Functional Excipients for Suppository Applications

Skin Delivery Platform

BASF Pharma Solutions 2016
# The Skin Delivery Platform
Major areas of activity are in 4 pillars

## PLATFORM : SKIN DELIVERY

<table>
<thead>
<tr>
<th>Dermal Drug Delivery</th>
<th>Mildness</th>
<th>Sensory</th>
<th>Formulation Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrate how our excipients can:</td>
<td>Demonstrate <em>(in vitro and in vivo)</em> how our excipients:</td>
<td>Utilize excipient selection to:</td>
<td>Understanding of BASF excipient and API portfolio basics:</td>
</tr>
<tr>
<td><strong>Accelerate drug penetration through skin</strong></td>
<td><strong>Are mild and non-irritating</strong></td>
<td><strong>Create pleasing experience for improved compliance</strong></td>
<td><strong>Understanding of excipient behavior</strong></td>
</tr>
<tr>
<td><strong>Target delivery to the epidermis or dermis or systemic</strong></td>
<td><strong>Can be use to reduce or mitigate effects (stinging, itching, redness, etc.) induced by irritating excipients or APIs.</strong></td>
<td><strong>Develop formulations that provide emotional benefits to those suffering from significant dermal diseases.</strong></td>
<td><strong>Design formulations with BASF excipients and APIs</strong></td>
</tr>
<tr>
<td><strong>Aid in retention of actives on the outer surface of the skin when needed</strong></td>
<td></td>
<td></td>
<td><strong>Understand role of excipient selection in microstructure and product performance</strong></td>
</tr>
<tr>
<td><strong>Test formulations <em>in vitro and in silico</em> to determine drug delivery potential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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BASF Pharma Solutions
**Skin Delivery Platform**
We offer broad functionality for formulating solutions to solve dermal and transdermal challenges

<table>
<thead>
<tr>
<th>Liquids</th>
<th>Semi Solids</th>
<th>Films/Solids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvents</td>
<td>Emollience</td>
<td>Matrix building</td>
</tr>
<tr>
<td>Functional solubilization</td>
<td>Penetration enhancement</td>
<td>Plasticizing</td>
</tr>
<tr>
<td></td>
<td>Emulsification</td>
<td>Film forming</td>
</tr>
<tr>
<td></td>
<td>Viscosity modification</td>
<td>Transdermal-film construction</td>
</tr>
</tbody>
</table>

Mild ingredients for Pharmaceutical Applications
Suppository bases are used in the manufacture of suppositories (for rectal administration) and pessaries (for vaginal administration). They can be hydrophobic or hydrophilic.

**Functional mechanism**

Suppositories should melt at just below body temperature (37°C), thereby allowing the drug to be released either by erosion and partition if the drug is dissolved in the base or by erosion and dissolution if the drug is suspended in the base. Hard fat suppository bases melt at approximately body temperature. Hydrophilic suppository bases also melt at body temperature and typically also dissolve or disperse in aqueous media. Thus, release takes place via a combination of erosion and dissolution.

**Physical properties**

The important physical characteristic of suppository bases is melting range. In general, suppository bases melt between 27° and 45°. However, individual bases usually have a much narrower melting range within these temperature boundaries, typically 2°–3°. The choice of a particular melting range is dictated by the influence of the other formulation components on the melting range of the final product.

**Chemical properties**

Hard fat suppository bases are mixtures of semisynthetic triglyceride esters of longer-chain fatty acids. They may contain varying proportions of mono- and diglycerides and also may contain ethoxylated fatty acids. They are available in many different grades that are differentiated by melting range, hydroxyl number, acid value, iodine value, solidification range, and saponification number.

Hydrophilic suppository bases are mixtures of hydrophilic semisolid materials that in combination are solid at room temperature and yet release the drug by melting, erosion, and dissolution when administered to the patient. Hydrophilic suppository bases have much higher levels of hydroxyl groups or other hydrophilic groups than do hard fat suppository bases. Polyethylene glycols that show appropriate melting behavior are examples of hydrophilic suppository bases.

**General chapters**

The following general chapters may be useful in ensuring consistency in selected suppository base functions: Fats and Fixed Oils (401), Congealing Temperature (651), Melting Range or Temperature (741), and Pharmaceutical Dosage Forms (1151).

**Additional information**

Some materials included in suppositories based on hard fats have much higher melting ranges. These materials typically are microcrystalline waxes that help stabilize molten suspension formulations. Suppositories also can be manufactured from glycerinated gelatin.
Suppositories

Suppositories are dosage forms adapted for application into the rectum. They melt, soften, or dissolve at body temperature. A suppository may have a local protectant or palliative effect, or may deliver a drug substance for systemic or local action.

