Formulation Facilitation of Powder Blends, Sugar-Free Coatings and HME with an Unique Polyol

Presented by Bodo Fritzsching, BENEO-Palatinit GmbH
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Content of lecture

- About BENEO - Palatinit GmbH
- Pharmaceutical grade isomalt
  – a multifunctional polyol

  * What is galenIQ™?
  * Manufacture and excipient range
  * General properties
- Powder blends
  (for direct compression, sachets, pouches and dry suspensions)
- Sugar–free coating and film–coating
- Hot Melt Extrusion – feasibility
- Summary

About BENEO-Palatinit GmbH

> **BENEO** – Part of a global organization

SÜDZUCKER GROUP
5.8 bn € turnover; ~ 20,000 people

Sugar	Specialities	Fruit
SÜDZUCKER, AGRANA, SAINT LOUIS SUCRE, Tereos, Surafti	Functional Ingredients: beneo orafti · palatinit · remy Bio-Ethanol: crop energies Starch: AGRANA Frozen Food & Portion Pack: Freiberger, PortionPack Europe	Juice & Fruit Concentrates: AGRANA

BENEO-Palatinit GmbH's PHARMA Department

Innovation & Science Support

- specialty excipient sales
- world wide agency network
- application technology
- pharma-ceutical technology
- cGMP QM/QC
- passionate team
- regulatory support
- nutritional science

Support in Formulation Design


Frame Formulation Development
- ð Wet Granulation
- ð Direct compression

Tabletting
- ð State of the Art Fette P1200i Rotary Press

Sugar(free) Coating and Film Coating
- ð Driam Variomat Lab-Coater and Open Pan

High-boiled lozenges
- ð Bosch Batch Cooker

Pharmaceutical grade isomalt

– a multifunctional polyol

* What is galenIQ™?
* Manufacture and excipient range
* General properties

What is galenIQ™?

§ galenIQ™ (pharmaceutical grade isomalt) is a filler/binder, tablet & capsule diluent, coating agent…

§ it complies with the isomalt monographs of the current Ph. Eur., BP, USP-NF and is approved for use in Japan and China

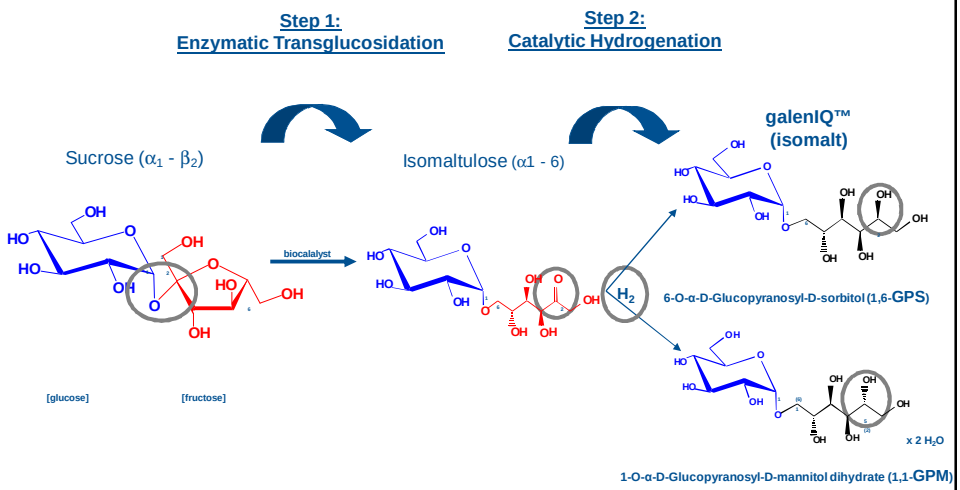
§ galenIQ™ is manufactured under cGMP guidelines for pharmaceutical excipients (IPEC-PQG)

§ under its generic name „isomalt“, galenIQ™ is listed in all major reference books for pharmaceutical excipients and in the US FDA/CDER Inactive Ingredient Database

