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Review

Surging footprints of mathematical modeling for prediction of transdermal permeability

Neha Goyal, Purva Thatai, Bharti Sapra *

Pharmaceutics Division, Department of Pharmaceutical Sciences, Punjabi University, Patiala, India

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ABSTRACT

In vivo skin permeation studies are considered gold standard but are difficult to perform and evaluate due to ethical issues and complexity of process involved. In recent past, a useful tool has been developed by combining the computational modeling and experimental data for expounding biological complexity. Modeling of percutaneous permeation studies provides an ethical and viable alternative to laboratory experimentation. Scientists are exploring complex models in magnificent details with advancement in computational power and technology. Mathematical models of skin permeability are highly relevant with respect to transdermal drug delivery, assessment of dermal exposure to industrial and environmental hazards as well as in developing fundamental understanding of biotransport processes. Present review focuses on various mathematical models developed till now for the transdermal drug delivery along with their applications.

1. Introduction

Skin is the largest organ of the human body having a very complex structure. Due to unique structural and physicochemical properties, it is very different from other biological and microporous membranes. It consists of multi-layers including epidermis (thin outermost layer), dermis (a thicker middle layer) and subcutaneous tissue layer i.e. hypodermis (innermost layer). The skin performs three main functions i.e. protection, regulation and sensation. The regulatory function of the skin attracts the interest of scientists for developing formulations for skin [1]. Transdermal permeation occurs through three pathways namely: the diffusion through the lipid lamellae; the transcellular diffusion through the keratinocytes and lipid lamellae; permeation through appendages, hair follicles and sweat glands. The drugs should have sufficient lipophilicity to partition into SC but also should have sufficient hydrophilicity to pass through the epidermis and eventually through the systemic circulation. For most of the drugs, the rate

* Corresponding author. Pharmaceutics Division, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India. Fax: 0175-3046335.
E-mail address: bhartisaprapbi@gmail.com or bhartijatin2000@yahoo.co.in (B. Sapra).
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determining step for drug transport is transit across the SC [2]. A large number of experimental and theoretical investigations have been carried out on the skin permeability. The prediction of percutaneous permeation is attracting attention of researchers in Cosmeceutical and pharmaceutical industry. Hence, development of mathematical models of epidermal and dermal transport seemed to be essential for the optimization of percutaneous delivery of drugs and for evaluation of their toxicity [3]. Mathematical models of skin permeability are highly relevant to the fields of transdermal drug delivery and in developing fundamental understanding of biotransport processes. Modeling of percutaneous permeation provides an ethical and viable alternative to laboratory experimentation. *In vivo* skin permeation studies are considered gold standard, but are difficult to perform and evaluate due to ethical issues and complexity of the process involved [4]. *In vitro* measurement of skin permeation can be done simply by using diffusion cell. Although it is easy and viable, this method is time consuming. In light of the above factors, research in developing mathematical modeling for transdermal drug delivery is at a high pace these days.

Mathematical models are the collection of mathematical quantities, operations and relations together with their definitions and they must be realistic and practical. The mathematical model is based on the hypotheses that consider mathematical terms to concisely describe the quantitative relationships. Many models have been proposed till now; however, earlier mathematical modeling was not in that much progress as in present scenario. In addition to establishing the required mathematical framework to describe these models, efforts have also been made to determine the key parameters that are required for the use of these models. The first contribution to mathematical modeling was given by Takeru Higuchi; a pharmaceutical scientist who applied physical and chemical principles to the design of controlled release devices in 1961 [5]. He proposed an equation exhibiting a considerable initial excess of undissolved drug within an inert matrix with film geometry allowing for a surprisingly simple description of drug release from an ointment base. The importance of mathematical modeling was more clearly understood by the year 1979. Categorically, mathematical models can be divided into empirical and mechanistic models. However, detailed number of mathematical models developed for analyzing and predicting data of transdermal studies are summarized in Fig. 1.