Suppository bases typically include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol. The suppository base can have a notable influence on the release of the drug substance(s). Although cocoa butter melts quickly at body temperature, it is immiscible with body fluids and this inhibits the diffusion of fat-soluble drug substances to the affected sites. Polyethylene glycol is a suitable base for some antiseptics. In cases when systemic action is desired, incorporating the ionized rather than the non-ionized form of the drug substance may help maximize bioavailability. Although non-ionized drug substances partition more readily out of water-miscible bases such as glycerinated gelatin and polyethylene glycol, the bases themselves tend to dissolve very slowly, which slows drug substance release. Cocoa butter and its substitutes (e.g., Hard Fat) perform better than other bases for allaying irritation in preparations intended for treating internal hemorrhoids. Suppositories for adults are tapered at one or both ends and usually weigh about 2 g each.
Preparation

Cocoa butter suppositories have cocoa butter as the base and can be made by incorporating the finely divided drug substance into the solid oil at room temperature and suitably shaping the resulting mass, or by working with the oil in the melted state and allowing the resulting suspension to cool in molds. A suitable quantity of hardening agents may be added to counteract the tendency of some drug substances (such as chloral hydrate and phenol) to soften the base. The finished suppository melts at body temperature.

A variety of vegetable oils, such as coconut or palm kernel, modified by esterification, hydrogenation, or fractionation, are used as cocoa butter substitutes to obtain products that display varying compositions and melting temperatures (e.g., Hydrogenated Vegetable Oil and Hard Fat). These products can be designed to reduce rancidity while incorporating desired characteristics such as narrow intervals between melting and solidification temperatures, and melting ranges to accommodate formulation and climatic conditions.

Drug substances can be incorporated into glycerinated gelatin bases by addition of the prescribed quantities to a vehicle consisting of about 70 parts of glycerin, 20 parts of gelatin, and 10 parts of water.

Several combinations of polyethylene glycols that have melting temperatures that are above body temperature are used as suppository bases. Because release from these bases depends on dissolution rather than on melting, there are significantly fewer problems in preparation and storage than is the case for melting-type vehicles. However, high concentrations of higher molecular weight polyethylene glycols may lengthen dissolution time, resulting in problems with retention.

Several nonionic surfactant vehicles closely related chemically to the polyethylene glycols can be used as suppository vehicles. Examples include polyoxyethylene sorbitan fatty acid esters and the polyoxyethylene stearates. These surfactants are used alone or in combination with other suppository vehicles to yield a wide range of melting temperatures and consistencies. A notable advantage of such vehicles is their water dispersibility. However, care must be taken with the use of surfactants because they may either increase the rate of drug substance absorption or interact with the drug substance to reduce therapeutic activity. Compounding suppositories using a suppository base typically involves melting the suppository base and dissolution or dispersion of the drug substance in the molten base (see (795)). When compounding suppositories, the compounding professional prepares an excess amount of total formulation to allow the prescribed quantity to be accurately dispensed. In compounding suppositories, avoid caustic or irritating ingredients, carefully select a base that will allow the drug substance to provide the intended effect, and in order to minimize abrasion of the rectal membranes, reduce solid ingredients to the smallest reasonable particle size.
Suppository Preparation

Mold Calibration
- Target mass ~ 2 g
- Mold is volume based
- Base excipient filled into mold and weighed.
- Specific gravity of base material and API must be accounted for.

Composition Defined
- Base and API mass requirements determined
- Materials weighed

Melting and Mixing
- Base material is melted with mixing
- Additional excipients added with mixing.
- API added while mixing

Molding and cooling
- Melted mixture with API is poured into molds
- Solidifies while cooling.
USP NF Monograph: Hard fat
(BASF offers a series of Hard fats under brand name Novata®)

Hard Fat
DEFINITION: Hard Fat is a mixture of glycerides of saturated fatty acids.

IMPURITIES
- **Residue on Ignition (281):** NMT 0.05%
- Alkaline Impurities Sample: 2.0 g

Analysis: Dissolve the Sample in a mixture of 1.5 mL of alcohol and 3.0 mL of ether. Add 0.05 mL of bromophenol blue TS, and titrate with 0.01 N hydrochloric acid to a yellow endpoint.

