Nanotechnology in oral dosage forms.

A. Sallam.

Pharmaceutical Dosage Forms

- Solutions
- Capsules
- Tablets
- Ointments, Creams
- Transdermal systems
- Inhalation Products

- Liposomes
- Drug-eluting Stents
- Nano-system

Simple

Drug Delivery Systems

Immediate Release ———> Modified Release

Complex
Nanotechnology in medicine is a relatively new field of science and technology.

1- Diagnostic applications.
2- Nanoparticles are designed for improving bioavailability and targeted drug delivery. The use of such carriers improves the drug biodistribution, targeting active molecules to diseased tissues while protecting healthy tissue.
3- Regenerative medicine where nanotechnology allows developing biocompatible materials which support growth of cells used in cell therapy.
4- Nanomedicine can contribute to the development of a personalised medicine both for diagnosis and therapy.
The global nanomedicine market was valued at $53 billion in 2009, and is forecast to increase at a compound annual growth rate (CAGR) of 13.5% to reach more than $100 billion in 2014. Nanomedical products for cancer are one of the largest market segments, worth nearly $20 billion in 2009. This sector is expected to increase at a CAGR of 11% to reach $33 billion in 2014. Nanomedicine for central nervous system related indications is another major market sector, valued at nearly $11 billion in 2009 and expected to reach $18 billion by 2014, an 11.1% CAGR.
Regulations.

There are existing regulatory frameworks addressing the basic rules of safety and effectiveness of nanotechnology based medicine, whether molecular assemblies or medical devices.

However, there is a need to clarify or to modify these regulations which mobilise many experts.
The US National Nanotech Initiative

Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometres, where unique phenomena enable novel applications.

Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale.

Nanomedicine is the application of nanotechnology to medicine.
The European Technology Platform on Nanomedicine

Nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale.

Nanomedicine has potential impact on the prevention, early and reliable diagnosis and treatment of diseases.
According to FDA: “Nanomedicine is really no different than any other new technology that would be incorporated into FDA products. So with that in mind, we feel comfortable using our present regulatory framework. However, we felt there is need for guidance to help this industry as it moves forward.

We recognised a need for additional information in various areas, such as biosafety. FDA and other agencies are working together on that. But for now, we just do not see the need for regulations written specifically for nano-engineered materials in the products FDA regulates”.

“The existing regulatory framework can accommodate the types of nanoparticle therapeutics under development and when needed, adapt to address new challenges. Current published guidance may be applicable to nanoparticle therapeutics.

Staff is working on addressing the need for guidance documents that address nano-related issues as well as the regulatory science to bring to bear this emerging technology”.
~200 Companies are involved in nanomedicine R&D.

> 40 Nanomedicine products registered.


<table>
<thead>
<tr>
<th>Nanoformulation</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsion</td>
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<tr>
<td>Micelle</td>
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<tr>
<td>Nanoemulsion</td>
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<td>Nanocrystal</td>
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<tr>
<td>Liposomes</td>
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<tr>
<td>Microemulsion</td>
<td>44</td>
</tr>
<tr>
<td>Nanoparticle</td>
<td>73</td>
</tr>
<tr>
<td>Nanosuspension</td>
<td>1</td>
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</table>
Nanotechnology in oral dosage forms.
Poor water solubility for many drugs and drug candidates remains a major obstacle to their development and clinical application.

Approximately 40% of potential new drugs identified by pharmaceutical companies are poorly soluble in water, which greatly hinders their clinical translations.

Low water solubility limits the bioavailability and absorption of these agents.
Several strategies and formulations have been employed to overcome these limitations.
Existing strategies such as:
1. Complexing drugs with cyclodextrins
2. Salt formation of ionizable drugs
3. Prodrugs
4. The use of co-solvents, surfactants, solid dispersions, ....etc.
5. SEDDS.
have been shown to:
   improve drug solubility
   improve drug dissolution
   improve the drugs’ bioavailability
   BUT WITH LIMITATIONS.
Nano techniques are used to overcome these limitations for drug solubilization/dissolution/bioavailability particularly for highly potent drugs.
The micronization of drug powders is insufficient to overcome bioavailability problems of many very poorly soluble drugs. Therefore, a consequent step was to shift to nanosization since saturation solubility and dissolution rate can be enhanced according to Noyes-Whitney equation.
Examples of these nanocarriers:
Polymeric nanoparticles,
Polymeric micelles,
Solid lipid nanocarriers,
Self nanoemulsifying DDS,
Dendrimers,
Liposomes,
and Nanocrystals.
However, the safety and long-term effects of nanoformulations must not be overlooked.