2. Empirical models

Empirical models are based on experimental data. These models are not based on physical principles and also not on assumptions made with respect to relationship between different variables. Empirical models are computer based modeling developed by Meuring Beynon in early 1980s. The main software used in empirical modeling is TKEDEN.

2.1. *Multiple linear regression models*

Multiple linear regression models help in relating two or more independent variables and a dependent variable by fitting a

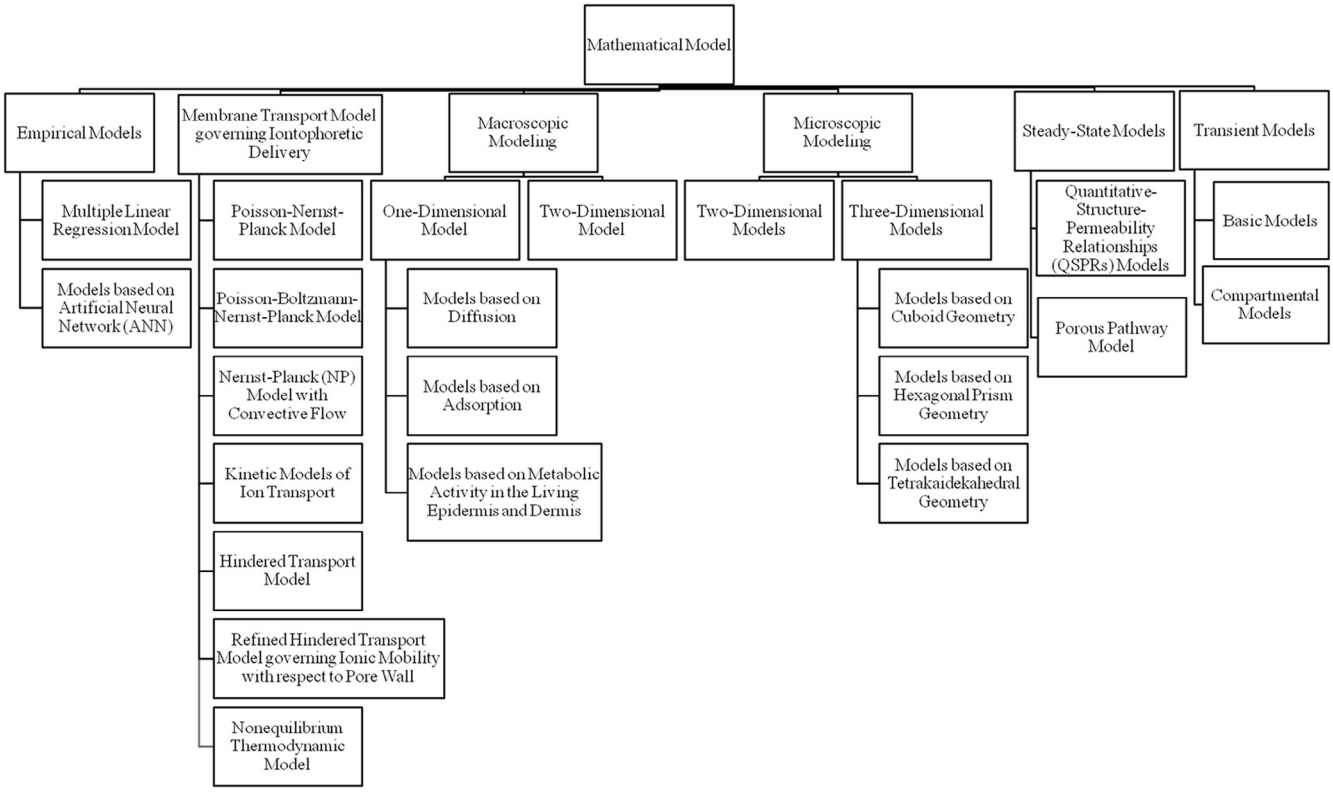

Fig. 1 – Classification of various mathematical governing transdermal permeation models.