§ main field of application:
oral solid-dosage forms

galenIQ™ the smart excipient

Non-animal origin - manufacture of galenIQ™



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galenIQ™ (isomalt Ph.Eur., BP, USP-NF) - excipient range

Direct compression Sachets Dry suspensions Dry compaction	Agglomeration Wet granulation Dry compaction Film Coating	Blending Capsule filling Starter pellets Hot melt extrusion	Sugarfree Coating	High Boiled Lozenges
DC-grade d_{50} 200µm	NLT 90% <50µm	d_{50}* 380µm	d_{50} 770 µm	d_{50} 980µm
galenIQ™ 720	galenIQ™ 800 galenIQ™ 801	galenIQ™ 960	galenIQ™ 981	galenIQ™ 990
DC-grade d_{50} 180µm	NLT 90% <100µm	d_{50} 830µm		
galenIQ™ 721	galenIQ™ 810	galenIQ™ 980		

1:1 GPS/GPM ratio
Solubility in water: 25g/100g at 20°C

3:1 GPS/GPM ratio
Solubility in water: 42g/100g at 20°C

galenIQ the smart excipient

*Typical data within specification of the different galenIQ™ grades

Physico-chemical properties of galenIQ™

- § different solubilities
- § very low hygroscopic
- § highly resistant against enzymatic and acidic degradation
- § heat stable; melting range: 145 to 150 °C
- § no reaction with amino groups
- § no incompatibilities with API's faced
- § unique morphology

- § equilibrated sweetness (no aftertaste, taste profile similar to sucrose with half the sweetening power)
- § non cariogenic
- § low glycemic – suitable for diabetics

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Pharmaceutical grade isomalt in powder blends

Application of powders blends

Intermediate products for the production of dosage forms:

- Tablets, capsules, granules, emulsions, suspensions etc.

Powder blends for direct use by the patient:

- Pouches for direct oral application
- Sachets/pouches resp. dry suspensions to mix with water prior to ingestion





Excipient requirements for powder blends

- ü excellent flowability
- ü high physical stability during process of mixing
- ü high dilution potential and content uniformity
- ü specific morphology to prevent segregation
- ü chemical stability
- ü low hygroscopicity
- ü direct compressible
- ü pleasant sweet taste
- ü suitable for all patients
- ü economical……

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Agglomerated isomalt – galenIQ™ 720 and 721

	galenIQ™ 720	galenIQ™ 721
Chemical composition	1:1 GPS / GPM	3:1 GPS / GPM
Preferred Application	direct compression dry suspensions	direct compression sachets/pouches
Solubility in water at 20°C (g/100 g)	25	42
Bulk density (g/l)	450	450
Tapped density (g/l)	504	504
Hausner factor	1,12	1,12
Carr index	10	10
Angle of repose	33°	31°
Flowability (s/100 g) (orifice d = 6 mm)	55	57

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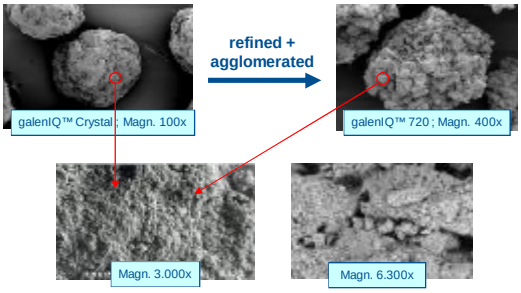
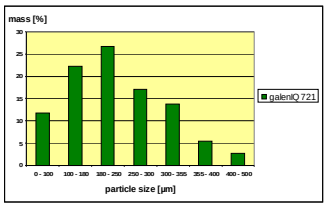
* typical values

galenIQ™'s unique morphology and particle size distribution*



- almost spherical
- large and porous surface area
  - ð prevents segregation, ensures homogeneity of the mix and gives content uniformity
- wide range of different API particle size distributions can be used
- low compaction forces in tabletting



Agglomerated galenIQ™ 720 and 721:

Low fines content (< 63 µm)

ð Allows to incorporate higher concentrations of active ingredients

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* typical values from random batches

High agglomerate stability during mixing

Particle size distribution of galenIQ™ 720 prior, after 2 min and 15 min of mixing utilizing a high shear plough shear mixer at 120 rpm

Mixer Type Loedige M20

	prior	after 2 min	after 15 min
d 5	63 µm	43 µm	35 µm
d 50	239 µm	224 µm	217 µm
d 95	513 µm	501 µm	491 µm

galenIQ™ 720 exhibits high agglomerate stability during the process of mixing.

