectroscopy Number-Average Molecular Weight Determination for Lactide or Lactic Acid and Glycolide or Glycolic Acid Polymers, *PF* 50(5)	A Practical Approach to Compendial Nomenclature and Testing For Lactide and Glycolide Polymers and Related Polymeric Excipients, *PF* 48(2)
DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester, *PF* 48(6)	USP DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester RS		
DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid, *PF* 49(5)	USP DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid RS	<316> Gel Permeation Chromatography Molecular Weight and Polydispersity Determination for Lactide or Lactic Acid and Glycolide or Glycolic Acid Polymers using Universal Calibration, *PF* 50(5)	USP Responses to Comments on Stimuli Article: "A Practical Approach to Compendial Nomenclature and Testing for Lactide and Glycolide Polymers and Related Polymeric Excipients", *PF* 49(6)
DL-Lactide homopolymer 14000 Acid, *PF* 50(4)	Over **10 Analytical Reference Materials (ARMs)*** for LG polymers of different ratios and molecular weights		

Guideline: Synthetic Polymers (Cont'd)

- **Polyvinyl Alcohol *USP* Monograph**

Polyvinyl Alcohol
***USP–NF* 2024**
$H(C_2H_4O)_m(C_4H_6O_2)_nH$
Vinyl alcohol and vinyl acetate copolymer (87:13); A saponified polyvinyl acetate; Poly(ethanol)co(vinyl acetate).

DEFINITION
Polyvinyl Alcohol is a water-soluble synthetic resin, represented by the formula $(C_2H_4O)_m(C_4H_6O_2)_n$, in which the average value of m+n lies between 444 and 4440. It is prepared by 85%–89% hydrolysis of polyvinyl acetate. The apparent viscosity, in mPa · s, at 20°, of a 4% (w/w) aqueous solution is NLT 85.0% and NMT 115.0% of that stated on the label.



- Additional polymers that are NOT covered by the current Polyvinyl Alcohol *USP* monograph will be developed as following examples:
  - Vinyl Alcohol Homopolymer 60000
  - Vinyl Alcohol and Vinyl Acetate (75:25) Copolymer 50000

Excipient General Chapters (EXC GCs) - Related to Analytics

Excipient General Chapters (EXC GCs)

Use of Iterative Approach – NMR, GPC, and Advanced Technique-based Methods for Complex Excipients

- Advanced studies for lipids and polymers are in support of establishing appropriate nomenclature
- According to Excipient Request for Revision Guideline, the following guideline can be used.
  - USP is actively engaged in updating official *USP–NF* monographs that utilize outdated technology, have safety/environmental concerns, or are missing procedures for key aspects such as identification, assay, and impurities. USP implements evolving and iterative approaches to introduce **new techniques, some initially, through development of general chapters that cover multiple monographs** that will be considered on a case-by-case basis.

EXC GCs (Cont'd)

Use of Iterative Approach

- For several umbrella monographs, USP has developed discriminating analytical tools to label appropriately for different types of polymeric excipients.
  - Refer to below examples:
    - ⟨312⟩ Molecular Weight Determination for Alginates, *To be Official on 01-Aug-2024*
    - ⟨313⟩ Molecular Weight and Polymer Chain Length Determination for Polypropylene Glycol Fatty Ethers, *Official as of 01-Aug-2023*
    - ⟨314⟩ Molecular Weight Determination for Copolymers Containing Alkyl Methacrylate or Alkyl Acrylate, *Official as of 01-Dec-2023*

EXC GCs (Cont'd)

Use of Iterative Approach

- USP has always taken an iterative (stepwise) approach to developing standards, continuously evolving its standards from inception to official status to further revision in response to stakeholder input and advances in technology and regulatory science.

