Biopharmaceutics: Challenges to Pharmaceutical Industry

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Objective

- To present recent biopharmaceutics challenges that facing pharmaceutical Industry and to highlight how to resolve such confronts for efficient utilization of biopharmaceutic concepts.

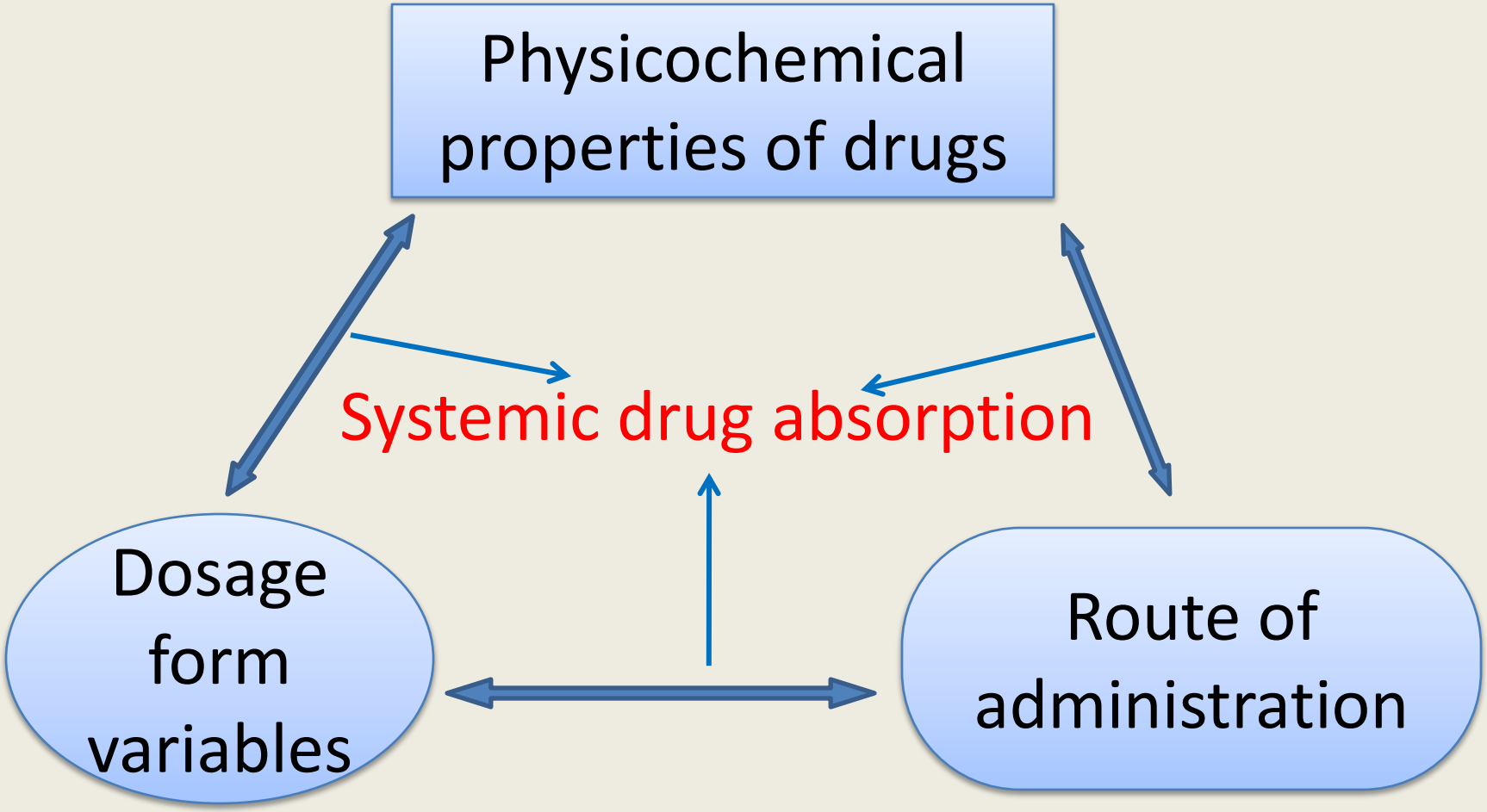
Content

1. **General Introduction**
    - *What is Biopharmaceutics?*
        - *Application fields of biopharmaceutics:*
            - *What the term bioavailability implies?*
2. **Biopharmaceutics and Pharmaceutical Industry**
3. **Biopharmaceutics challenges facing the Pharmaceutical industry**
    - *Excipients challenges*
        - *Challenges related to BCS and dissolution rate criteria*
            - *SUPAC-related challenges*
4. **Conclusion**
5. **References**

1. General Introduction

What is Biopharmaceutics?