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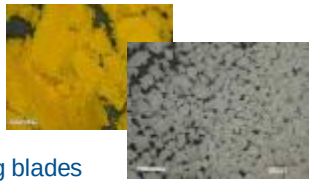
Particle size distribution by volume measured with laser diffraction technology.

Case study: Content uniformity of Chinolin-yellow and galenIQ™ 721 powder blends

Reference substance (very cohesive and lumpy):

- 1, 20 + 40 % Chinolin yellow E104; d_{50} 10 µm



Equipment and process parameter:

- 3 liter lab scale bin blender with fixed blending blades
- Rotational speed 20 rpm
- Fill level 70% (v/v)

Sampling:

- after 0; 1; 2; 3; 5; 10; 20; 30 minutes
- amount: 1g; three sampling spots

Analysis:

- spectral photometric analysis

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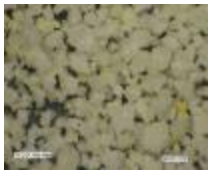
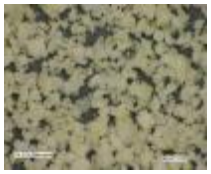
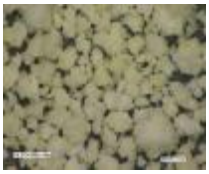
Blend uniformity of low dosage powder mix using galenIQ™ 721 as carrier

99 % galenIQ™ 721 + 1% Chinolin yellow E 104 (reference substance)







a) after 1 min b) after 3 min c) after 5 min

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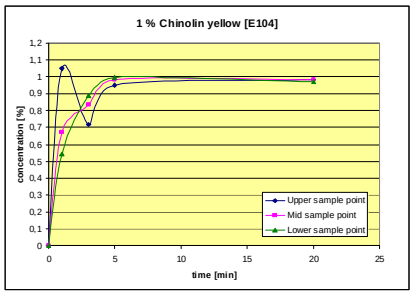
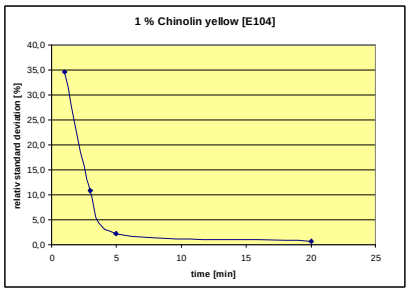
Blend uniformity of low dosage powder mix using galenIQ™ 721 as carrier



Concentration of reference substance in galenIQ™ 721 matrix as a function of blend time.



Relative standard deviations as a function of blend time.

Blend uniformity after 5 minutes

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Concentration of reference substance (Chinolin yellow) determined by spectral photometric analysis.

Low dosage example - powder blend with Glibenclamide

§ **5 mg Glibenclamide** (psd 100% < 40µm) - **formulation for direct compression**

Ingredient	Function	Content / Tablet [mg]	Content [%]
Glibenclamide (powder)	Active Ingredient	5	4,0
galenIQ™ 721	**Binder and Filler**	**115,625**	**92,5**
Crospovidone CL	Superdisintegrant	3,75	3,0
Mg Stearate	Lubricant	0,625	0,5
Sum		125	100,00

Content uniformity

rel. std. dev. **1,1 %**

Glibenclamide / tablet: **4,98 mg** (average of 10 tablets)

ð Excellent content uniformity provided by galenIQ™
ð Direct compression instead of wet granulation

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Low dosage example - powder blend with Theophylline monohydrate

§ **25 mg Theophylline** (psd 100% < 100µm) **- formulation for direct compression**

