SBIA-DMF Drug substance workshop

March 3 & 4, 2021 (Virtual)

Synthetic Therapeutic Polymers: Recommended documentation for API sameness

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March 3 & 4, 2021
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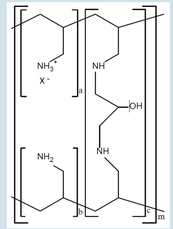
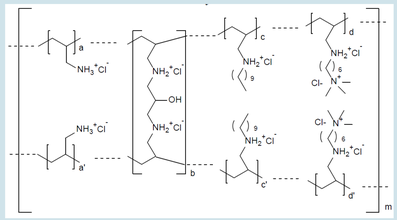
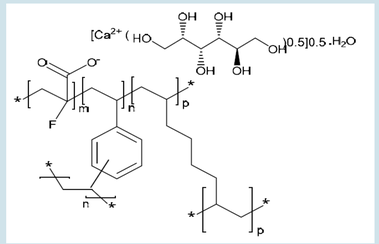
BACKGROUND

- Sevelamer Hydrochloride, Sevelamer Carbonate, Colesevelam Hydrochloride and Patiromer are an FDA-approved drugs.
- Currently sevelamer and colesevelam have approved generic equivalents.
- Sevelamer is a scavenger of Phosphate ions and used to treat hyperphosphatemia in patients with kidney decease.
- Colesevelam is a bile acid scavenger and used as cholesterol lowering drug,
- Patiromer is used lower potassium levels in Blood.

Sevelamer Salts	Colesevelam Hydrochloride	Patiromer Calcium Sorbitex
		
If c = 1, a+b=9: Where, a= Number of amines in salt form; b= Number of amines as free base; c=Number of amines involved in cross linkage. m= Large number to indicate extended polymer network X^- = Cl^- or $HCO3^-$	**where:** a + a' = 2; Number of amines with no alkylation; b = 1; Number of amines involved in cross linkage c + c' = 7; alkylated with a decyl group d + d' = 6; with 6-trimethylammonium hexyl group m = amount of extended polymeric network	m=number of 2-fluoro-2-propenoate groups = 0.91 n, p – number of crosslinking groups n + p = 0.09 H_2O – associated water *- indicates an extended polymeric network

CHARACTERIZATION:

Intermediate:

- Appropriate molecular weight of polyallylamine.
- Degree of cross coupling by solid state NMR
- Side-by-side comparative data of intermediates from at least three batches to show consistency from batch to batch.

API:

- Compare structural signatures utilizing advanced orthogonal techniques such as Elemental analysis, Solid state ^{13}C NMR, FTIR,TGA, DSC, Swell Index, Total titratable Amines, etc.
- Physicochemical properties: physical form, particle size distribution, bulk density, tapped density, swelling ratio, surface morphology, compressibility, etc.
- Biological properties: Comparable in-vitro activity.

Side-by-side comparative data from at least three batches of the test API and at least three batches of the API extracted from different lots of RLD..

CHALLENGES IN CHARACTERIZATION:

- No fixed MW and structure: Heterogenous complex mixtures of small molecules
- This kind of molecules are not soluble in any solvent.
- These drugs are not absorbed from the gut, not metabolized, and is excreted in unchanged .
- The properties cannot be fully characterized by traditionally using methods for simple API.
- Each complex API has different properties and product specific issues should be applied to show API sameness.

GENERAL APPROACHES TO ESTABLISH API SAMENESS:

Complex API sameness can be demonstrated through a comprehensive, **totality of evidence approach**.

- Process development for appropriate starting material and CPPs.
- The orthogonal characterization of the final API for Structure confirmation, Structure signature analysis,
- Appropriate Impurity profile.
- Accessing Biological activity, if necessary
- Literature in support/justification for the analytical methods used for the characterization.
- Comparison of the all the above data with API in reference listed drug (API)

MANUFACTURING PROCESS:

- Justification of starting materials to obtain the API with equivalent structural signatures as API in RLD.
- Establishing controls for the key starting materials, intermediates and raw materials.
- Establish acceptable ranges for CPPs based on API sameness data.
- Demonstrate the analytical methods are suitable to be used for IPC, CPP and for the analysis of KSM, intermediates.
- Establish adequate release/stability specifications including impurity profile for API based on the data obtained for API extracted from RLD.
- Batch data to support consistency production of the API with proposed acceptance criteria.
- Manufacturing process should be in compliance with cGMP regulations.

CONCLUSIONS:

To establish sameness, the generic version of cross coupled polymeric APIs,

- Totality of evidence is followed.
- Develop the manufacturing process with appropriate quality of starting materials, intermediates to obtain the structure defined in the label.
- Compare structural fragment analysis, physicochemical properties with API in RLD.
- Compare In-vitro biological activity
- Provide necessary literature support or scientific justification when new process/analytical methods are used.

