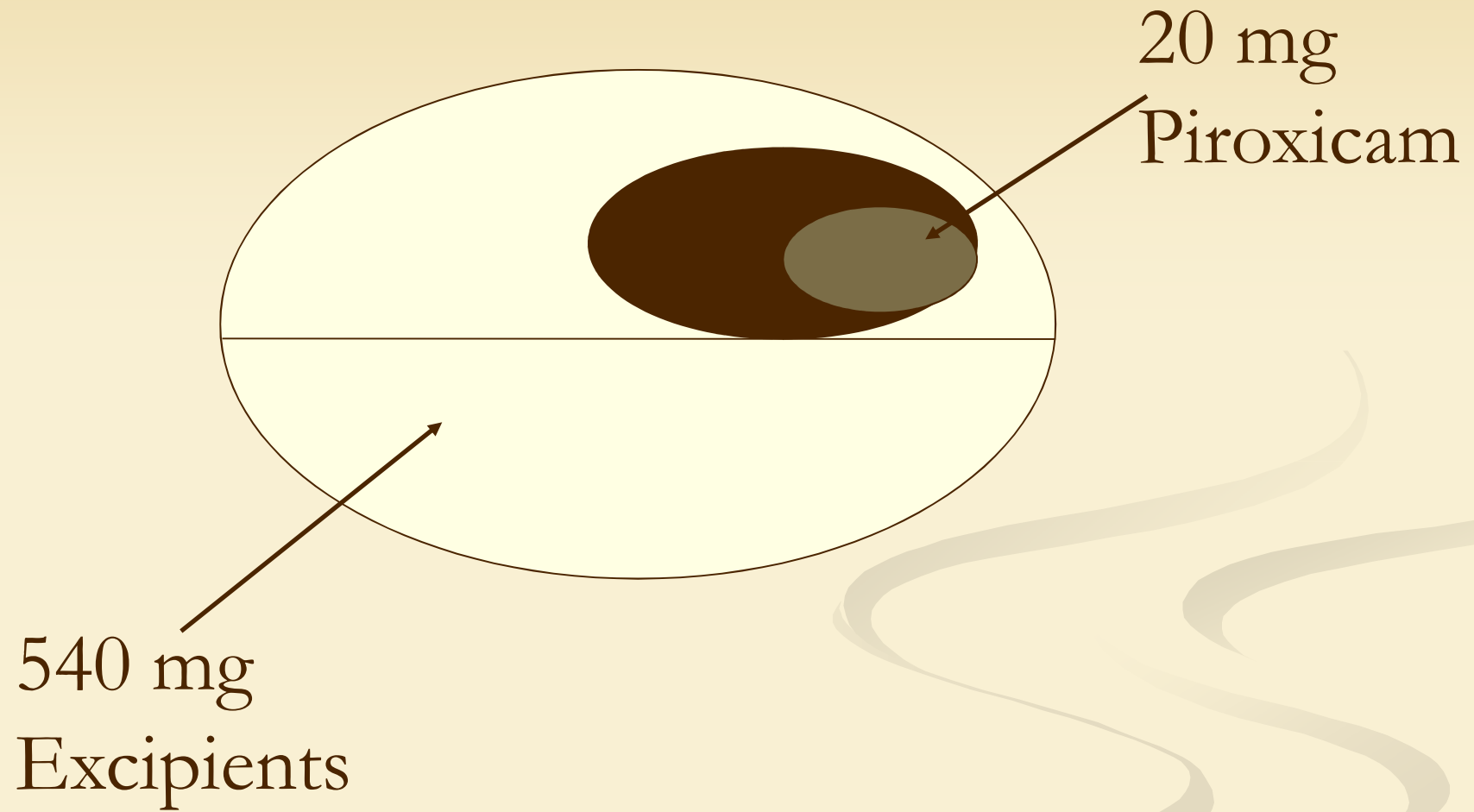


*Functionality-Related
Characteristics of
excipients and
pharmaceutical
development*

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« Excipienttherapy »

History of functionality testing

- 1994: USP conference on functionality testing
- 1995: Ph. Eur. Workshop on functionality testing
- 1995: Ph. Eur. Commission decides inclusion of functionality-related tests
- 2002: EDQM Excipient Symposium
 - Discussions with manufacturers and regulators on current and future developments
- 2002: General monographs on substances for pharmaceutical use
- 2008: General chapter on FRCs published
- 2008-2009: Publication of monographs of excipients with F.R.C.