Chapter #	Chapter Title	Publication
<315>	NMR Spectroscopy Number-Average Molecular Weight Determination for Lactide or Lactic Acid and Glycolide or Glycolic Acid Polymers	September 2024, *PF*50(5)
<316>	Gel Permeation Chromatography Molecular Weight and Polydispersity Determination for Lactide or Lactic Acid and Glycolide or Glycolic Acid Polymers Using Universal Calibration	September 2024, *PF*50(5)
<317>	ICP OES TESTING FOR SODIUM HYDROXIDE AND POTASSIUM HYDROXIDE	May 2024, *PF*50(3)
<320>	NMR SPECTROSCOPY FOR THE DETERMINATION OF DEGREE OF HYDROLYSIS FOR POLYVINYL ALCOHOL AND VINYL ALCOHOL HOMOPOLYMER, AND MONOMER RATIO FOR VINYL ALCOHOL AND VINYL ACETATE COPOLYME	Prospectus published

EXC GCs (Cont'd)

Use of Iterative Approach

- For several monographs in the PDG (Pharmacopeial Discussion Group) workplan, USP has developed analytical tools that are in the following chapters
  - Refer to below examples:
    - <901> Detection of Asbestos in Pharmaceutical Talc, *Official as of 01-Dec-2023*
    - <1901> Theory and Practice of Asbestos Detection in Pharmaceutical Talc, *Official as of 01-Dec-2023*
    - <470> Determination of Ethylene Glycol, Diethylene Glycol and Triethylene Glycol in Polyethylene Glycol, *Published in September 2024 PF 50(5)*

EXC GCs (Cont'd)

- GCs <312> to <320> allow stakeholders to use advanced analytical methods for establishing excipient quality specifications for the simple and complex excipients, as appropriate, even though they are not yet applicable or ready to be included in the official monograph, as per **General Notices (GN) 3.10**, "Applicable general chapters"**.
- **USP **General Notices (GN) 3.10**, "Applicable general chapters" means general chapters numbered below 1000 or above 2000 that are made applicable to an article through reference in GN, a monograph, or another applicable GC numbered below 1000
- Traditional test specifications based on viscosity techniques are still in use in many polymeric excipient monographs. To address public needs, the chapters <312> to <316> and <320> provide additional analytics in addition to viscosity and titration.
- Atomic absorption (AA) test specifications are implemented in sodium hydroxide and potassium hydroxide monographs. The GC <317> offers additional analytics to accommodate public demands.

On Going Work with FDA: Tool(s) in Addressing Q1

Complex Generics: Definition of Q1

- Q1* (Qualitative sameness) means that the test product uses the **same inactive ingredient(s)** as the reference listed drug (RLD)
- Source and structural specific excipient monograph title may help define the sameness of inactive ingredients. Work through LG Polymer Joint Subcommittee (JS) and Excipient NL JS' FDA liaisons
  - LG Polymers
    - Ring-opening manufacturing: Lactide and Glycolide (75:25) Copolymer 20000 Acid
    - Polycondensation manufacturing: Lactic Acid and Glycolic Acid (75:25) Copolymer 10000

* FDA CRCG Webinar on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned, Dec. 6, 2022, "*Considerations for the Qualitative Sameness Evaluation of a Proposed Generic Formulation*"

On going Work with FDA: GSRS Office

- FDA Draft Guidance Using the Inactive Ingredient Database, Guidance for Industry, July 2019, USP sent the comments
- USP works closely with the FDA to address the gaps between excipient nomenclature titles, preferred names in the Global Substance Registration System (GSRS), and the article names in the Inactive Ingredient Database (IID) to reach harmonization.
- Example:
  - Change Diethylene Glycol Stearates (in *USP–NF*)

    to
  - Diethylene Glycol Mono- and Dipalmitostearate in alignment with FDA GSRS and IID

On Going Work FDA (Cont'd)

Nomenclature: PLGA vs. LG Polymer

- USP LG polymer JS considered terms like "PLGA","PLG", "PLA", "PL", "Polyesters" but thought these terms are not suitable because:
  - Two main synthesis routes for this type of polymers (ring opening and condensation).
  - The JS members did not want to show any bias in naming these excipients
- The LG Polymer JS including FDA liaisons work to fix the issues:
  - The nomenclature for LG polymers is inconsistent in the market and in FDA's GSRS and IID, including for LG polymers with the same properties.
  - The names do not reflect factors in the LG polymer manufacturing, such as methodology, post-synthesis processing, or specifying what the monomer ratio represents
- USP and FDA collaborations lead to harmonization on nomenclature of LG polymers, and thus will help drug companies that develop LG polymer-based formulations.

