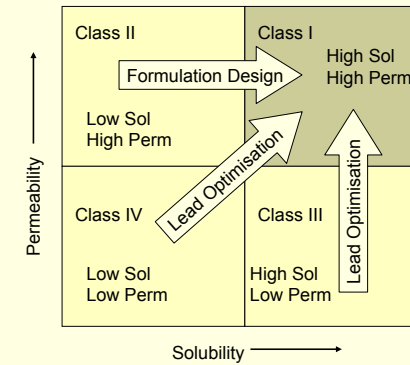


Self-microemulsifying drug delivery system as nanosystems for bioavailability enhancement of flavonoids in vitro

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Biopharmaceutical classification system



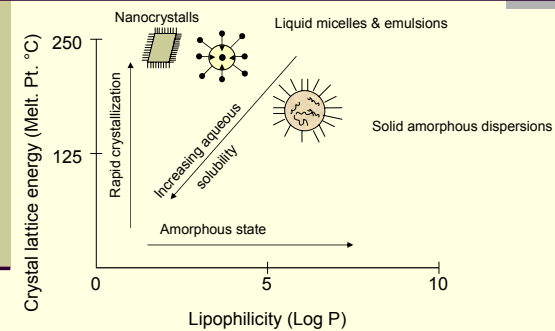
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Some of the reasons for the increasing interest in lipid-based systems

- an improved understanding of the manner in which lipids enhance oral bioavailability and reduce plasma profile variability;
- the general trend for new drug candidates being less water soluble and more potent (thereby allowing for lower unit doses);
- formulation versatility;
- an improved ability to address the key issues of technology transfer and manufacture scale-up;
- the choice of different encapsulation technologies;
- the higher purity and better characterization of lipidic excipients;
- possible metabolic and biopharmaceutic advantages;
- life cycle management issues.

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Physical properties of drugs with low solubility and relationship to some enabling technologies



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Characteristic features, advantages of the various types of lipid formulations

	Characteristics	Advantages	Disadvantages
Type I	Non-dispersing; requires digestion	GRAS status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	SEDDS without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25-2 μm)
Type IIIA	SEDDS/SMEDDS with water soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IIIB	SMEDDS with water-soluble components and low oil content	Clear dispersion; drug absorption without digestion	Likely loss of solvent capacity on dispersion

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The main criteria for choice of lipid formulations

1. Does the formulation self-emulsify or remain poorly dispersed in water?
2. When the formulations makes contact with water are some of the components lost by dissolving in the aqueous phase?
3. Is the dispersed formulation digestible by lipase?

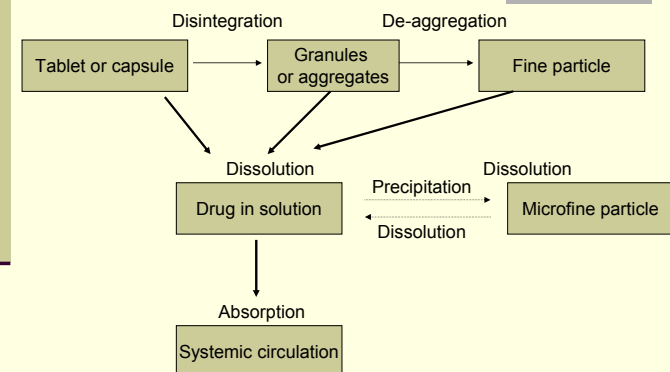
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Fundamental factors affecting oral drug absorption

- Physiological factors (e.g, GI pH, gastric emptying rate, intestinal motility, blood flow, GI mucin and bile, and co-ingested food).
- Physicochemical factors
- Dosage form

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The drug absorption process (schematic)



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Formulation of poorly water-soluble drugs for oral administration

Lipid formulations

- ❑ Simple solutions
- ❑ self-emulsifying drug delivery systems (SEDDS)
- ❑ self-microemulsifying drug delivery systems (SMEDDS)
- ❑ systems with very little oil and disperse to form micellar solutions