Functionality is based upon:

- Molecular structure
- Chemical properties
- Physical properties
- In some cases impurities

Inorganic impurities

- Heavy metals
- Sulfite

Organic impurities

- Proteins
- Additives
- Degradation products
- Monomers
- Residual solvents
- Pesticides
- Microbial contamination

Additives

- Silicon dioxide 0,5%
- Butylated hydroxytoluene 200 ppm
- Alpha Tocopherol 0,1-0,2 %
- Hydrogen peroxide ppm
- Glyoxal max 200 ppm


Degradation products of excipients

Benzyl alcohol



Benzyl aldehyde
+ Hydrogen peroxide

Functionality is influenced by:

- Formulation
 - Manufacturing process
- 
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Functionality testing

The direct testing of the concerned function of an excipient in a particular formulation and manufacturing process to verify that the excipient provides the intended functionality.

Direct compression excipient

- Tablet machine
- Precompression and compression force
- Punch
- Speed

Film former excipient

The functionality depends on:

- Formulation:

 - Type of liquid dispersion

 - Plasticizer

Functionality-related characteristics

A controllable physical or chemical characteristic of an excipient that is shown to impact on its functionality.

To define FRCs

- Actual function(s) of the excipients must be known
- Relevant propertie(s) identified
- Defined tests
Necessity to develop standardised methods to characterise the properties of excipients.

Monographs of excipients

- Definition
- Characters
- Identification
- Tests:
 - Chemical and microbiological purity
 - Physical characteristics associated with chemical structure

F.R.C. in the E.P.

- Non-mandatory section to excipients monographs
- Typical uses
- Control methods
 - E.P. general analytical methods
 - Possibility of other control methods

FRC in the E.P.

- Name of the FRC
- Recommended method
- With or without acceptance criteria

Monographs

Mandatory section

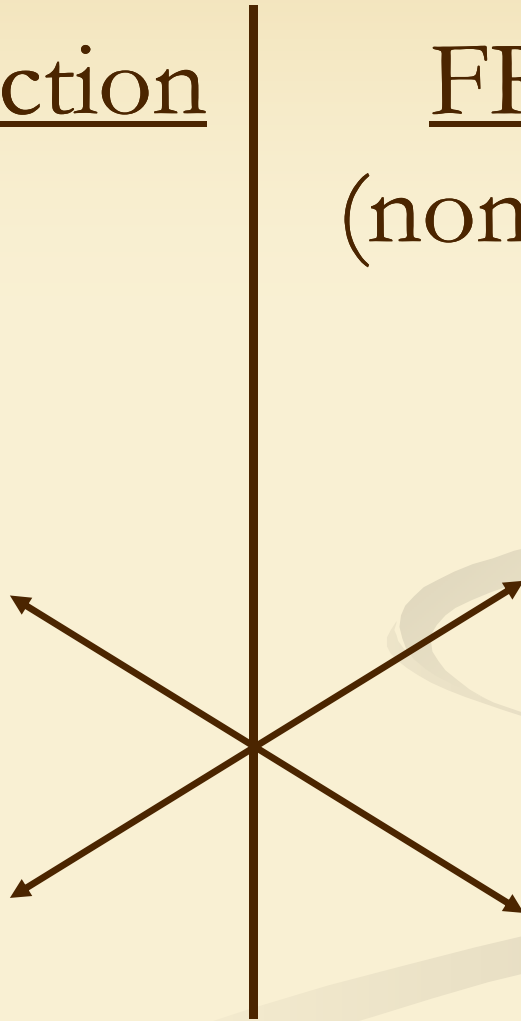
FRC section
(non mandatory)

Test 1

Test 2

Test 2

Test 1



Interests

- To help manufacturers of drug products to define specifications based on standard analytical method
- A common language by manufacturers, users, assessors.

