Artificial Intelligence in Pharmaceutics

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FDA Generic Drug Science and Research Initiatives
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Overview

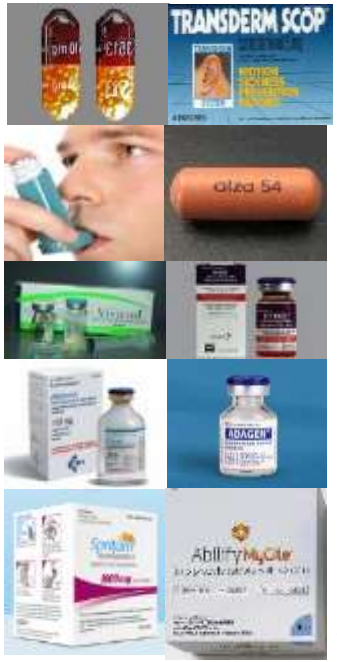
- Current problems of formulation development
- Principle of computational pharmaceutics
- Case study: solid dispersion
  - Predicting physical stability of solid dispersions;
  - Predicting in vitro dissolution and in vivo performance of solid dispersion;
  - PharmSD: a novel AI-based computational platform for solid dispersion formulation design
- Summary

Modern Pharmaceutics

1G Physical pharmacy — **2G Nanomedicine and biopharmaceuticals**

1950's — **1980's**

	Time	Drug Delivery Systems
1G	1952	The first sustained-release technology Spansule®
	1950s 1960s	The first pressurized metered dose inhaler (MDI) The first dry powder inhalation (DPI)
	1979	The first transdermal patch Transderm Scop®
	1980s	The first elementary osmotic pump product Osmosin®
2G	1984	The first microsphere VIVITROL®
	1990	The first PEGylated protein Adagen®
	1995	The first FDA-approved liposome Doxil®
	2005	The first FDA-approved nanoparticle Abraxane®
	2015	The first FDA-approved 3D print drug Spritam®
	2017	The first FDA-approved digital drug Abilify MyCite®
	2018	The first siRNA drug Patisiran
	2019	Rybelsus (semaglutide) oral tablets
	2020	The first mRNA vaccine



www.fda.gov

Drug Discovery Today, 2017, 22(8), 1201-1208 & Pharmaceutics, 2018, 10(4), 263

Current problems of formulation development

- Lab experiments with unclear mechanism;
- Trial-and-error by personal experiences;
- Laborious, time-consuming & high cost;

Question:

Can we predict pharmaceutical formulations?

