国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION

中国药科大学 CHINA PHARMACEUTICAL UNIVERSITY

Guidance on Pharmaceutical Excipient Suitability Studies (PESS) with Chinese Pharmacopeia （Volume 4）: Basics and Examples

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Introduction

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- **Background: CHP 2015 increased monographs to 270 (vs 2010ed only 135), including 23 excipients for injection use.**
- **China FDA (now NMPA) published new China DMF based registration of pharmaceutical excipients and packaging materials, which permit the excipients comply to CHP monographs submit DMF with a brief manufacturing documents.**
- **PESS allow stakeholders (regulatory agency, excipient provider, and user) correctly justify whether claimed excipients suitable to the claims.**

Introduction

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Objectives

- The PESS is the basis for selecting pharmaceutical excipients. The principle of PESS is critical material attributes (CMA) based material analysis and final product (FP)-related researches.
- To guide to verificate the suitability of CHP monograph to the claimed pharmaceutical excipients with:
  - Different manufacturing processes
  - Different sources of raw materials
  - Physical, chemical properties of pharmaceutical excipients
  - For injection, inhalation and ophthalmic, safety issues
- To guide the user to validate the excipient suitability in the FP. Validation will be based on formulation, usage and dosage and also drug-excipients interaction

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CHP monographs PESS: 3 Parts

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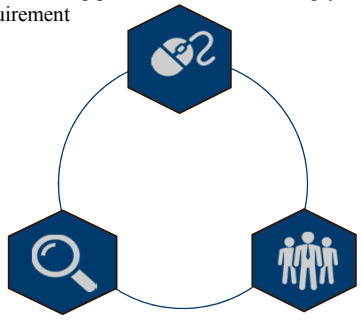
1. Verification of excipient to CHP monograph: same manufacturing process under GMP, comply with the monograph requirement



2. Verification CHP excipient suitability to claimed FP：whether the excipient suitable to FP need to evaluate based on the safety, functionality of the excipient itself, and interaction of drug-excipient, sometimes economy.

FP related researches on CMC, efficacy and safety

Outline of PESS Guidance

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Basic framework for《Guideline on suitability of pharmaceutical excipients》:

a) Foreword
b) Monograph suitability to the Chinese Pharmacopoeia on claimed excipient
c) Consideration of sources and methods of preparation for pharmaceutical excipients
d) Application of pharmaceutical excipients and dosage considerations
e) Study on safety suitability of pharmaceutical excipients
f) Documentations for the suitability study of pharmaceutical excipients

Verification of CHP monograph

Factors	Basical requirements		Guidance	Report
Source and preparation methods	Natural excipients	Plant sources: structural composition, genetic modification, pesticide residues, allergenic substances, heavy metals, etc. should comply with relevant regulations.	ChP<251>	Affirmation, COA and verification report should be submitted
		Animal sources: composition, TSE, virus, genetically modified organisms, pesticide residues, allergic substances, heavy metals, etc. should comply with relevant regulations	Guidance on animal excipients<Drafting>	Affirmation, COA and verification report should be submitted
	Semi-synthetic excipients	Provide chemical composition, structure, preparation process, quality requirements and quality standards		Affirmation, COA and verification report should be submitted
	Synthetic excipients	Structure, molecular weight, related substances, impurities should meet the requirements	ChP<251>	Affirmation, COA and verification report should be submitted
Levels	High-risk pharmaceutical excipients should be separately set for quality standards		Announcement of the General Administration of the SFDA (2016, number 134)	COA report should be submitted

specification	Vendor and user agreement to develop FRCs methods and limits	ChP(2015)<9601>	Examination report for FRCs
Biosafety	New excipients, high-risk excipients changing the route of administration , excipients increasing the dosage of	Guidance on the biosafety of excipients<Drafting>	Verification Report of GLP Lab
Compatibility with drug	Compatibility of drugs and pharmaceutical excipients and their effects	Guidance on the compatibility of pharmaceutical excipients and drugs<Drafting>	Compatibility study report
Prescription screening	Screening prescriptions and processes, determining the type, grade, specification, dosage of pharmaceutical excipients, and preparation process	ChP(2015)<9601>、ICH Q8	Optimization of formulation and validation report

Only applicable to excipients manufactured under GMP

Scheme of PESS

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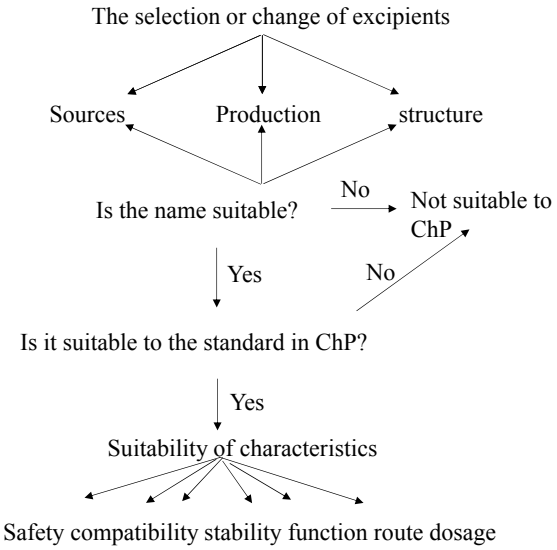