Behaviour of Materials

- Solid state properties
- Powder properties
- Impact of process parameters

**Relations between primary
properties and secondary properties
of the solid state and of the
particulate solid and sources of
modifications**

**Doelker STP Pharma Pratiques
9(5) 399-409, 1999**

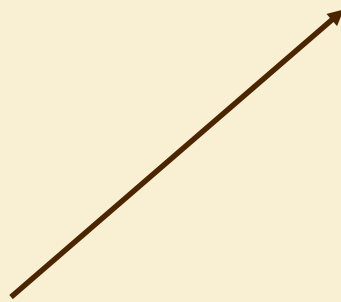
Primary properties

Secondary properties

Impurities

Residual solvents

Additives



Crystalline structure

- polymorphism

- solvate



- amorphous

Crystalline defects

Habitus

Particle size

Mechanical properties

Plasticity

Hardness

Comprimability

Surface properties

Surface energy

Polarity

Wetting

Mechanical stress

- milling

- compression

Temperature

Humidity

Solubility

Dissolution

Bioavailability

Pharmacological activity

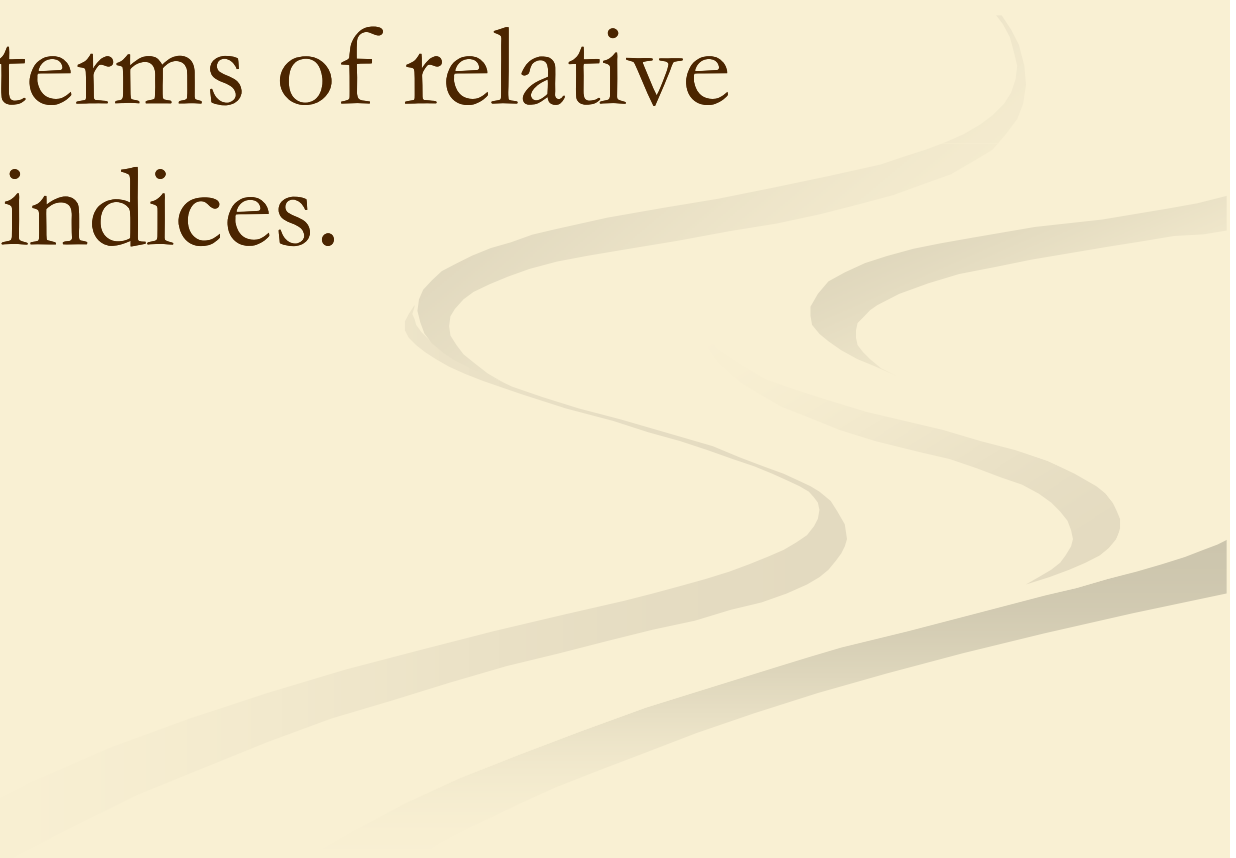
Hygroscopicity, stability

Characterisation of raw materials in solid form

Scale of scrutiny	Properties studies
Molecule	Structure, Phase analysis, Polymorph, Crystallinity, Solubility, Mechanical
Particulate	Particle size and shape, Surface, Dissolution
Bulk	Packing, Flow, Compaction
Machine	Compressibility

Behaviour of Materials

Evaluated in terms of relative performance indices.

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FUNCTIONALITY- RELATED CHARACTERISTICS

Examples

Crospovidone as disintegrant

- Hydration capacity

The hydration capacity is the ratio of the mass of the residue to the initial mass of the sample. It is typically 3 to 9

- Particle-size distribution (2.9.31)

- Powder flow (2.9.36)

Crospovidone used as suspension stabiliser

■ **Settling volume**

Croscarmellose *sodium*

used as disintegrant

- Settling volume
 - Degree of substitution
 - Particle size distribution
(2.9.31 or 2.9.38)
 - Hausner ratio
(2.9.36)
- Mandatory

Croscarmellose *sodium*

used as disintegrant

■ **Settling volume**