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Office of Pharmaceutical Quality, FDA/CDER

Examples of Polymers with Cross Coupling

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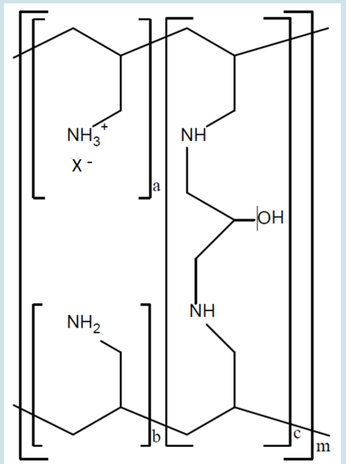	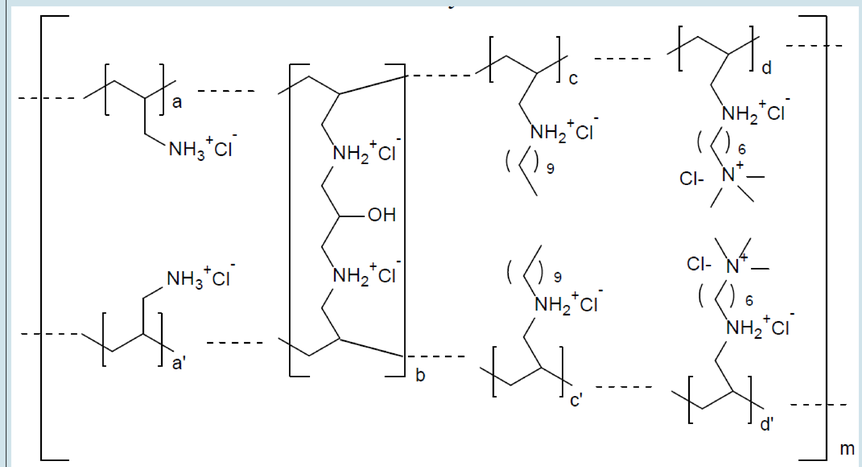	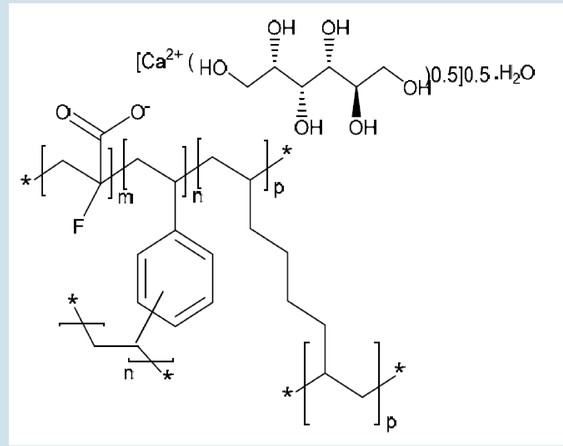
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Challenges in Characterization

- No fixed MW and structure: Heterogenous polymeric mixtures of small molecules and treated as a single active ingredient.
- Insoluble in all types of solvents
- These drugs are not absorbed from the gut, not metabolized, and is excreted in unchanged.
- The properties cannot be fully characterized by traditionally using methods for simple API.
- Each complex API has different properties and product specific issues should be applied to show API sameness.

General approach to Establish API Sameness

Complex API sameness can be demonstrated through a comprehensive, **totality of evidence approach**.

- Process development for appropriate starting material and CPPs.
- The orthogonal characterization of the final API for Structure confirmation, Structure signature analysis.
- Appropriate impurity profile.
- Accessing Biological activity, if necessary

Literature in support/justification for the analytical methods used for the characterization, if needed.

Comparison of the all the above data with API in reference listed drug (API)

Manufacturing Process

- Justification of starting materials to obtain the API with equivalent structural signatures as API in RLD.
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- Manufacturing process should be in compliance with cGMP regulations.

Characterization of Intermediates

A complete characterization of intermediates polyallylamine and cross coupled intermediate:

- Appropriate molecular weight of polyallylamine.
- Degree of cross coupling by solid state NMR.
- Other characterization methods to support the structure proposed.
- Side-by-side comparative data from at least three batches to show consistency from batch to batch.

Characterization of API

Compare structural signatures utilizing advanced orthogonal techniques.

- Elemental analysis for carbon (C), hydrogen (H), oxygen (O), and other elements present in the API, Solid state ^{13}C NMR, FTIR, TGA, DSC, swell index, Total titratable amines, etc.
- Physicochemical properties: physical form, particle size distribution, bulk density, tapped density, swelling ratio, surface morphology, compressibility, etc.
- Biological properties: Comparable in-vitro activity.

Side-by-side comparative data from at least three batches of the test API and at least three batches of the API extracted from different lots of RLD.

Conclusions

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Resources

Controlled Correspondence Related to Generic Drug Development Draft Guidance for Industry:

https://www.fda.gov/media/109232/download

Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry:

https://www.fda.gov/media/107626/download

Product-specific Guidance:

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

DMF Website:

https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs

Thank You!

We look forward to seeing you at the Workshop on March 3rd and 4th, 2021

Send questions regarding this poster to: DMFworkshop2021@FDA.HHS.GOV by February 15, 2021.