Flexible Solutions: Materials Program

- Based on our stakeholders' feedback, USP is working on flexible solutions that can be made available in a short time to address pain points across the drug lifecycle.
  - For example, the need for quality reference materials for early R&D or manufacturing to help adapt to industry's rapidly changing environment.
  - To this end, USP is providing certain analytical reference materials called ARMs to address current and immediate needs.
  - The ARMs are different from USP RS and are released through a process developed by USP's subject matter experts. The ARMs are of the same high quality that you have come to expect and trust.
    - The ARMs release process is based on internal policies, standard operating procedures, and requirements as defined by USP's Quality Management System. USP is an ISO 9001:2015 certified facility. ARMs are different from official USP Reference Standards. ARMs are not required for compendial compliance.

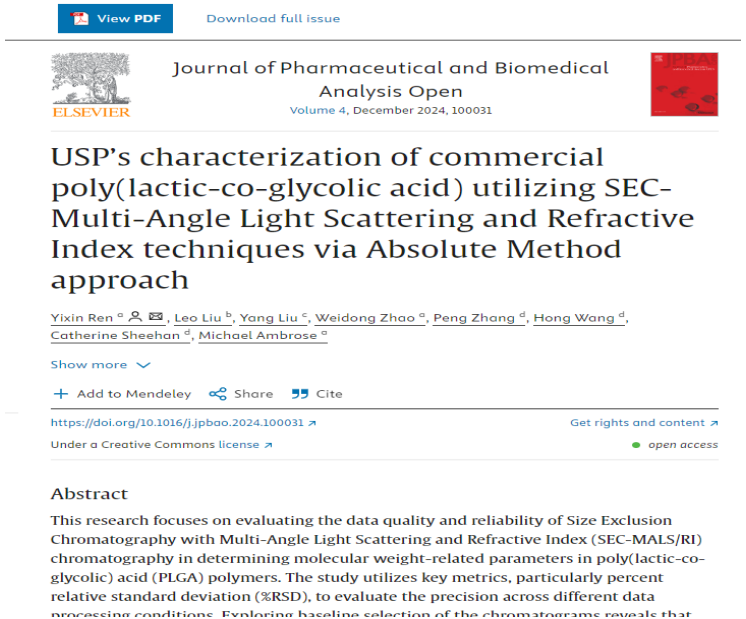
Flexible Solutions – Technical Guide and ARMs: LG Polymers

Analytical Reference Materials (ARMs)	Technical Guide including Case Study
Coming soon! 14 Analytical Reference Materials (ARMs)* for LG polymers of different ratios, molecular weights, and end group	**Coming soon!** Stay tuned!

USP LG Polymer webpage: LG Polymers (usp.org)

*Analytical Reference Materials (ARM) are released using a process developed by USP's subject matter experts. The release process is based on internal policies, standard operating procedures, and requirements as defined by USP's Quality Management System. USP is an ISO 9001:2015 certified facility. ARMs are different from official USP Reference Standards. ARMs are not required for compendial compliance.

- USP LG polymer peer-reviewed paper in the Journal of Pharmaceutical and Biomedical Analysis *Open*
- The absolute method developed has great potential: good repeatability has been achieved.
- USP will optimize and validate the method and consider introducing it in an application note or technical guide



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Journal of Pharmaceutical and Biomedical Analysis Open
Volume 4, December 2024, 100031

USP's characterization of commercial poly(lactic-co-glycolic acid) utilizing SEC-Multi-Angle Light Scattering and Refractive Index techniques via Absolute Method approach