The application route and dosage of pharmaceutical excipients should be studied combined with specific formulation studies. If the pharmaceutical excipients in the preparation exceed the application route and exceed the dosage, the corresponding evidence for the application of the excipients (safety study, etc.) should be validated.
According to administration, the pharmaceutical excipients may have different **level**s, i.e. high risk, medium risk and low risk. Different LEVEL excipients usually have large differences in internal quality. Excipients for injection use, for inhalation use, et al, are high risky level. Excipients with high risky monographs are recommend to the corresponding preparation. If high risky preparation use lower level one, validation need to perform.

Grade of excipients

- Pharmaceutical excipients can be divided into different grades according to particle shape, particle size and density. The same excipients with different grades often have different functional related characteristics. Excipient suppliers should correctly label (including functional related characteristics). Suitability studies should include the selection and screening of grades. Pharmaceutical production and formulation prescriptions should validate the suitability of the grades of the used excipients.

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Basic principles of selecting excipients

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The suitability study of pharmaceutical excipients is the basis for scientific selection of medicinal excipients, including the suitability of pharmaceutical excipients for different types of formulation, different production processes, different usages and dosages, and different sources of raw materials.

- Full understanding of the characteristics of excipients
- Understand the active substance itself
- Choose excipients according to the process developed by the dosage form
- Choose excipients based on the dose of the drug
- Choose excipients according to the dosage form
- Select excipients according to drug-release characteristics

Examples

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Starch：

- Sources of raw materials：wheat, potato, cassava, corn
- Functions: bulking agent, disintegrating agent, binding agent, glidants
- Different manufacturers

Polysorbate 80：

- Grades: injection grade, normal grade
- Solubilization and stability ability to different drugs: complex components of traditional Chinese medicine, single poorly soluble drugs
- Different manufacturers, different production techniques

Lactose：

- Route of administration：oral, inhalation
- Different manufacturers, different production techniques： Meggle Group vs made in China

Examples

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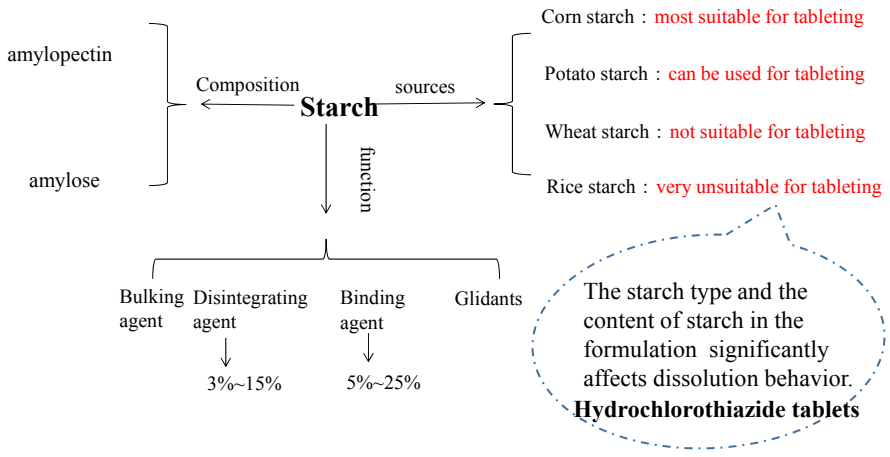

Examples

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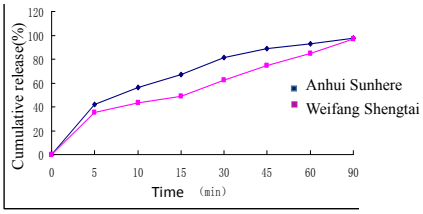
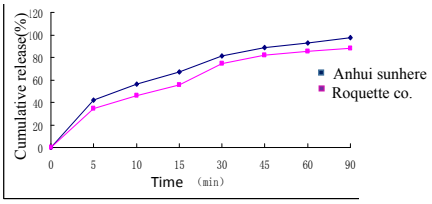
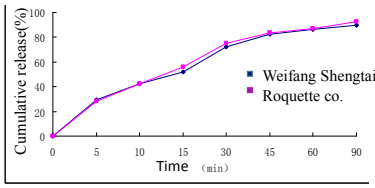


The release behavior using cornstarch from Weifang Shengtai company and Anhui Sunhere Pharmaceutical Excipients Co.



The release behavior using cornstarch from Anhui Sunhere Pharmaceutical Excipients Co. and roquette co.



The release behavior using cornstarch from Weifang Shengtai company and roquette co.