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Biological activity of flavonoids

Antioxidative effect

Antithrombotic effect

Hepatoprotective effect

Anti-inflammatory effect

Capillaroprotective effect

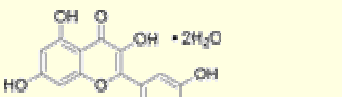
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Materials

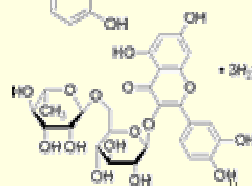
Taxifolin (2 β (R), 3 α (S)-3',4',5,7-tetrahydroxyflavanonol, syn. **Dihydroquercetin**)



Quercetin (3,3',4',5,7-Pentahydroxyflavone dihydrate) + 2H₂O



Rutin (Quercetin-3-rutinoside hydrate, syn. **Vitamin P**) + 2H₂O



Disadvantages of flavonoids

- ☞ slightly soluble in water
- ☞ slow dissolution rate from solid oral forms
- ☞ effectiveness of flavonoids was discounted by its poor water solubility and low bioavailability after oral administration

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The purposes of the present work were to:

- develop self-microemulsifying drug delivery systems (SMEDDS) with different flavonoids (rutin, quercetin and taxifolin);
- characterize SMEDDS;
- evaluate their bioavailability in vitro.

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Advantages of SMEDDS:

- Low viscosity;
- Great ability as drug delivery vehicles;
- Widened properties as absorption promoters;
- Easiness of preparation, which do not require much energy and the use of special equipments;
- They are comprised of aqueous and oily components and therefore can accommodate both hydrophilic as well as lipophilic drugs.

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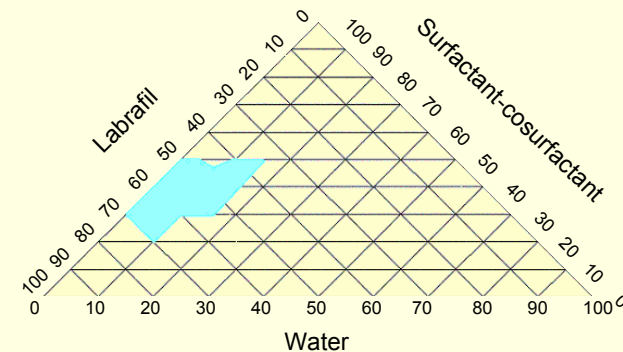
Technology of self-microemulsifying drug delivery systems



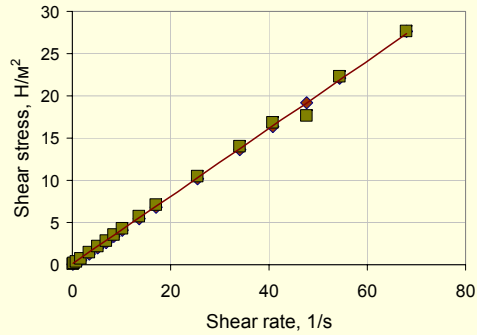
- SMEDDSs were prepared using surfactant, cosurfactant and oil phase
- All SMEDDS consist of 2% flavonoids
- The technology of SMEDDS was included:
 - Dissolution of flavonoid
 - Addition of water solution to lipid phase

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Pseudoternary Phase Diagram Indicating the Efficient SMEDDS Region (Blue color)



Rheology behavior of SMEDDS of Taxifolin



SMEDDS of Taxifolin is **Newtonian liquid**

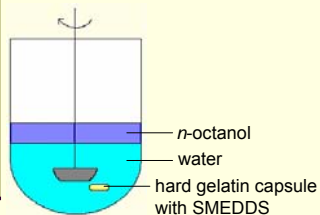
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Traditional dissolution medium

- Dilute acid (0.001 N-0.1 N HCl)
- Buffered aqueous solution (pH 4-8)
- Simulated gastric fluid (with or without enzymes)
- Simulated intestinal fluid (with or without enzymes)
- Surfactants (with or without acids or buffers)