Biopharmaceutics!



Application fields of biopharmaceutics:

- projects in late discovery and early development of drugs to achieve
  - a reduction in project failures
  - for a greater understanding of the applicability and implications.

Application fields of biopharmaceutics:

- It uses quantitative methods and theoretical models to
  - evaluate the effect of the API, DS and RA on the therapeutic requirements of the API and DS.

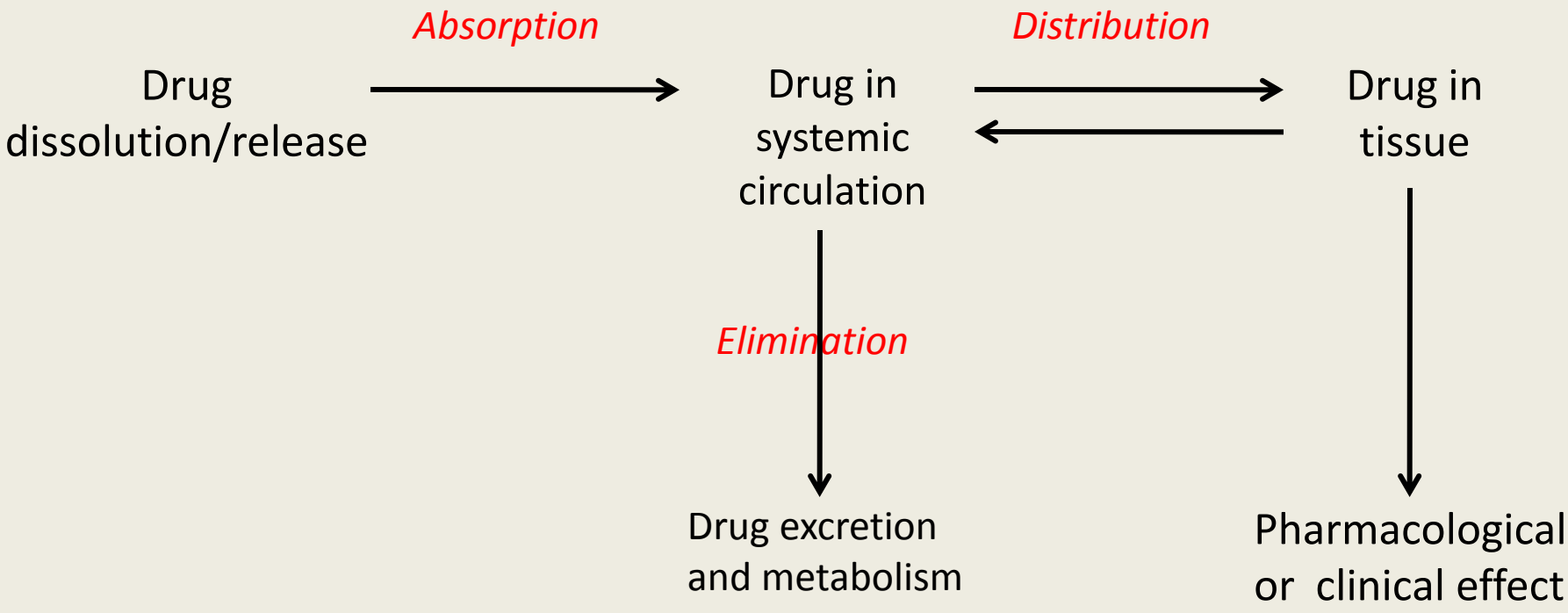
Application fields of biopharmaceutics:

- it assures protection and stability of the API and DS and allows for DS design to deliver the API at a specific rate as to optimize the therapeutic effect and minimize any adverse effects.

- *Application fields of biopharmaceutics:*

  It involves factors that influence:

  - protection and stability of the drug within the drug product
  - the rate of drug release from the drug product
  - the rate of dissolution of the drug at the absorption site
  - the availability of the drug at its site of action.


Absorption
Distribution
Drug dissolution/release
Drug in systemic circulation
Drug in tissue
Elimination
Drug excretion and metabolism
Pharmacological or clinical effect

- *What the term bioavailability implies?*

Types of Biopharmaceutics Studies

In vivo*:*

Bioavailability studies

Acute pharmacological effect

Clinical study

In vitro*:*

Dissolution/release study

Permeability study

Biotransformation study

Summary

- Drug, drug product, physiological and anatomical factors, PD and PK of the drug, manufacturing and patient variables constitute an integrated components that form the biopharmaceutics considerations in drug product design.