Ingredient	Function	Content / Tablet [mg]	Content [%]
Theophylline monohydrate	Active Ingredient	25	5,0
galenIQ™ 721	Binder and Filler	452,5	90,5
Crospovidone CL	Superdisintegrant	20	4,0
Mg Stearate	Lubricant	2,5	0,5
Sum		500	100,00

Content uniformity

rel. std. dev. **1,2 %**

Theophylline monh. / tablet: **24, 87 mg** (average of 10 tablets)

ð **Excellent content uniformity provided by galenIQ™**

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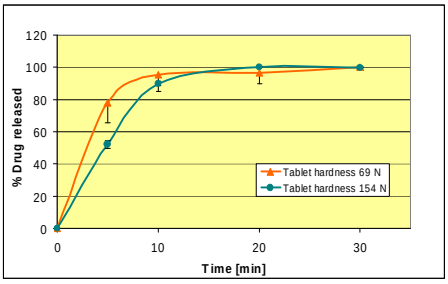
Source: University Groningen, NL

Excursion: Tablet characteristics

Compaction Forces	10 kN	20 kN	Using low soluble galenIQ™ 720 20 kN
Crushing strength	69 N	154 N	154 N
Friability	0,6%	0,5%	0,4%
Disintegration Time (no disk)	12 s	261 s	331 s

Dissolution profile Theophylline mono-hydrate 25 mg

USP requirement: release of min. 80 % after 45 minutes is reached already after 10 minutes.



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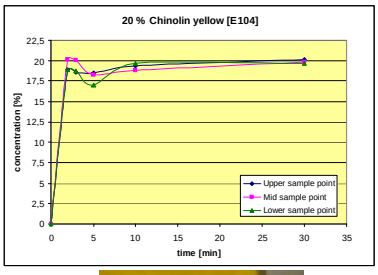
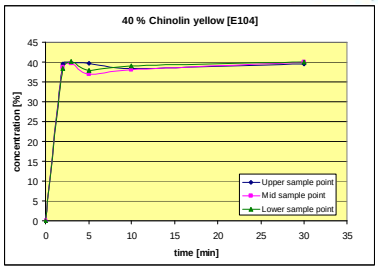
Tableting in technical scale, 13 mm, high speed
Source: University Groningen, NL

Blend uniformity of high dosage powder blends using galenIQ™ 721 as carrier





- **20 % Chinolin yellow**
- **blend uniformity after 10 minutes**
- **rel. standard deviation at 10 min: 1.4%**
- **good flowability**

- **40% Chinolin yellow**
- **blend uniformity after 10 minutes**
- **rel. standard deviation at 10 min: 1.2%**
- **moderate flowability**

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High dosage example powder blend with Ibuprofen

§ **400 mg Ibuprofen 50 - formulation for direct compression or sachets (with slight modifications)**

Ingredient	Function	Content / Tablet [mg]	Content [%]
Ibuprofen	Active Ingredient	400	60,6
galenIQ™ 721	**Binder and Filler**	**220**	**33,3**
Crospovidone CL	Superdisintegrant	28	4,2
PEG 6000	Lubricant (Disintegrant, reduces friability)	6,5	1,0
Mg Stearate	Lubricant	5,5	0,8
Sum		675	100,00

Content uniformity

API / tablet: **393,4 mg** (avg. of 10 tablets)

rel. std. dev. **0,9 %**

ð Excellent content uniformity & very high dilution potential of galenIQ™

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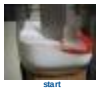
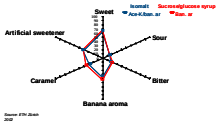
Source: German contract manufacturer

Summary agglomerated isomalt - galenIQ™ 720 and 721 in powder blends

- excellent flowability
- low fines content, large surface area and porous surface structure
- prevents segregation, ensures homogeneity and content uniformity of the powder mix
- API's of various particle size distributions can be mixed into a galenIQ™ 720/721 matrix
- provides a pleasant sweet taste !
- Ideal for e.g. sachets/pouches for direct oral application, dry powder suspensions/syrups, etc. tablets (e.g. chewables, lozenges, effervescents)