Acceptance criteria: NMT 0.15 mL of 0.01 N hydrochloric acid

SPECIFIC TESTS
- Melting Range or Temperature, Class II (741): The melting temperature does not differ by more than 2° from the nominal value given in Labeling.
- **Fats and Fixed Oils, Acid Value (401):** NMT 1.0
- **Fats and Fixed Oils, Hydroxyl Value (401):** NMT 70
- **Fats and Fixed Oils, Iodine Value (401):** NMT 7.0
- **Fats and Fixed Oils, Saponification Value (401):** 215–255
- **Fats and Fixed Oils, Unsaponifiable Matter (401):** NMT 3.0%

ADDITIONAL REQUIREMENTS
- Packaging and Storage: Preserve in tight containers at a temperature that is 5° or more below the melting range stated in the labeling.
- Labeling: The labeling includes the nominal melting temperature, which is 27°–44°.
## Functional Excipients for Suppositories

**Structurant/Matrix builders (Per FDA IID listing)**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Compendial name and status</th>
<th>IID Rectal</th>
<th>IID Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novata® series</td>
<td>Coconut oil/palm kernel oil glycerides, hydrogenated</td>
<td>1734.9 mg</td>
<td>2375 mg</td>
</tr>
<tr>
<td>Kolliwax® CA</td>
<td>Cetyl alcohol USP/NF, Ph. Eur., JP</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kolliwax® CSA 50</td>
<td>Cetostearyl alcohol 50 USP/NF, Ph.Eur, JP</td>
<td><strong>NA</strong></td>
<td><strong>NA</strong></td>
</tr>
<tr>
<td>Kolliwax® CSA 70</td>
<td>Cetostearyl alcohol 70 Ph.Eur.</td>
<td><strong>NA</strong></td>
<td><strong>NA</strong></td>
</tr>
<tr>
<td>Kolliwax® SA</td>
<td>Stearyl alcohol USP/NF, Ph. Eur., JP</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kollisolv® PEG 1000</td>
<td>Polyethylene glycol 1000, USP/NF</td>
<td>1658 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Kollisolv® PEG 1450</td>
<td>Polyethylene glycol 1450 USP/NF</td>
<td></td>
<td>*9.75 mg</td>
</tr>
<tr>
<td>Kollisolv® PEG 3350</td>
<td>Polyethylene glycol 3350 USP/NF</td>
<td>1425.96 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Kollisolv® PEG 8000</td>
<td>Polyethylene glycol 8000 USP/NF</td>
<td>52 mg</td>
<td></td>
</tr>
<tr>
<td>Kollidon® CL</td>
<td>Crospovidone USP/NF, Ph. Eur., JP</td>
<td>116.1 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Urethral suppository  ** CSA type is not indicated in IID
### Novata® Hard Fat Series Offering

<table>
<thead>
<tr>
<th>Novata®</th>
<th>PRD-No.</th>
<th>Article-No.</th>
<th>CAS.-No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novata® B PH</td>
<td>30531224</td>
<td>50209107</td>
<td>67701-26-2</td>
</tr>
<tr>
<td>Novata® BC PH</td>
<td>30531225</td>
<td>50209108</td>
<td>67701-26-2</td>
</tr>
<tr>
<td>Novata® BCF PH</td>
<td>30531226</td>
<td>50209109</td>
<td>67701-26-2</td>
</tr>
<tr>
<td>Novata® BD PH</td>
<td>30531227</td>
<td>50209110</td>
<td>67701-26-2</td>
</tr>
</tbody>
</table>

**Properties:**

<table>
<thead>
<tr>
<th>Novata®</th>
<th>B PH</th>
<th>BC PH</th>
<th>BCF PH</th>
<th>BD PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid value</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Iodine value</td>
<td>≤3.0</td>
<td>≤3.0</td>
<td>≤3.0</td>
<td>≤3.0</td>
</tr>
<tr>
<td>Peroxide value</td>
<td>≤3.0</td>
<td>≤3.0</td>
<td>≤3.0</td>
<td>≤3.0</td>
</tr>
<tr>
<td>Alcaline impurities (mL)</td>
<td>≤0.15</td>
<td>≤0.15</td>
<td>≤0.15</td>
<td>≤0.15</td>
</tr>
<tr>
<td>Total ash (%)</td>
<td>≤0.05</td>
<td>≤0.05</td>
<td>≤0.05</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Unsaponifiable (%)</td>
<td>≤0.6</td>
<td>≤0.6</td>
<td>≤0.6</td>
<td>≤0.6</td>
</tr>
<tr>
<td>Hydroxyl value</td>
<td>20 – 30</td>
<td>30 – 40</td>
<td>20 – 30</td>
<td>5 – 15</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>33.5 – 35.5</td>
<td>33.0 – 34.5</td>
<td>35 – 37</td>
<td>33.5 – 35.5</td>
</tr>
<tr>
<td>Heavy metals as sum Pb (ppm)</td>
<td>≤10.0</td>
<td>≤10.0</td>
<td>≤10.0</td>
<td>≤10.0</td>
</tr>
</tbody>
</table>