Yixin Ren [a], Leo Liu [b], Yang Liu [c], Weidong Zhao [a], Peng Zhang [d], Hong Wang [d], Catherine Sheehan [d], Michael Ambrose [a]

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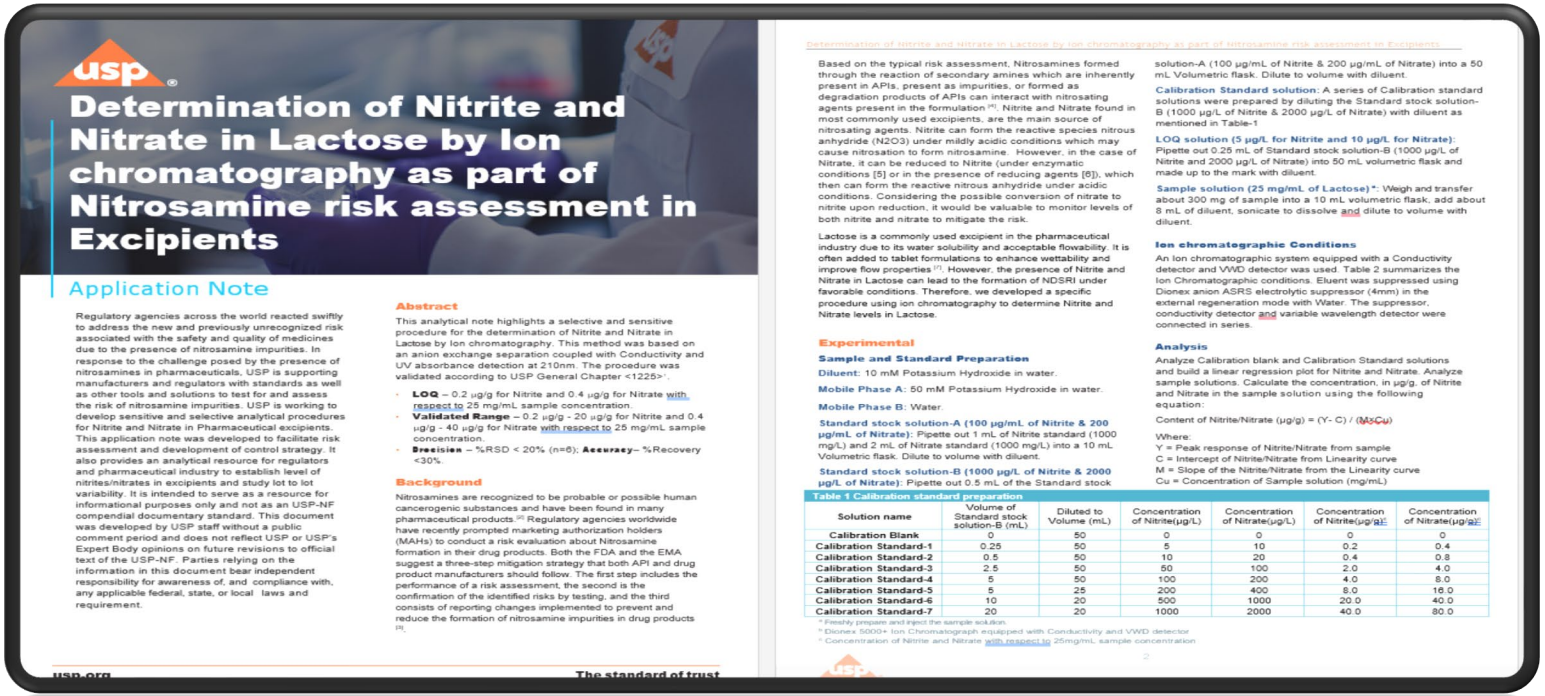
Abstract

This research focuses on evaluating the data quality and reliability of Size Exclusion Chromatography with Multi-Angle Light Scattering and Refractive Index (SEC-MALS/RI) chromatography in determining molecular weight-related parameters in poly(lactic-co-glycolic) acid (PLGA) polymers. The study utilizes key metrics, particularly percent relative standard deviation (%RSD), to evaluate the precision across different data processing conditions. Exploring baseline selection of the chromatograms reveals that