Alchemy

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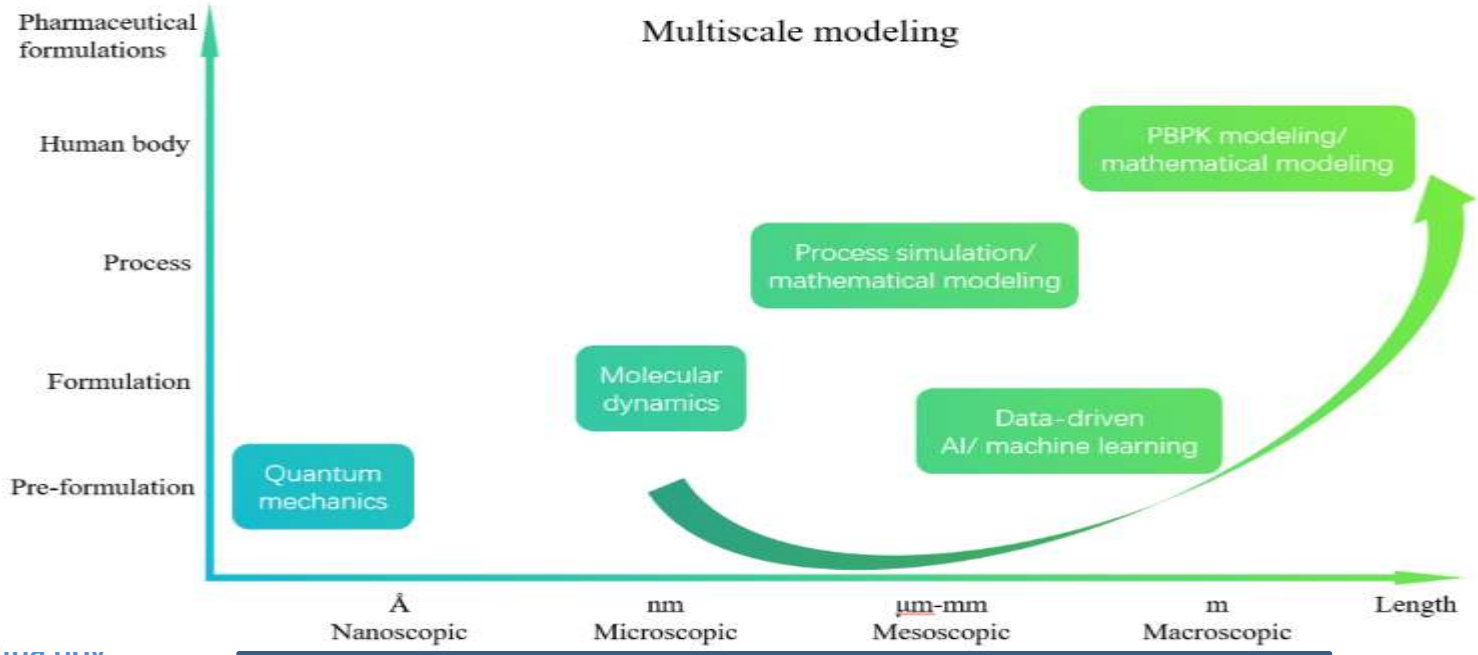
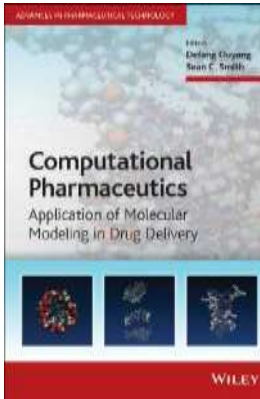
Computational Pharmaceutics

(2011 -2021)

Development of the integrated computational methodology for *in silico* formulation design





www.rua.gov

Journal of Controlled Release, 2021, under review

Case study: Solid Dispersions

- **Water-insoluble drugs:** over **40%** of APIs, over **70%** of drug candidates;
- **Solid dispersion**: a dispersion of APIs in hydrophilic polymers at the solid state;
- Carriers: PEG, PVP, Poloxamer, HPMCAS, Soluplus; Eudragit, ---
- Preparation methods: hot-melt extrusion/spray-drying
- Over **20** products in the markets since 1960's.

www.fda.gov

International journal of pharmaceutics 231.2 (2002): 131-144.

Molecules, 2018, 23, 1697.

Marketed solid dispersion products

Order	Products	API	Excipient	Manufacturing Method	Dosage Form	Company
1	Afeditab	Nifedipine	Poloxamer/PVP	Spray drying	Tablet	Elan
2	Afinitor	Everolimus	Hydroxypropyl methylcellulose	Spray dried	Tablet	Novartis
3	Certican	Everolimus	Hydroxypropyl methylcellulose	Spray dried	Tablet	Novartis
4	Cesamet	Nabilone	PVP	-	Tablet	Valeant
5	Crestor	Rosuvastatin	HPMC	Spray drying	Tablet	AstraZeneca
6	Florfenicol	Florfenicol	Enteric cellulose	-	Powder	Hebei Huaqiang
7	Gris-PEG	Griseofulvin	PEG-6000	Melt-extrusion	Tablet	Pedinol
8	Incivek	Teleprevir	HPMCAS-M	Spray drying	Tablet	Vertex
9	Intelence	Etravirin	HPMC	Certican	Tablet	Tibotec
10	Isoptin	Verapamil	HPC/HPMC	Spray drying	Tablet	Abbvie
11	Kaletra	Lopinavir	PVP	Melt extrusion	Capsule	Abbvie
12	Kalydeco	Ivacaftor	HPMCAS	Spray drying	Tablet	Vertex
13	Nivadil	Nivaldipine	HPMC	Spray drying	Tablet	Fujisawa
14	Novir	Ritonavir	PVP	Melt-extrusion	Tablet	Abbott
15	Onmel	Itraconazole	HPMC	Melt-extrusion	Tablet	Sebela
16	Prograf	Tacrolimus	HPMC	Spray drying	Capsule	Fujisawa
17	Rezulin	Troglitazone	HPMC	Spray drying	Tablet	Parke Davis
18	Shuilinjia	Silibinin	Lecithin	-	Capsules	Tianjin Tasly
19	Sporanox	Itraconazole	HPMC	Spray drying on sugar beads	Capsule	Janssen
20	Stivarga	Regorafenib	Povidone K25	-	Tablet	Bayer
21	Votubia	Everolimus	Hydroxypropyl methylcellulose	Spray dried	Tablet	Novartis
22	Zelboraf	Vemurafenib	Hypromellose acetate succinate	Precipitation	Tablet	Roche
23	Zortess	Everolimus	HPMC	Spray drying	Tablet	Novartis