Place 75 ml of *water R* in a 100 ml graduated cylinder and add 1.5 g of the substance to be examined in 0.5 g portions, shaking vigorously after each addition. Dilute to 100.0 ml with *water R* and shake again until the substance is homogeneously distributed. Allow to stand for 4 h. The settling volume is between 10.0 ml and 30.0 ml.

Maltodextrin

The degree of hydrolysis, expressed as dextrose equivalent (DE), is less than 20 (nominal value)

- **Dextrose equivalent within 2 DE units of the nominal value**
- **Other tests: pH, Sulphur dioxide, Heavy Metals, Loss on drying, Sulphated ash**

Maltodextrin used as filler and binder in tablets and capsules

■ **Dextrose equivalent** (see Tests)

■ **Particle-size distribution** (2.9.31 or 2.9.38)

■ **Powder flow** (2.9.36)

Hypromellose used as binder,
viscosity-increasing agent or
film former

■ **Apparent viscosity**

■ **Degree of substitution**

Mandatory

Hypromellose used as matrix former in prolonged-release tablets.

- **Apparent viscosity**
 - **Degree of substitution**
 - **Molecular mass distribution (2.2.30).**
 - **Particle-size distribution (2.9.31 or 2.9.38).**
 - **Powder flow (2.9.36).**
- Mandatory**

Xanthan Gum used as viscosity-increasing agent

- Apparent viscosity

Mandatory

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Xanthan Gum used as matrix former in prolonged-release tablets

- **Apparent viscosity** Mandatory
- **Particle-size distribution** (2.9.31 or 2.9.38)
- **Powder flow** (2.9.36)

Carbomers used as viscosity-increasing agents and gelling agents

- **Apparent viscosity** Mandatory
- **Carboxylic acid groups** Mandatory

Aims of Pharmaceutical Development

- To justify the type of dosage form selected
- To justify the qualitative and quantitative composition of the drug product
- To justify the manufacturing process
- To identify critical parameters (formulation parameters and process parameters)
- To define specifications of critical formulation parameters


For the purpose specified in the application

Pharmaceutical Development

As a function of the drug
substance

- Therapeutic properties.
- Chemical properties.
- Physical properties.
- Biopharmaceutical properties.