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Isomalt – copolymer in film-coating

Isomalt – a copolymer in film-coating

Function	Product	Typical composition* [%]
Polymer	HPMC, HPC, PVA	**10 – 60**
Plasticizer	PEG, Propylene Glycol, Glycerol	**0 – 20**
Pigment	Iron Oxides, natural Pigments (TiO_2)	**0 – 50**
Copolymer	Lactose, Polydextrose or **galenIQ™ 801**	**10 – 40**

Aqueous Suspension of 15 – 20 % DS are prepared.

Advantages of galenIQ™:

- **excellent adhesion of film on tablet**
- **available in pharmaceutical quality**
- **lactose free**
- **shorter process times**
- **formulation more economical**

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* by weight of the dry film coating composition and of the non-water ingredients of the aqueous coating suspension
Source: US Patent 5630871 - Film coatings and film coating compositions based on cellulosic polymers and lactose

Sugar-free coating with isomalt

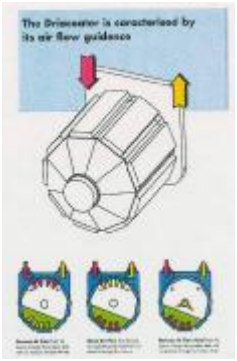
Equipment requirements and basic operations of sugar-free pan coating

§ Type of equipment:

- all open or closed systems
- automated systems with perforated drums (similar to film-coating)
- preparation/storage tank and spraying system for aqueous sugar solutions (single phase nozzles)

§ Basic operations:

- Application of solution
- Distribution of solution
- Concentration of solution
- Set off crystallization
- Drying of the panned goods (e.g. 20°C, < 20% rh)



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galenIQ™ 981 coating – basic formulation

Ingredient	%
galenIQ™ 981*	65,00
Water	31,95
Gum Arabic	2,05
Titanium Dioxide**	1,00
Color/Flavor	as required

* amount (dms) can be adjusted (range 55 to 72 %)
Depending on the type and format of the centers to be coated

** may not be required depending on final color

***Alternatively, HPMC or surfactants such as gelatin or polysorbates can be used

§ Dissolve galenIQ™ until crystal free in water whilst stirring and heating (70 - 80 °C)

§ Stop heating

§ Add gum arabic solution and TiO_2 or color homogeneously
(if required, e.g. talcum or calcium carbonate can be added to reduce tendency to stickiness)

§ Adjust and keep temperature during processing at 50 - 55 °C

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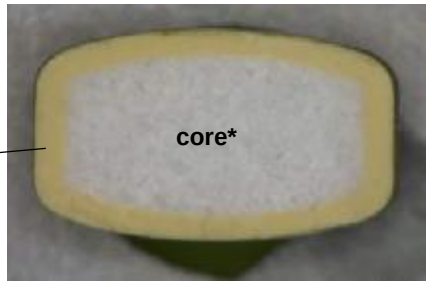
galenIQ™ 981 in sugar-free coating

Even difficult tablet shape can be covered well with galenIQ™ 981 coating.



*** tablet of galenIQ™ 721 + 0,5 % Mg St.**

**** coating time 4 h 45 min;**
coating layer: 48,8 % of total tablet weight

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Benefits of galenIQ™ 981 in sugar-free coating

Outperforming Sucrose:

- Perfect appearance
- Better stability against moisture
- Suitable for diabetics
- Faster automated process

Excellent appearance

- Smooth surface
- Brilliant colors
- Closed edges

Smooth shape

- Intake friendly
- High patient acceptance
- Easy to swallow

Overall easy handling

- Stable coating solution
- Short coating time
- Low process temperatures
- Some API's can be added to coating syrup/ suspension

Taste masking and protection

- Prevents initial taste influence of APIs
- Protects the API against light and humidity

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Isomalt in Hot Melt Extrusion