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Molecules, 2018, 23, 1697.

1. Predicting physical stability of solid dispersions by machine learning techniques

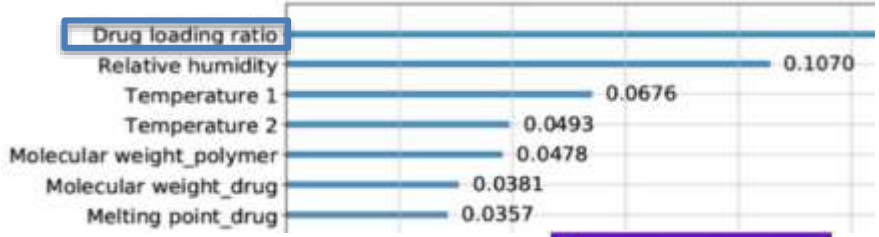
Data extraction (646 data sets) → Data standardization (molecular descriptor) → Data splitting strategy → Prediction model and feature contribution

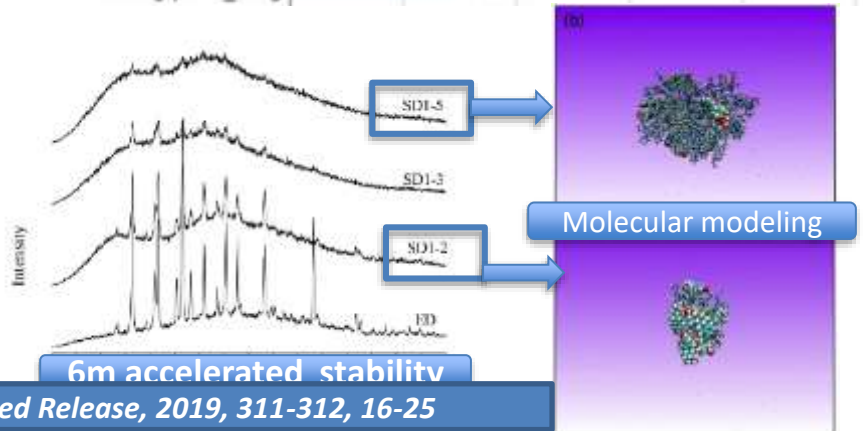
Machine learning

- 8 machine learning algorithms;
- Random forest: 82.50% accuracy;

Experimental validation:

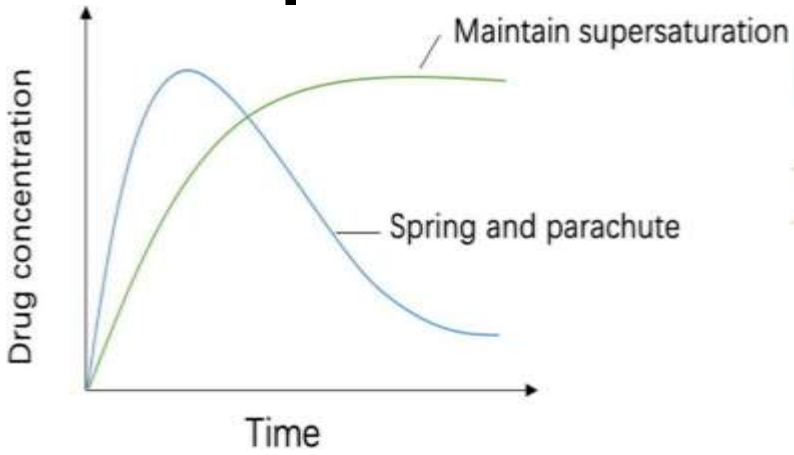
- 17β-estradiol/PVP formulation
- weight ratios: 1:2, 1:3, 1:5