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Company	Type	Lot number	Water
Anhui Sunhere Pharmaceutical Excipients Co	SH-L	161006	4.50%
		170806	5.49%
	SH-M	170801	8.31%
	SH-H	170826	7.33%
Weifang Shengtai company		20170602	11.45%
		20170414	10.92%
Roquette co.	Maize Starch B	E3609	12.55%
	Maize Starch B	E4554	12.41%

High moisture affects the disintegration efficiency of starch, making dissolution of tablets slower.

Examples

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Different provider

Anhydrous lactose VS monohydrate

Alpha-lactose

Beta-lactose

Species

Factory

Quality

Lactose

Application

Tablet

Capsule

Freeze-dried product

inhalation

Sources, purity, miscellaneous protein, etc

Requirements for the inhalation formulation characteristics:

(morphology, particle size, specific surface area, bulk density, fluidity), content, impurities, moisture, microbial limits, heat/bacterial endotoxin, protein content

Examples-suitability study for different route of administration

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For injection
- Bacterial endotoxin
- Microbial limits (2015 Chinese Pharmacopoeia, General Principles 1105 and 1106)
- Sterility requirements(2015 Chinese Pharmacopoeia, General Principles 1101)

Oral formulation Requirements on microbes are lower than that of injection

External formulation Requirements on microbes are lower than that of oral formulation

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Examples

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The suitability study of pharmaceutical excipients with different viscosity

HPMC
- HPMC (low viscosity)
  - Binding agent for tablet
  - Porogen for sustained or controlled release tablets
- HPMC (high viscosity): Retarding agent and controlled release agent for hydrophilic gel matrix sustained release tablets

Examples

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The suitability study of pharmaceutical excipients with different doses

- The functions of HPMC with different concentration in formulation

Functions	Doses
Binding agent, disintegrants for Granules, tablets, pills	1.5%-4.0% solution
Film-forming material for film coating	2.0%-4.0% solution
Thickeners for colloidal preparations and suspending agent for suspensions	0.5%-15% solution

Examples

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The suitability of excipients with different molecular weight

PEG	PEG(200,400,600)	PEG-4000, PEG-6000
Function in formulations	Solubilizer in injection	Baes used in ointments and suppositories

Examples

Prepare process

Magnesium stearate

- Mixing time affects tablet dissolution
- The formulation with the same dose of magnesium stearate in direct tableting is more hydrophobic than the granulation formulation.

Incompatibility

- magnesium stearate: aspirin, iron salts, some vitamins, alkaloids, and drugs sensitive to magnesium ions, strong organic acid salts
- Lactose compatibility: Pharmaceutical preparations containing aspirin, theophylline, penicillin, and phenobarbital should avoid the use of lactose.

Examples- Excipients

Different functional excipients and its key standard

Tab. Different functional excipients

Functions	Excipients	Key standard
Diluent	Lactose, sucrose, kaolin, basic calcium carbonate, calcium carbonate, calcium phosphate	Color, particle size, particle size distribution, heavy metals, moisture, microbial limits
Binders	Water, alcohol, starch slurry, gelatin solution, xanthan gum, sodium alginate, carboxymethyl cellulose, polyethylene glycol, pyrrolidone	Viscosity, foreign matter, residue on ignition, pH, microbial limit
Lubricant	Magnesium stearate (calcium), talc, stearic acid, mineral oil, sodium chloride, sodium benzoate, polyethylene glycol	Particle size, water, melting point range, microbial limit
Disintegrating agent	Corn starch, methyl cellulose, sodium carboxymethyl cellulose, alginic acid, microcrystalline cellulose	Foreign matter, moisture content, viscosity, microbial limits
Pigment	Dyes and shades specified by FD&C. and D&C	Identification, volatile organic content, color grade
Flavor	Volatile oil, dry spices	Refractive index, specific gravity, solubility, alcohol content
Sweetening agent	Mannitol, lactic acid, sorbitol, saccharin, aspartame	Water content, heavy metals, residues on ignition, specific rotation

Examples

The microbial limit study for different route of administration

Tab. Microbial limit study for routes of administration

Formulation	Total amount of microorganisms (cfu/g,ml)	The total amount of mold and yeast (cfu/g,ml)	Colonies not allowed
Tablet/Capsule	1000	100	Escherichia coli, Salmonella
Oral liquid formulation	100	10	E.coli
Suppository	1000	100	
Nasal medications	100	10	Staphylococcus aureus、Pseudomonas
Inhalation	100	10	Staphylococcus aureus, Pseudomonas aeruginosa, gallbladder-tolerant Gram-negative bacteria
Vaginal medication	100	10	Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans
Transdermal preparation (each piece)	100	10	Staphylococcus aureus、Pseudomonas

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Summary

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- Excipient PESS is aim to guide:

1. Excipient provider to verificate the applicability of the CHP monograph to the claimed excipient. Only manufactured under GMP can be validated.
2. Drug product manufacturer to validate the suitability of excipients comply with CHP monographs.
3. NDA and ANDA researcher to validate the excipients when choose CHP monograph excipients.