Biopharmaceutics and Pharmaceutical Industry

Biopharmaceutics concept is ultimately evolved to include:

- Production technology
- QC and QA
- Specifications of material/ equipment/ processing.

- The association between the Biopharmaceutics and Pharmaceutical Industry has become more profound since early 1990

- Released guidance related to IVIV correlation; BCS; Biowaivers; Bioequivalence studies for generic products ….etc) has strengthen the interrelation of both.

An initiative to form a focus group for the discussion of Biopharmaceutical issues within the Pharmaceutical Industry was started at the 1999. Two main objectives were defined:

1	2
The promotion of scientific education and training in the field of biopharmaceutics	Promote a focus on biopharmaceutical issues at scientific meetings and conferences

Challenges facing the Pharmaceutical industry

Biopharmaceutics challenges facing the Pharmaceutical Industry are originated from the concepts themselves. How?

In general, confronts could be classified as:

- BCS and dissolution rate-related
- Excipients-related
- In vitro-in vivo correlation-related (IVIVC)
- Scale up and postaproval changes (SUPAC)-related
- Bioequivalence-related
- Supplier change-related
- Dissolution test-related
- Process and equipment-related
- Drug-related.

This presentation is going to focus on challenges that are related to

Excipients

BCS and dissolution rate

SUPAC

Excipients-related challenges

- Excipients are pharmacodynamically inactive substances that are added to a formulation to provide certain functional properties to the drug and dosage form.

- Excipients may be added to:
  - improve the compressibility of the active drug,
  - stabilize the drug from degradation,
  - decrease gastric irritation,
  - control the rate of drug release/absorption from the absorption site,
  - increase drug bioavailability

- However, upon utilizing excipients of low quality or from non-reputable vendor, problems might occur as these material might:
  - Affect drug dissolution rate
  - Influence drug pharmacokinetic parameters
  - Affect the rate and extent of drug absorption.
  - increase the retention time of the drug in the GI tract
  - act as carriers to increase drug diffusion across the intestinal wall.

- It is obvious then that excipients can be crucial determinants of product performance and quality.

So what is the challenge?

- The challenge is that unlike active ingredients, excipients are not currently subject to regulatory control in terms of GMP unless they are novel materials
- Then what are the benefits of the Guide to GMP for Bulk Pharmaceutical Excipients?

- the Guide though not having any regulatory status, provides much useful information on quality systems and is a good reference for performing audits of excipient facilities.

Then how to resolve this?

It is so simple though expensive. (follow 1-4)

- Excipients should be:
  1. sourced directly from a reputable vendor who has quality systems in place to ensure consistent manufacture and control.
  2. Procurement from brokers is to be discouraged.

3. Auditing such providers for the presence of quality systems and controls should be the norm.
4. Application of a validation program to establish reliability of the supply source

- Adopted validation program stated in 4 should consider:
  - The nature of the excipient and medicinal product.
  - The conditions under which the materials are manufactured and controlled.
  - The nature and status of the supplier, and his understanding of the Good Manufacturing Practice (GMP) requirements of the pharmaceutical industry.
  - The Quality Assurance system of the manufacturer.

BCS and dissolution rate-related challenges

BCS !!!!

condition	comments
solubility	A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of water over a pH range of 1–8
dissolution	An immediate release (IR) drug product is considered rapidly dissolving when not less than 85% of the label amount of the drug substance dissolves within 30 min using the USP apparatus I at 100 rpm (or apparatus II at 50 rpm) in a volume of 900 ml or less
permeability	A drug substance is considered highly permeable when the extent of absorption in humans is to be >90% of an administered dose based on mass balance determination

- in vivo bioavailability or bioequivalence study requirement for certain IR solid oral drug products might be waived if API meets very specific criteria.

This is the power of BCS.

- The BCS provides criteria for determining the rate limiting factor for drug absorption from oral dosage forms.
- Therefore, it may influence the choice of drug candidate for further development, prediction and elucidation of food interactions, choice of formulation, and IVIVC in the dissolution testing of oral dosage forms.

- BCS can used to make the development process more efficient. How? (next slide)

- For example, in the case of a drug placed in BCS Class II where dissolution is the rate-limiting step to absorption, formulation principles such as polymorph selection, salt selection, complex formation, and particle size reduction (i.e., nanoparticles) could be applied earlier in development to improve bioavailability.

- BCS is a useful tool. Then where are the challenges?

- The current BCS class boundaries are too conservative in certain aspects, which could lead to the loss of promising compounds in early development stages or prevent biowavers from being granted for drugs that exhibit Class I behavior in physiologically relevant conditions.

Do U catch it?

