

THE PHARMA INNOVATION

Factors Effecting on Drug Distribution

Ashok Kari¹, Gandhu Sateesh¹, Bharatha Suresh¹, Bodavula Samba Siva Rao^{2*}

1. Dhanvanthari Institute of Pharmaceutical Sciences, Kothagudem, Khammam. A.P., India
2. Khammam College of Pharmacy, Khammam. A.P., India

This study of drug distribution investigates the influence of drug solubility and dissolution on its release from inert geopolymer pellets of three different sizes (1.5×1.5 , 3×6 , and 6×6 mm), having the same geopolymer composition and containing highly potent opioid fentanyl, sumatriptan, theophylline, or saccharin. Scanning electron microscopy, nitrogen sorption, drug solubility, permeation, and release experiments were performed, and estimates of the drug diffusion coefficients and solubilities in the geopolymer matrix were derived with the aid of finite element method (FEM). FEM was mainly focus on the drug distribution further employed to investigate the effect of a non-uniform drug distribution on the drug release profile. When inspecting the release profiles for each drug, it was observed that their solubilities in the geopolymer matrix imposed a much greater influence on the drug release rate than their diffusion coefficients. Concentrating the initial drug load in FEM into non uniformly distributed drug regions inside the matrix created drug release profiles that more closely resembled experimental data than an FEM-simulated uniform drug distribution did. The presented FEM simulations and visualization of drug release from geopolymers under varying initial and dynamic conditions should open up for more systematic studies of additional factors that influence the drug release profile from porous delivery vehicles.

Keyword: Drug absorption, Drug distribution, Drug dissolution, Drug solubility

INTRODUCTION: After entry in to the systemic circulation either by intravascular injection or by absorption from any of the various extravascular sites, the drug is subjected to a number of processes called as disposition processes.

The process of drug transfer from the capillary in to the tissue fluid is mainly diffusional, the membrane thickness, diffusion coefficient of the drug and concentration gradient across the capillary membrane are important factors in determining the rate of drug diffusion

Corresponding Author's Contact information:
Bodavula Samba Siva Rao*
Department of Pharmacy, Khammam College of Pharmacy,
Khammam, Andhra Pradesh, India
E-mail: siva69pharma@gmail.com

Kinetically if a rug diffuses rapidly across the membrane in such away that blood flow is the rate limiting step in the distribution of drug, then the process is perfusion or flow limited If drug

distribution is limited by the slow diffusion of the drug across the membrane in the tissue, then the process is termed as diffusion or permeability limited. The time for drug distribution is generally measured by the distribution half-life or the time for 50% distribution. The volume of each of these real physiological compartments can be determined by use of specific tracers or markers. The plasma volume can be determined by use of substances of high molecular weight or substances that are totally bound to plasma albumin.

Distribution of drug throughout the body is not uniform, because the different tissues receive the drug from plasma at different rates and different extents.

DISPOSITION:

Disposition is defined as the processes that tend to lower the plasma concentration of the drug

The major drug disposition processes are:

- Distribution
- Elimination

Distribution:

In Which involves reversible transfer of a drug between compartments (or) from one location to another with the body.

ELIMINATION:

Which causes irreversible loss of drug from the body. Elimination is further divided in to two process

- Biotransformation(Metabolism)
- Excretion

The inter-relationship between drug distribution, bio-transformation and excretion and the drug in plasma is shown in Figure 1.

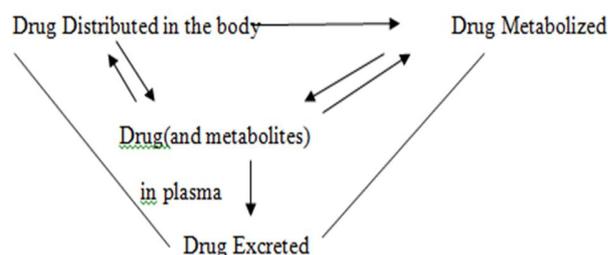
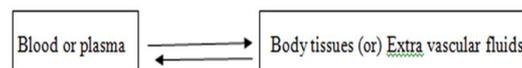


Fig 1

Distribution process is carried out by the circulation of blood, one of the compartment is always the blood (Or) the plasma and the other represents extra vascular fluids and other body tissues.



Definition of Distribution:
 Distribution is reversible transfer of a drug between the blood or plasma and extra vascular fluids and tissues.

KINETICS OF DISTRIBUTION

Distribution Half-life, Blood flow & Drug uptake by Organs:

The process of drug transfer from the capillary in to the tissue fluid is mainly diffusional, the membrane thickness, diffusion coefficient of the drug and concentration gradient across the capillary membrane are important factors in determining the rate of drug diffusion

Kinetically if a drug diffuses rapidly across the membrane in such a way that blood flow is the rate limiting step in the distribution of drug, then the process is perfusion or flow limited.