Recently, more emphasis has been placed onto understanding the role of the route of particle administration as a potential source for toxicity.
**Oral**

**Advantage:**
- Non-invasive means of NP delivery

**Disadvantage:**
- First-pass metabolism in the liver – potentially hepatotoxic
- Potential for translocation into systemic circulation
- Requires intact intestinal mucosa for NP uptake

**Pulmonary**

**Advantage:**
- Non-invasive means of NP delivery
- Large surface area
- Local action
- Avoidance of first-pass metabolism in the liver

**Disadvantage:**
- Local toxicity
- Potential for translocation into systemic circulation

**Transdermal**

**Advantage:**
- Non-invasive means of NP delivery
- Large surface area
- Local action

**Disadvantage:**
- Local irritation
- Potential for translocation into systemic circulation

**Intravenous**

**Advantage:**
- Systemic delivery of NP
- Systemic action

**Disadvantage:**
- First-pass metabolism in the liver – potentially hepatotoxic
- Systemic toxicity

Liver Toxicity

Being the site for first-pass metabolism, the liver is particularly sensitive to NP toxicity and has consistently been shown to accumulate administered substances, even long after cessation of exposure.

Thorough evaluation of NP mediated hepatocellular toxicity thus remains of prevailing importance.
Neoral® Microemulsion

Optically clear mixture: 10 - 200 nm. Too small to deflect light

Poorly water soluble peptide: cyclosporine A

Immunosuppressant drug: indicated for prevention of organ rejection and psoriasis.

Oral administration

Dr. Evelyne Vuaridel  NANOTECHDAY FRIBOURG  OCTOBER 2009
TRIGLIDE Tablets

Nanotechnology Technique: High-pressure homogenization.

Drug: Fenofibrate

Inactive ingredients:
Carboxymethylcellulose sodium, croscarmellose sodium, lecithin, sodium lauryl sulfate.

Indication:
Hypercholesterolemia. Lipid-regulating agent.

Manufacturer, status:
SkyePharma/Sciele, approved in 2005
TRIGLIDE 160 mg tablet exhibits a similar extent of absorption but 32% higher rate of absorption compared to the 200 mg micronized fenofibrate capsule under low-fat fed conditions.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021350s005lbl.pdf
Rapamune Tablets:

Nanotechnology Technique: Media milling
Drug: Sirolimus
Sirolimus is insoluble in water

Inactive ingredients: Povidone, Poloxamer 188

Indication: Immunosuppression

Manufacturer, status: Elan/Wyeth, approved in 2000
Rapamune

The inert tablet cores are composed of lactose monohydrate (diluent, PhEur), macrogol 8000 (binder, PhEur), magnesium stearate (lubricant, PhEur), and talc (glidant, PhEur).

The tablet coating is composed of several layers of coatings consisting of the Nanodispersion (NanoCrystal Colloidal Dispersion), Sirolimus and stabiliser (Poloxamer 188).
Megace ES

Nanotechnology Technique: Media milling

Trade name: Megace ES. is a concentrated formula supplied as an oral suspension containing 125 mg of megestrol acetate per mL.

Drug: Megestrol. Solubility at 37°C in water is 2 µg per mL.

Inactive ingredients: Hydroxypropyl methylcellulose, docusate sodium

Indication: Antianorexia
Dosage form: Oral suspension

Manufacturer, status: Elan/Par Pharmaceuticals, approved in 2005
Megace ES Pharmacokinetic Properties:

Plasma concentrations of megestrol acetate after administration of 625 mg (125 mg/mL) of Megace® ES oral suspension are equivalent under fed conditions to 800 mg (40 mg/mL) of megestrol acetate oral suspension.
Megace® ES 625 mg (5 mL x 125 mg/mL)

Megestrol Acetate Oral Suspension 800 mg (20 mL x 40 mg/mL)
Nanosized drug crystals of Posaconazole

Elaine Merisko-Liversidge, Gary G. Liversidge

Advanced Drug Delivery Reviews 63 (2011) 427-440
Nanosized drug crystals of Posaconazole, an antifungal agent, a poorly-water soluble drug. Nanosizing was achieved using wet media milling technology.