- Suggestions have been made to further improve the applicability of BCS in the industry and are summarized in a BCS workshop report by Polli. Of particular importance are the suggestions that are likely to affect the future solubility and dissolution classifications of the BCS. They are as follows:

1. The pH range for solubility studies should be limited to only include pH 1.2, 4.5, and 6.8.
2. The solubility of amphoteric compounds should be determined at the isoelectric point if it occurs between pH 1.2 and 6.8.
3. An intermediate solubility class should be introduced given the tendency of many acids and bases to be highly soluble at pH 6.8 and 1.2, respectively.
4. The dose : solubility ratio should be increased from 250 to 500 ml, particularly at pH values of 4.5 and 6.8, which are representative of the small intestine where the fluid volume is greater than the stomach.
5. The dissolution classification should be broadened from at least 85% dissolved in 30 minutes to at least 85% dissolved in 60 minutes.

- On the other hand, The implementation of BCS guidance to utilize in vitro dissolution tests as a surrogate for in vivo BE studies and the incorporation of the BCS into drug development strategies exemplifies the rapidly evolving function of the dissolution test.

But

- Some differences are far away from resolution. For example, the JP does not recognize USP Apparatus 3 and maintains a different approach to delayed-release products.
- How dissolution is granted to be similar when tested on different apparatus? No way.

SUPAC-related challenges

- After a drug product is approved for marketing by the regulatory authority, the manufacturer may want to make a manufacturing change.
- The pharmaceutical industry, academia and the FDA developed a series of guidances for the industry that discuss scale-up and postapproval changes, generally termed, SUPAC guidances

- These SUPAC guidances are for manufacturers of approved drug products who want to change:
  - a component and composition of the drug product
  - The batch size
  - The manufacturing site
  - The manufacturing process or equipment
  - The packaging.

- These guidances describe various levels of postapproval changes according to whether the change is likely to impact on the quality and performance of the drug product.
- The level of change as classified by the FDA as to the likelihood that a change in the drug product might affect the quality of the product.

Postaproval change levels

Change level	example	comment
Level 1	**Deletion or partial deletion of an ingredient to affect the color or flavor of the drug product**	**Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance**
Level 2	**Quantitative change in excipients greater that allowed in a Level 1 change**	**Level 2 changes are those that could have a significant impact on formulation quality and performance**
Level 3	**Qualitative change in excipients**	**Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. A Level 3 change may require in vivo bioequivalence testing**

- It should be emphasized that to characterize a change as level 2 and 3 is not a trouble-free decision since level of variation is subjective. Here exists the challenge.

Conclusion

Excipients of different sources; differences in production and quality control testing equipments; assumptions involved in different concepts and models related to biopharmaceutics classification system, in vitro-in vivo correlation, and scale up and post-approval changes constitute the confront that impede the effective utilization of biopharmaceutics concept by the pharmaceutical industry.

References

1. Amidon, G.L.; Lennernas, H.; Shah, V.P.; Crison, J.R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research 1995, 12, 413–420.)
2. European Pharmacopoeia, 5th Ed.; Directorate for the quality of medicines of the Council of Europe: Strasbourg Cedex, France, 2001; Vol. 1, 67,075.)
3. FDA regulatory guidances, FDA website for regulatory guidances. www.fda.gov/cder/guidance/index.htm).
4. FDA regulatory guidances, FDA website for regulatory guidances.www.fda.gov/cder/guidance/index.htm).
5. Guidance for Industry, immediate release solid oral dosage forms, scale up and post approval changes, and in vivo bioequivalence documentation. FDA: CDER, USA, 1995.
6. Kingsford, M.; Eggers, .J.; Soteros, G.; Maling, T.J.B.; Shirkey, R.J. An in vivo-in vitro correlation for the bioavailability of frusemide tablets. J. Pharm. Pharmacol. 1984, 36,536–538.
7. Mervcill, A. A good manufacturing practices guide for bulk pharmaceutical excipients. Pharm. Technol. (USA) 1995, 19, 34–40.
8. Polli, J.E. Summary workshop report: biopharmaceutics classification system—implementation challenges and extension opportunities. J. Pharm. Sci., 2004, 93 (6), 1375– 1381
9. Rules and Guidance for Pharmaceutical Manufacturers and Distributors; Medicines Control Agency (UK), HMSO: London, 1997, Section 5, Annex 8.
10. SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, FDA, Guidance for Industry, Sept. 1997.
11. Yazdanian, M.; Briggs, K.; Jankovsky, C.; Hawi, A. The ‘‘high solubility’’ definition of the current FDA guidance on biopharmaceutical classification system may be too strict for acidic drugs. Pharm. Res. 2004, 21 (2), 293–299.

Thanks