Flexible Solutions – Application Note: Nitrite in Excipients

- To address stakeholders' needs to understand nitrite and nitrate levels in Excipients
- The first App Note was published



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Determination of Nitrite and Nitrate in Lactose by Ion chromatography as part of Nitrosamine risk assessment in Excipients

Application Note

Regulatory agencies across the world reacted swiftly to address the new and previously unrecognized risk associated with the safety and quality of medicines due to the presence of nitrosamine impurities. In response to the challenge posed by the presence of nitrosamines in pharmaceuticals, USP is supporting manufacturers and regulators with standards as well as other tools and solutions to test for and assess the risk of nitrosamine impurities. USP is working to develop sensitive and selective analytical procedures for Nitrite and Nitrate in Pharmaceutical excipients. This application note was developed to facilitate risk assessment and development of control strategy. It also provides an analytical resource for regulators and pharmaceutical industry to establish level of nitrites/nitrates in excipients and study lot to lot variability. It is intended to serve as a resource for informational purposes only and not as an USP-NF compendial documentary standard. This document was developed by USP staff without a public comment period and does not reflect USP or USP's Expert Body opinions on future revisions to official text of the USP-NF. Parties relying on the information in this document bear independent responsibility for awareness of, and compliance with, any applicable federal, state, or local laws and requirement.

Abstract

This analytical note highlights a selective and sensitive procedure for the determination of Nitrite and Nitrate in Lactose by Ion chromatography. This method was based on an anion exchange separation coupled with Conductivity and UV absorbance detection at 210nm. The procedure was validated according to USP General Chapter <1225>[1].

- **LOQ** – 0.2 µg/g for Nitrite and 0.4 µg/g for Nitrate with respect to 25 mg/mL sample concentration.
- **Validated Range** – 0.2 µg/g - 20 µg/g for Nitrite and 0.4 µg/g - 40 µg/g for Nitrate with respect to 25 mg/mL sample concentration.
- **Precision** – %RSD < 20% (n=6); **Accuracy**– %Recovery <30%.

Background

Nitrosamines are recognized to be probable or possible human cancerogenic substances and have been found in many pharmaceutical products.[2] Regulatory agencies worldwide have recently prompted marketing authorization holders (MAHs) to conduct a risk evaluation about Nitrosamine formation in their drug products. Both the FDA and the EMA suggest a three-step mitigation strategy that both API and drug product manufacturers should follow. The first step includes the performance of a risk assessment, the second is the confirmation of the identified risks by testing, and the third consists of reporting changes implemented to prevent and reduce the formation of nitrosamine impurities in drug products [3].

Based on the typical risk assessment, Nitrosamines formed through the reaction of secondary amines which are inherently present in APIs, present as impurities, or formed as degradation products of APIs can interact with nitrosating agents present in the formulation [4]. Nitrite and Nitrate found in most commonly used excipients, are the main source of nitrosating agents. Nitrite can form the reactive species nitrous anhydride (N_2O_3) under mildly acidic conditions which may cause nitrosation to form nitrosamine. However, in the case of Nitrate, it can be reduced to Nitrite (under enzymatic conditions [5] or in the presence of reducing agents [6]), which then can form the reactive nitrous anhydride under acidic conditions. Considering the possible conversion of nitrate to nitrite upon reduction, it would be valuable to monitor levels of both nitrite and nitrate to mitigate the risk.

Lactose is a commonly used excipient in the pharmaceutical industry due to its water solubility and acceptable flowability. It is often added to tablet formulations to enhance wettability and improve flow properties [7]. However, the presence of Nitrite and Nitrate in Lactose can lead to the formation of NDSRI under favorable conditions. Therefore, we developed a specific procedure using ion chromatography to determine Nitrite and Nitrate levels in Lactose.

Experimental

Sample and Standard Preparation

Diluent: 10 mM Potassium Hydroxide in water.

Mobile Phase A: 50 mM Potassium Hydroxide in water.

