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Review of Advanced Analytical Methods in Complex Polymeric Drug Substance Characterization

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PURPOSE

Synthetic polymers that elicit a therapeutic response are a unique class of complex active pharmaceutical ingredients (APIs) that present inherent challenges in demonstrating pharmaceutical equivalence for generic drug product development. To date, FDA has approved six drug products containing synthetic polymeric APIs for the treatment of diseases including hyperkalemia, hypercholesterolemia, etc. (e.g., VELTASSA® (patiromer sorbitex calcium oral powder), and WELCHOL™ (colesevelam hydrochloride)). In general, these polymers are a heterogenous mixture composed of random copolymers, which are synthesized from two or more monomers with certain degrees of crosslinking and different molecular weights. The structural diversity and complexity make the characterization of polymeric APIs challenging and require appropriate analytical methodologies for proper identification and assessment of these APIs in terms of sameness. We reviewed the literature reports on critical analytical measures and technologies for polymeric API characterization and provided rationales of applying appropriate analytical methods as well as statistical methods in demonstration of equivalence of generic polymeric drug products.

METHODS

We performed an in-depth literature search using publicly available information (e.g., PubMed) to identify key quality attributes for demonstration of the polymeric API sameness, and to evaluate how the current analytical methodologies of polymer materials can be applied to assess the chemical structure and the key quality attributes of complex polymeric APIs.

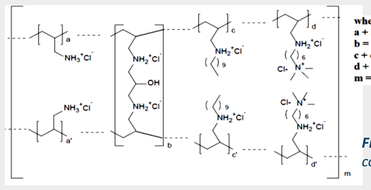


Figure 1. The API structure of colesevelam hydrochloride.

An example to demonstrate the complexity of polymeric APIs is colesevelam hydrochloride. The API structure (Figure 1) contain a few key elements: 1) Polyallylamine backbone; 2) The crosslinking component containing hydroxypropane group; 3) Side chain or functional groups containing decyl and (6-trimethylammonium) hexyl group, and 4) Counter ion component (chloride). The analytical methods should be focused on characterization of these elements to demonstrate API sameness.

RESULTS

Our literature research and studies revealed the critical analytical methods that can be used to characterize the key physicochemical, structural, and morphological properties of the polymeric APIs. These analytical methods include, but are not limited to: ^{13}C Solid State (SS) nuclear magnetic resonance (NMR) spectroscopy, Fourier-transform infrared spectroscopy (FT-IR)/Raman spectroscopy, dynamic light scattering (DLS) on particle size and distribution, swelling index measurement, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). In addition, our research evaluated the key statistical methods used in demonstrating equivalence of generic polymeric drug products.

1. ^{13}C Solid State (SS) NMR

High-resolution ^{13}C SSNMR spectroscopy is a crucial analytical method and potentially more effective to characterize polymeric materials due to their low solubility. ^{13}C SSNMR can provide information about the carbon backbone chain structure (Figure 2a), conformation, crystal structure, and molecular dynamics of the polymer.

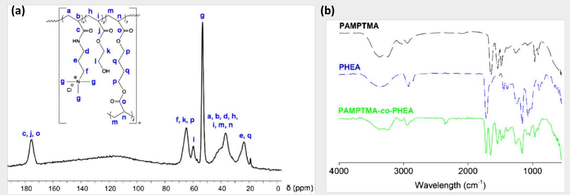


*Figure 2. a) ^{13}C SSNMR of a poly((3-acrylamidopropyl)trimethylammonium chloride) (**PAMPTMA**)-co-poly(2-hydroxyethyl acrylate)) (**PHEA**) polymer. This polymer has backbone structure and functional group (i.e., quaternary ammonium group) similar to colesevelam. b) FTIR spectra of **PAMPTMA** homopolymer (black dashed line), **PHEA** homopolymer (blue dot-dashed line) and **PHEA-co-PAMPTMA** hydrogel (green solid line). Quaternary ammonium group shows absorption bands at 1470 cm^{-1} and –N–H stretching at 1540 cm^{-1}. Figures are reprinted from Mendonça, Patrícia V. et al, Pharm. Res. **2017**, 34, 1934-1943.*

2. FT-IR/Raman spectroscopy

FT-IR and Raman spectroscopy provide measurements on characteristic functional groups. In the case of colesevelam, FT-IR can identify the characteristic absorption bands from the quaternary ammonium group. (Figure 2b).

3. Particle Size with Particle Size Distribution

Particle size is closely related to the molecular weight and the surface area of the polymer (Figure 3). In the case of colesevelam hydrochloride, its particle size is related to surface area which may affect the rate of the absorption of bile acids. Comparable particle size and particle size distribution is essential in demonstrating API sameness.