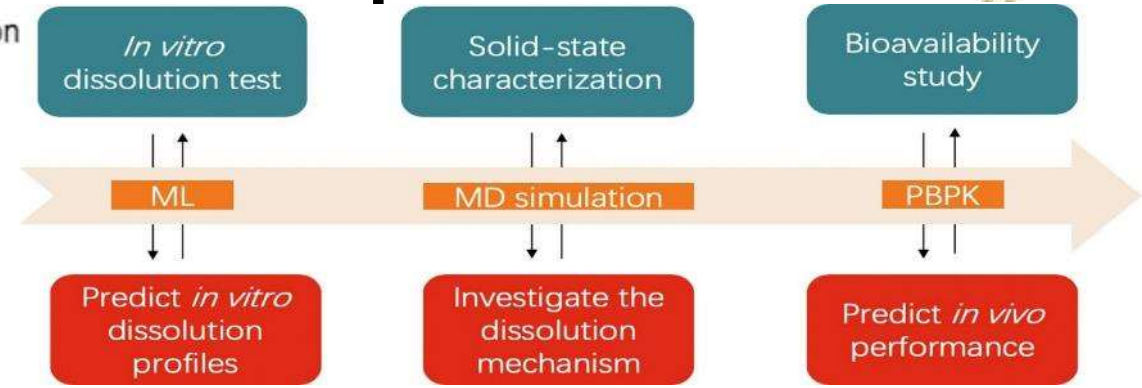




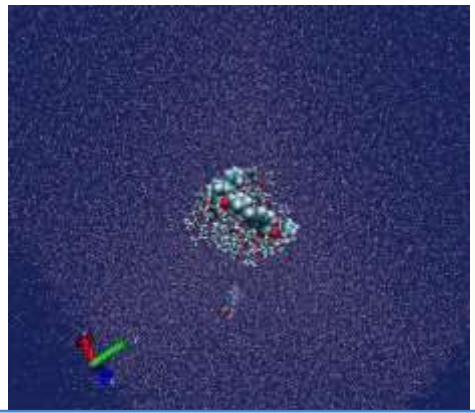
Chemical Physics Letters 554 (2012) 177–184; Journal of Controlled Release, 2019, 311-312, 16-25

2. Predicting in vitro dissolution and in vivo performance of solid dispersion





- **The classification model:**
- **Regression model for the "maintain supersaturation" dissolution profiles**