Mobile Phase B: Water.

Standard stock solution-A (100 µg/mL of Nitrite & 200 µg/mL of Nitrate): Pipette out 1 mL of Nitrite standard (1000 mg/L) and 2 mL of Nitrate standard (1000 mg/L) into a 10 mL Volumetric flask. Dilute to volume with diluent.

Standard stock solution-B (1000 µg/L of Nitrite & 2000 µg/L of Nitrate): Pipette out 0.5 mL of the Standard stock solution-A (100 µg/mL of Nitrite & 200 µg/mL of Nitrate) into a 50 mL Volumetric flask. Dilute to volume with diluent.

Calibration Standard solution: A series of Calibration standard solutions were prepared by diluting the Standard stock solution-B (1000 µg/L of Nitrite & 2000 µg/L of Nitrate) with diluent as mentioned in Table-1

LOQ solution (5 µg/L for Nitrite and 10 µg/L for Nitrate): Pipette out 0.25 mL of Standard stock solution-B (1000 µg/L of Nitrite and 2000 µg/L of Nitrate) into 50 mL volumetric flask and made up to the mark with diluent.

Sample solution (25 mg/mL of Lactose)*: Weigh and transfer about 300 mg of sample into a 10 mL volumetric flask; add about 8 mL of diluent, sonicate to dissolve and dilute to volume with diluent.

Ion chromatographic Conditions

An Ion chromatographic system equipped with a Conductivity detector and VWD detector was used. Table 2 summarizes the Ion Chromatographic conditions. Eluent was suppressed using Dionex anion ASRS electrolytic suppressor (4mm) in the external regeneration mode with Water. The suppressor, conductivity detector and variable wavelength detector were connected in series.

Analysis

Analyze Calibration blank and Calibration Standard solutions and build a linear regression plot for Nitrite and Nitrate. Analyze sample solutions. Calculate the concentration, in µg/g, of Nitrite and Nitrate in the sample solution using the following equation:

Content of Nitrite/Nitrate (µg/g) = (Y- C) / (M*Cu)

Where:
Y = Peak response of Nitrite/Nitrate from sample
C = Intercept of Nitrite/Nitrate from Linearity curve
M = Slope of the Nitrite/Nitrate from the Linearity curve
Cu = Concentration of Sample solution (mg/mL)

Table 1 Calibration standard preparation

Solution name	Volume of Standard stock solution-B (mL)	Diluted to Volume (mL)	Concentration of Nitrite(µg/L)	Concentration of Nitrate(µg/L)	Concentration of Nitrite(µg/g)[c]	Concentration of Nitrate(µg/g)[c]
Calibration Blank	0	50	0	0	0	0
Calibration Standard-1	0.25	50	5	10	0.2	0.4
Calibration Standard-2	0.5	50	10	20	0.4	0.8
Calibration Standard-3	2.5	50	50	100	2.0	4.0
Calibration Standard-4	5	50	100	200	4.0	8.0
Calibration Standard-5	5	25	200	400	8.0	16.0
Calibration Standard-6	10	20	500	1000	20.0	40.0
Calibration Standard-7	20	20	1000	2000	40.0	80.0

* Freshly prepare and inject the sample solution.
** Dionex 5000+ Ion Chromatograph equipped with Conductivity and VWD detector
[c] Concentration of Nitrite and Nitrate with respect to 25mg/mL sample concentration

Summary

- USP continues to work with stakeholders to address all compendial needs and to ensure that the excipient standards are current and up-to-date.
- USP uses iterative approaches and engages stakeholders early in the development of standards by promoting dialogue, scientific input, exchange of information, collaboration with both FDA and industry, etc.
- USP has expanded its capabilities to create reference materials faster than ever before, while maintaining the quality USP is known and trusted to provide. These products help industry deliver more high quality, low-cost generic medicines to patients faster.
- USP is committed to meet more quality testing needs as the industry continues to evolve. From the challenges of complex generics to cell and gene therapies, USP is there with more solutions every day.

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