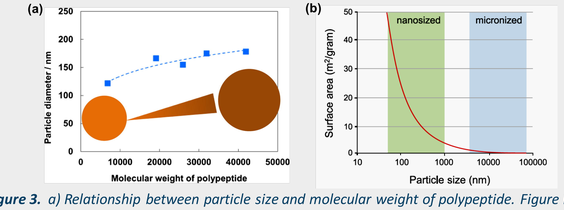
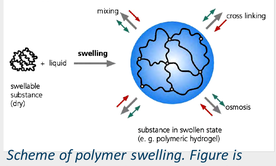


*Figure 3. a) Relationship between particle size and molecular weight of polypeptide. Figure is reprinted from Tetsu Yonezawa et al, Adv. Powder Technol. **2017**, 28, 1966-1971. b) Relationship between particle size and surface area of nano- and micro-particles. Figure is reprinted from Hywel D. Williams et al, Pharmacol. Rev. **2013**, 65, 315-499.*

4. Swelling Index

Swelling index is a characteristic factor to analyze crosslinking of polymer. It measures the absorption ability of solvent by a crosslinked polymer, which is directly related to the degree of crosslinking and molecular weight.



$$\overline{M}_c = -V_1\rho_p\frac{(\phi_p^{1/3} - \phi_p/2)}{[\ln(1-\phi_p) + \phi_p + \chi_1\phi_p^2]}$$

M_c = the number average molecular weight of the polymer between crosslinks
V_1 = the molar volume of the solvent
ρ_p = the polymer density
ϕ_p = the volume fraction of polymer in the swollen gel
χ_1 = the Flory-Huggins interaction parameter between solvent and polymer

*Figure 4. Scheme of polymer swelling. Figure is reprinted from Wack, H. et. al. Proceedings of the First International Conference on Self Healing Materials **2007**, 18-20.*

5. Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TGA)

DSC analysis provides information about the glass translation temperature of test samples which is characteristic of polymer structure and cross-linking degree (Figure 5a). TGA can analyze functional group and ion content (Figure 5b).

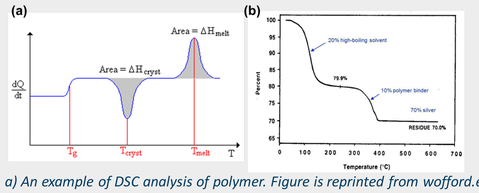
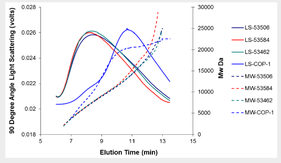


*Figure 5. a) An example of DSC analysis of polymer. Figure is reprinted from wofford.edu; b) An example of TGA measurement of polymer. Figure is reprinted from Prime et al, Poly. Eng. Sci **1992**, 32, 1286.*

Statistical Methods

Selection of proper statistical methods is essential in quantifying the sameness/difference between generic products and the reference list drug (RLD), especially when it is needed in analyzing data from bioequivalence studies.



Sample	GA	Copolymer-1
Mean % <6 kDa	34.8 (±1.9)	2.7 (±0.7)*
Mean % 6–10 kDa	39.4 (±1.2)	10.5 (±0.6)*
Mean % >10 kDa	25.9 (±1.7)	86.8 (±1.3)*

*Two-tailed *t* test *p* value <0.01

*Figure 6. AFFF–MALS results and statistical analysis of glatiramer acetate from 3 different lots. Figure is reprinted from Sarah Rogstad et al, Anal. Bioanal. Chem. **2015**, 407, 8647-8659*

CONCLUSIONS

Several key analytical and statistical methods are recognized which are critical in providing information to establish API sameness of generic polymeric drug products. Some of these analytical methods are also recommended in FDA published product-specific guidances, which describe FDA's current thinking on the appropriate methodology for establishing bioequivalence of generic polymeric drug products.

For colesevelam hydrochloride, the FDA recommends characterization of critical physicochemical properties that are essential in demonstrating the sameness of chemical structure, molecular formula, and physical chemical properties between the generic product and the RLD. For example, ^{13}C SSNMR spectra, in combination with total titratable amine, chloride content analysis and FTIR/Raman spectroscopy, can identify the basic backbone structure, crosslinking component, side chain and counter ion of the polymer. Particle size, swelling index, and DSC/TGA provide additional information about its physicochemical properties.

In the product-specific guidance of colesevelam hydrochloride tablet,[1] FDA recommends the following characterization to support API sameness to the RLD:

1. Fundamental reaction scheme
2. Chemical structure and molecular formula
3. Physicochemical properties

Characterization methods includes: ^{13}C SSNMR spectra; Data for C, H, N, Cl, and Br content by elemental analysis; Chloride content by titration to quantify the degree of protonation; Total titratable amines by titration; Bromide content by titration; Particle size with particle size distribution; Swelling Index; Spectroscopic characterizations by FT-IR) and Raman spectroscopy; Glass transition temperature by DSC; TGA

[1] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Colesevelam%20hydrochloride_oral%20tablet_021176_RV09-15.pdf; **Most recently revised in Sep 2015**

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The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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