The mean particle size of the unprocessed crystals is approximately 53 μm with a broad distribution profile. While the nanosized dispersion has a narrow distribution profile with a mean size of 185 nm.
Bioavailability of a posaconazole nanodispersion. The pharmacokinetics of posaconazole when administered via oral gavage to fed/fasted male beagle dogs comparing the marketed product Noxafil® which is a crude water based liquid suspension (Mean~5.2 μm) and a nanosuspension (Mean 185 nm) at a dose of 10 mg/1 kg.

<table>
<thead>
<tr>
<th>Solvents</th>
<th>“as-is” drug*</th>
<th>Micronized drug*</th>
<th>Spray dried drug nanoparticles</th>
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<tbody>
<tr>
<td>0.1 N HCl</td>
<td>0.011</td>
<td>0.016</td>
<td>0.134</td>
</tr>
<tr>
<td>Acetate buffer</td>
<td>0.001</td>
<td>0.014</td>
<td>0.106</td>
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<tr>
<td>pH 4.5</td>
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<tr>
<td>Phosphate buffer</td>
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<td>0.012</td>
<td>0.105</td>
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<tr>
<td>pH 6.8</td>
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<tr>
<td>Water</td>
<td>0.000</td>
<td>0.001</td>
<td>0.073</td>
</tr>
</tbody>
</table>

*Solubility was tested in respective solvents containing surfactant and Stabilizer.
Plasma concentration–time profiles following oral administration of micronized suspension and drug nanosuspension to male Wister rats.
What is a Suitable Dissolution Method for Drug Nanoparticles?
Desmond Heng et al.

Cefuroxime Axetil (CFA), a cephalosporin antibiotic, was used as the model drug due to its **class II status**, whereby the **dissolution rate** is the limiting factor towards much improved oral bioavailabilities.
Experimental rate ratios between the nanoparticles and their unprocessed form were:

Flow-through cells, 6.95
Basket, 1.57 and
Paddles, 1.00.
Dissolution via dialysis was rate-limited by the membrane.
Nanosuspension of Tadalafil.

Wasfi Ebeedat (JUST) and A.Sallam (TQ).
Solubility of Tadalafil (mg/ml)
BCS: Class II.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.013</td>
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<tr>
<td>0.5% SLS</td>
<td>0.110</td>
</tr>
<tr>
<td>0.3% SLS</td>
<td>0.067</td>
</tr>
<tr>
<td>0.1N HCL</td>
<td>0.015</td>
</tr>
<tr>
<td>0.01N HCL</td>
<td>0.017</td>
</tr>
<tr>
<td>Acetate Buffer pH=4.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Phosphate Buffer pH=6.8</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Preparation of Tadalafil Nanosuspension:
Tadalafil/ Acetone.
Antisolvent/ Water containing stabilizer.
Sonication at 5 °C.
Removal of Acetone at RT.
HPC, HPMC, povidone (PVP K30), and pluronics (F68 and F127) are polymers suitable for use as stabilizers.

The chains should be long enough to provide a steric layer, but not too big to slow down dissolution.

Polysorbate 80 (nonionic), sodium laurylsulfate (SLS) and docusate sodium (DOSS) (both anionic) are some examples of suitable surfactant stabilizers for physical stability.

Also, surfactants often help in the wetting, electrostatic stabilization and dispersion of the drug particles, which are usually very hydrophobic.

HPMC E3, Povidone, DOSS, and SLS are some of the stabilizers that have been used in the nanocrystal formulations of drugs that are on the market.
Drug dissolution (release) for Tadalafil raw material (TD) in 0.3% SLS and in 0.3% SLS/0.05% Tween/0.05% Span80 and for Tadalafil nanosuspensions (TDTSp-N) in 0.3% SLS at 37 °C. Paddles, 50 rpm.
Drug dissolution (release) for Tadalafil raw material (TD) in 0.3% SLS and in 0.3% SLS/0.05% Tween/0.05% Span80 and for Tadalafil nanosuspensions (TDTSp-OH) in 0.3% SLS at 37 °C. Paddles 50rpm
Nano techniques are successful techniques, used to overcome these limitations for drug solubilization/dissolution/bioavailability particularly for highly potent drugs.
THANKS