BASF Pharma Solutions
Suppositories with Hard Fat - Examples

Canasa® (mesalamine, USP) 1000 mg Rectal Suppositories

Acetaminophen Suppositories USP, 650 mg
Pain Reliever/Fever Reducer

BASF Pharma Solutions
# Functional Excipients for Suppositories

## Solvents/Solubilizers (per FDA IID listing)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Compendial name</th>
<th>IID Rectal</th>
<th>IID Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollisolv® MCT 70</td>
<td>Medium chain triglycerides USP/NF, Ph. Eur.</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kollisolv® PG</td>
<td>Propylene glycol USP/NF, Ph. Eur., JP, FCC</td>
<td>NA</td>
<td>252 mg</td>
</tr>
<tr>
<td>Kollisolv® PEG 400</td>
<td>Polyethylene glycol 400 USP/NF, Ph.Eur, JP, FCC</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kollicream® IPM</td>
<td>Isopropyl myristate USP/NF, Ph. Eur.</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kollicream® OD</td>
<td>Octyldecaneol USP/NF, Ph.Eur.</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
# Functional Excipients for Suppositories

## Emulsifiers (per FDA IID listing)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Compendial name</th>
<th>IID Rectal</th>
<th>IID Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolliphor® PS 20</td>
<td>Polysorbate 20 USP/NF, Ph. Eur.</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Kolliphor® PS 60</td>
<td>Polysorbate 60 USP/NF, Ph. Eur., JP</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kolliphor® PS 80</td>
<td>Polysorbate 80 USP/NF, Ph. Eur.</td>
<td>72.15 mg</td>
<td>28 mg</td>
</tr>
</tbody>
</table>
Example: Indomethacin Suppositories (50 mg)
Matrix builder is Polyethylene glycol

1. **Formulation**

   **Phase I.**
   
   Indomethacin .................................................. 5.0 g  
   Butylhydroxytoluene ........................................... q.s.  
   Kollisolv® PEG 3350 ........................................ 141.0 g  
   Kollisolv® PEG 6000 ........................................... 14.0 g  

   **Phase II.**
   
   EDTA ............................................................... 16.3 mg  
   Water............................................................... 3.0 g  

2. **Manufacturing**

   Prepare Phase I with heating, melting and mixing. Prepare Phase II, mix with the melted mixture I and fill into the suppository molds. Allow to cool and solidify.

3. **Properties of the suppositories**

   Weight: ........................................................... 1.6 g  
   Color:............................................................. slightly yellowish
Example: Paracetamol Suppositories (150 mg)
Matrix builder is Polyethylene glycol

1. Formulation
Phase I
Paracetamol, fine powder .........................................15.4 g

Phase II
Aerosil 200 [4] ........................................................0.2 g
Kollisolv® PEG 1450..............................................129.0 g
Kollisolv® PEG 3350..............................................55.4 g

2. Manufacturing
Melt the mixture II and suspend the mixture I. Fill the molten mass in the molds for suppositories.

3. Properties of the suppositories
Weight .................................................................2.0 g
Solubility in water ..............................................easy
Color ...............................................................colorless

4. Physical stability: No crystallization after the storage of 6 weeks at 6 °C, 20 °C or 40 °C.
Proposed Suppository Base Formulations: PEGs and Poloxamers

**PEG FORMULATIONS**

- 70% Pluriol E® 1450
- 30% Pluriol E® 3350

- 55% Pluriol E® 3350
- 40% Pluriol E® 1450
- 5% Kollisolv® PEG 400

- 15% Kollisolv® PEG 400
- 85% Pluriol E® 3350

- 5% Kollisolv® PEG 400
- 60% Pluriol E® 1450
- 35% Pluriol E® 3350

Optionally add plasticizers such as Glycerin or Propylene Glycol (Kollisolv® PG).

**For difficult to dissolve APIs or rapid, emulsifying formulations:**

- 20% Kolliphor® RH 40
- 50% Pluriol E® 1450
- 30% Pluriol E® 3350

Innovative Poloxamer-based formulations

Kolliphor® P407 – Kolliphor® P188 (5:2 ratio)

Kolliphor® P124 can be used to add more mucoadhesive properties to the blend.