Dissolution process of solid dispersions

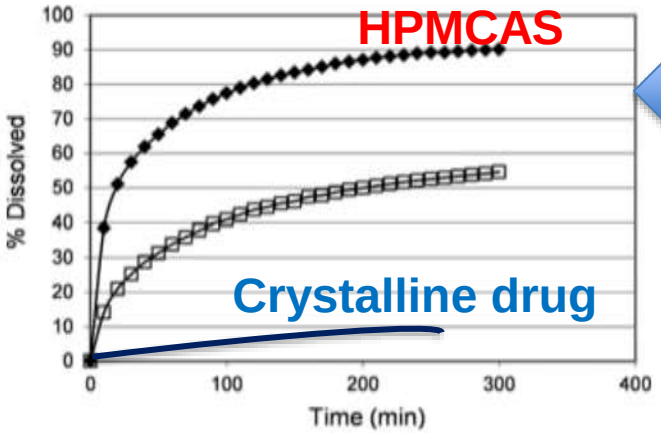
www.fda.gov

European Journal of Pharmaceutics and Biopharmaceutics, 2021, 158, 336–346

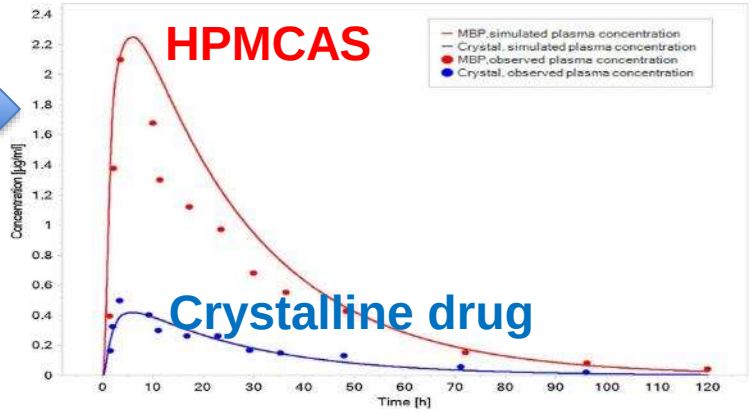
2. Predicting in vitro dissolution and in vivo performance of solid dispersion

- Water-insoluble drug: Vemurafenib;
- Formulations: HPMCAS solid dispersion.

J Pharm Sci, 2013. 102(3): p. 967-81.



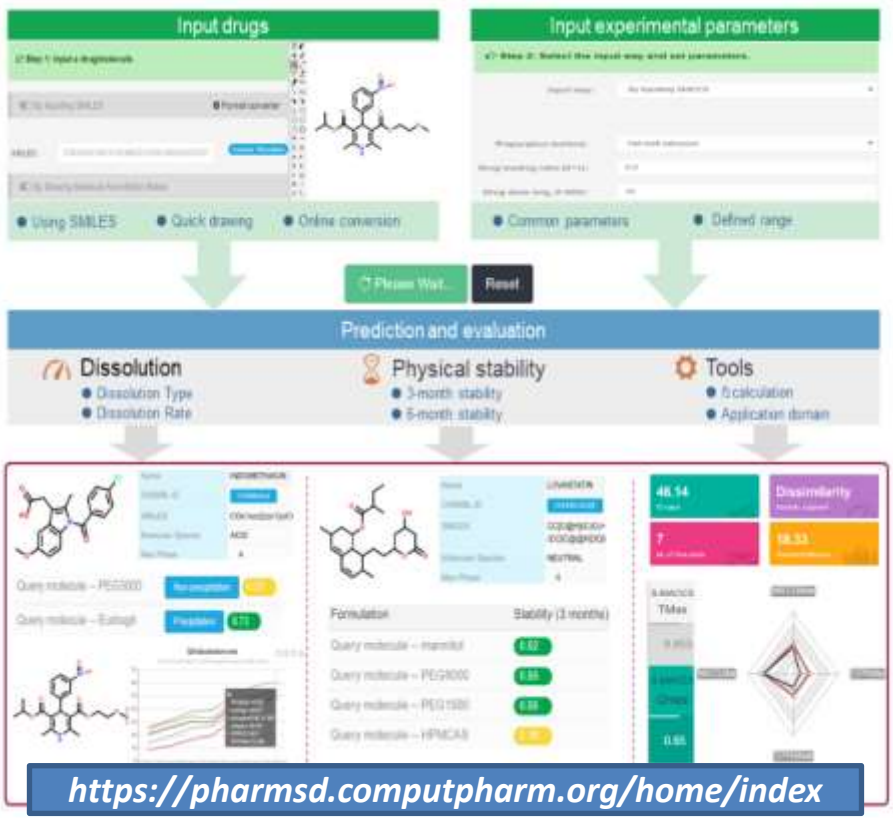
IVIVC



The dissolution profiles

Experimental PK profile *vs* PBPK modeling

3. PharmSD: a novel AI-based computational platform for solid dispersion formulation design



https://pharmsd.computpharm.org/home/index

Validation by 17 marketed SD formulations

- **63%** APIs in the application domains;
- **65%** of the SD formulations as stable;
- **88%** of the formulations as non-precipitation.

www.fda.gov

International Journal of Pharmaceutics, 2021, doi.org/10.1016/j.ijpharm.2021.120705

Summary

1G Physical pharmacy	2G Nanomedicine and biopharmaceuticals	3G Computational pharmacy
1950's	1980's	**2010's**

Current challenges

- Lack of high quality data!
- Lack of integrated digital tools;
- Lack of multidisciplinary scientists;

Future Opportunities

- Data sharing strategies;
- High-throughput and automatic experiments
- User-friendly digital tools;
- Scientific talent training

www.fda.gov

Journal of Controlled Release, 2021, under review

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Questions?

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