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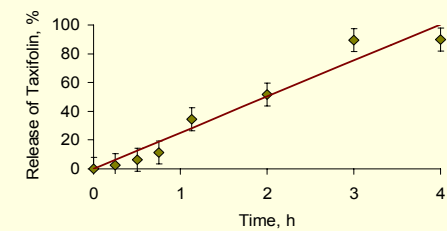
In vitro testing: Non-conventional dissolution test



- Modelling of oral application
- Paddle method, USP dissolution apparatus 2
- Dissolution medium: *n*-octanol:water 1:3
- Temperature 37 ± 0.5 °C
- Rotation speed 100 rpm

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In vitro testing: Taxifolin

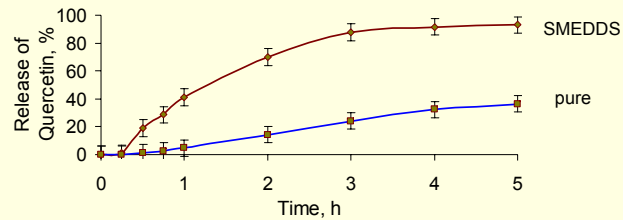


Taxifolin release from **SMEDDS** at modeling of oral application

The constants of rate release $0,8476 \text{ h}^{-1}$

20

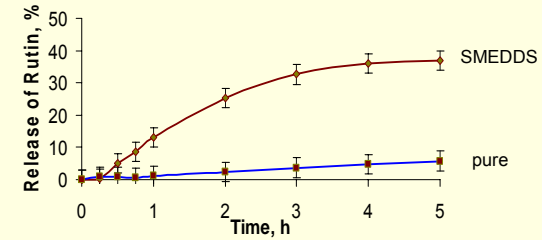
In vitro testing: Quercetin release from SMEDDS at modeling of oral application



The constants of rate release
 Pure Quercetin 0,1253 h⁻¹
 SMEDDS of Quercetin 0,7266 h⁻¹

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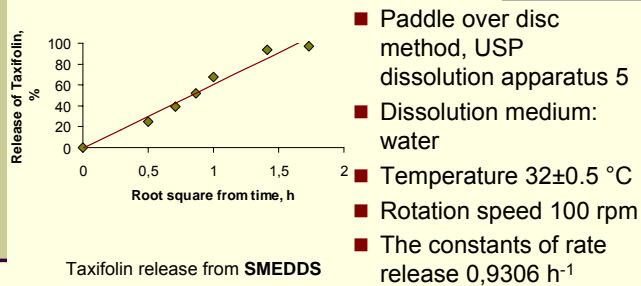
In vitro testing: Rutin release from SMEDDS at modeling of oral application



The constants of rate release
 Pure Rutin 0,0133 h⁻¹
 SMEDDS of Rutin 0,1222 h⁻¹

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In vitro testing 2. modeling of topical application

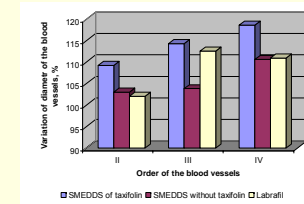


- Paddle over disc method, USP dissolution apparatus 5
- Dissolution medium: water
- Temperature 32±0.5 °C
- Rotation speed 100 rpm
- The constants of rate release 0,9306 h⁻¹

Taxifolin release from **SMEDDS**

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Vasodilatation effect in HET-CAM test of SMEDDS of Taxifolin

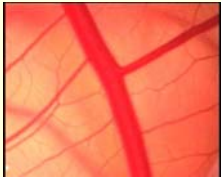


Vascular responses used to score test SMEDDS in the HET-CAM test

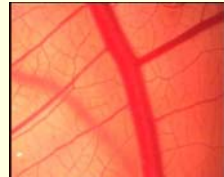
Vasodilatation effect in HET-CAM test of SMEDDS and oil phase

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Irritation testing using HET-CAM test



0 sec



100 sec

Vascular responses used to score test formulations
in the HET-CAM test

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Thank you for your attention



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