Physico-chemical properties

- Organoleptic characteristics
 - Hydrosolubility
 - Log P
 - pka
 - Polymorphism
 - Stability
 - Granulometry
- 
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Descriptive term	Approximate volume of solvent in millilitres per gram of solute			
	Very soluble	less than	1	
Freely soluble	from	1	to	10
Soluble	from	10	to	30
Sparingly soluble	from	30	to	100
Slightly soluble	from	100	to	1000
Very slightly soluble	from	1000	to	10 000
Practically insoluble	more than			10 000

Solubility

- Very soluble : the highest dosage will dissolve in a volume less than 250ml at all the pH.
- Very soluble (European Pharmacopoeia)
 - 1g of substance will dissolve in 1ml.

Biopharmaceutical properties

- Absorption site
- Systemic absorption
- Absolute bioavailability
- First hepatic pass effect
- Half-life
- Therapeutic window

The excipients chosen, their concentration and the characteristics that can influence the drug product performance (e.g. stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient.

The ability of excipients (e.g. antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality and to perform throughout the intended drug product should also be demonstrated.

At a minimum

- To define the critical parameters of the drug substances, excipients, container closure systems and manufacturing processes.
- To justify control strategies.
- Generally, critical parameters are identified through an assessment of the extent to which their variation can have an impact on the quality of the drug product

Critical characteristic

Any physical or chemical material characteristic that has been demonstrated to impact significantly on the manufacturability and/or performance of the final preparation.

FRC

Following a risk-based approach

Identification of the critical properties of the pharmaceutical substances relative to

- Manufacturing process.
- Performance of the final drug product.

Establish an acceptable range of the critical characteristics including for both physical and chemical properties.

Relation between critical properties and FRC

Lactose monohydrate



FRC

- Particle size distribution
- Bulk and tapped density

- For direct-compression :

Critical parameters

- Particle size
- Bulk and tapped density

- For diluent in wet granulation

No Critical parameters

- Except if insolubility of drug substance

Without further regulatory review

- Excipient supplier change
- Quantities of excipient to adapt as a function of quality

ex : magnesium stearate

talc

- Range of excipients for which there is no impact on process and drug product quality ex: degree of substitution of cellulose

F.R.C.



Critical parameters potentially based
on risk management



Critical parameters after D.o.E.



Control of critical parameters



Real Release Time

To define design space it is necessary to identify critical properties of the excipients



Functionality related characteristic



Control method

Particle size analysis


- The determination of the particle size by microscopy is the reference method.
- If the particle size is determined by laser
 - The operating conditions must be described
 - The results are expressed as :
 - D10
 - D50
 - D90

Dissolution and generic drug products

Comparison of the dissolution profile of the reference and of the test

- Discriminatory testing
 - pH
 - Agitation speed
 - Concentration of the drug substance
- Specifications
 - For immediate release solid dosage form :
 - $Q=75\%$ in less than 45min
 - For modified release solid dosage form
 - Operating conditions
 - at least 3 points

Discriminatory testing

- Ability to recognize the voluntary variations of only one parameter on dissolution.
 - Granulometry
 - Hardness
- 
- The slide features a light beige background with a decorative graphic of several overlapping, wavy, horizontal lines in a slightly darker shade of beige, located in the lower right quadrant.

Dissolution

Once bioequivalence has been shown in vivo, the in vitro dissolution method should serve as a quality control to discriminate between acceptable and non acceptable batches.

Dissolution

The specification for the in vitro dissolution of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product, which would be expected to be similar to those of the reference product.

Conclusions

- Progress with FRC.
- Control of critical parameters of an excipient for a given process and drug product.
- To improve the scientific pharmaceutical development which is the basis for a perfect control of a process.

Conclusion

- The quality of the drug product is built up through the chemical development of the drug substance and the pharmaceutical development of the drug product.
- The level of quality in the drug product should be reached in routine production.