Feasibility

An insight into BENEO Pharma R&D

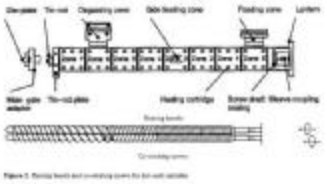
Twin-screw melt extruder.
Company Gabler, Germany

Hot-Melt-Extrusion

beneo pharma

Why HME? – Possible reasons

- enhance bioavailability of poorly soluble APIs
- protection of oxygen sensitive APIs
- no solvents required
- improve compressibility of blends



- well established technology
- extruders in all scales available

Typical components used:

- Carriers: Polymers (HPMC, HPC, PVP, PVP-VA 64, PEG 6000, …)

  and/or **sugar alcohols (e.g. isomalt)**

- Solubilizers (e.g. Lauroyl Macrogolglycerides….)
- Plasticizers (e.g. Triethylcitrate….)

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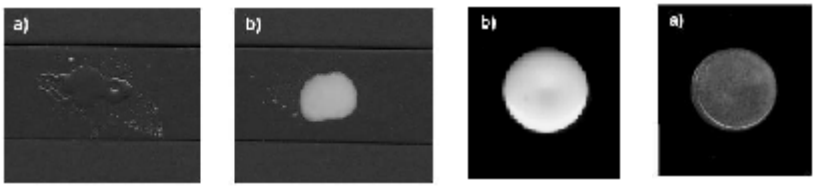
Feasibility Example with Carbamazepin (CBZ)

§ Isomalt (type galenIQ™ 960; 1:1 GPS:GPM ratio) extruded at 190 °C (374 °F)



Extruded isomalt 0-2% CBZ | Extruded isomalt 5% CBZ | Extruded isomalt 10% CBZ | Extruded isomalt 10% CBZ 25% PVP

§ up to 2% CBZ is dissolved in the extruded isomalt

§ to allow higher drug concentrations being dissolved, combinations with polymers such as PVP are recommended

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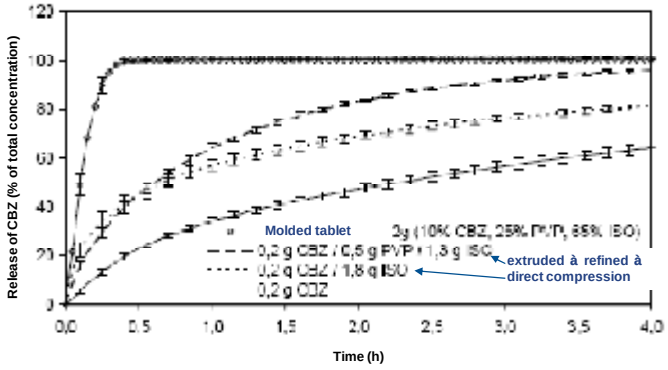
Source: Glasartige feste Lösungen schwerlöslicher Arzneistoffe in Zuckeralkoholen, PhD thesis Dissertation Martin Langer, 2003, University Düsseldorf, Germany

Feasibility Example with Carbamazepin (CBZ)

§ Isomalt matrix enhances the release of CBZ

§ in combination with PVP, desired release profiles can be designed



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Source: Glasartige feste Lösungen schwerlöslicher Arzneistoffe in Zuckeralkoholen, PhD thesis Dissertation Martin Langer, 2003, University Düsseldorf, Germany

Summary
Isomalt, a formulation design tool in HME

- well known excipient in amorphous dosage forms (medicated cough drops/high boiled lozenges)
- chemical and heat stable polyol
- melting range 145-150°C (293-302 °F)
- formation of a solid glass when cooled or
- formation of a solid crystalline dispersion
- Tg of glass: 50-63 °C ((122-145°F) depending on moisture content)
- stable glass at equilibrium conditions (45-50%rh; 20°C)
- fully soluble in water
- add polymers to depress recrystallization/increase Tg and to increase drug dissolution

galenIQ the smart excipient

Isomalt/galenIQ™ - multifunctional for your drug formulation technologies

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Need More Information? - ExcipientFest Booth # 20

galenIQ™ - The smart excipient

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