If drug distribution is limited by the slow diffusion of the drug across the membrane in the tissue, then the process is termed as diffusion or permeability limited.

The time for drug distribution is generally measured by the distribution half-life or the time for 50% distribution.

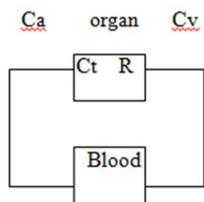
$$K_d = Q/VR$$

Where K_d = first order distribution constant

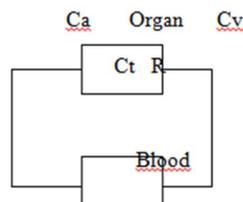
Q = Blood flow to the organ

V = Volume of the organ

R = ratio of drug concentration in the organ tissue to drug.



Diffusion limited model



Perfusion limited model

- Permeation of free or unbound drug present in the blood through the capillary wall (occurs rapidly) and entry into the interstitial/extracellular fluid (ECF)
- Permeation of drug present in the ECF through the membrane of tissue cells and into the intracellular fluid. This step is rate limiting and depends upon two major factors:
 - a) Rate of perfusion to the extracellular tissue
 - b) Membrane permeability of the drug

RESULTS & DISCUSSION:

APPARENT VOLUME OF DISTRIBUTION

It is defined as the hypothetical volume of body fluids into which a drug is dissolved or distributed, it is called as apparent volume of distribution.

A drug in circulation distributes to various organs and tissues

However there exists a constant relationship between X & C

$$X \propto C \text{ (or) } X = V_d C$$

V_d = Apparent volume of distribution

X = Amount of drug in the body

C = concentration of Drug in the plasma

$$\text{Apparent volume of distribution} = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}}$$

(or)

$$V_d = X/C$$

MATERIALS and METHODS:

STEPS IN DRUG DISTRIBUTION

Distribution of drug present in systemic circulation to extra vascular tissues involves following steps

FLUIDS COMPARTMENT OF A 70kg ADULT:

| Body fluid TBW | Volume in litres | %of body weight | %of |
|--------------------------------------|-------------------------|------------------------|------------|
| 1.Vascular fluid/blood | 6 | 9 | 15 |
| 2.Extra cellular Fluid 28 | 12 | 17 | |
| 3.Intracellular fluid 57 | 24 | 34 | |
| 4.Total body water 100 | 42 | 60 | |

The volume of each of these real physiological compartments can be determined by use of specific tracers or makers. The plasma volume can be determined by use of substances of high molecular weight or substances that are totally bound to plasma albumin.

Ex: High molecular weight dyes such as Evans blue, indocyanine green.

MARKERS USED TO MEASURE THE VOLUME OF REAL PHYSIOLOGICAL COMPARTMENTS

| Physiological fluid compartment | Markers Used | Approximate Volume |
|--|--|---------------------------|
| Plasma | Evans blue, <u>indocyanine green</u> , <u>I-131, albumin</u> . | 3 |
| <u>erythrocytes</u> | cr-51 | 2 |
| Extra cellular fluid | non-metabolisable saccharides like <u>raffinose, inulin, mannitol</u> . | 15 |
| Total body water | <u>D₂O, hto, antipyrine</u> . | 42 |

Certain generalizations can be made regarding the apparent volume of distribution of such drugs.

- Drugs which bind selectively to plasma proteins or other blood components ex: Warfarin have apparent volume of distribution smaller than true volume of distribution .The V_d of such drugs lies between blood volume and TBW volume. ex: Warfarin has V_d of about 10litres
- Drugs which bind selectively to extra vascular tissues .ex: Chloroquine have apparent volume of distribution larger than their real volume of distribution. The V_d of such drugs is always greater than TBW volume ex: Chloroquine has V_d of approximately 15,000 litres.

CONCLUSION:

Distribution is the very important pharmacokinetic parameter . It is also called disposition process. This process that tend to lower the plasma concentration of the drug.

REFERENCE:

1. A Text book of biopharmaceutics by Brahmankar.
2. Dissolution studies and evaluation etl-B.V.Sharma
3. Pharmacokinetic principles-Shankar BR Kumar
4. Detail study of Pharmaceutics-B.V.Rao
5. Pharmacokinetic drugs absorption- B.Venkateshwarlu
6. Indian Pharmacopiea
7. British Pharmacopiea
8. Guidelines of drug dissolution- v.R.Chopra.