

# Indian Journal of Pharmaceutical Sciences

Scientific Publication of the Indian Pharmaceutical Association

Indexed in Ind MED, EMBASE/Excerpta Medica, International Pharmaceutical Abstracts, Chemical Abstracts.

Volume 70

Number 1

January-February 2008

## CONTENTS

### REVIEW ARTICLES

#### A Decision Tree for Rapid Quality Assurance and Control of Rifampicin-Containing Oral Dosage Forms for Global Distribution for Tuberculosis Treatment

Y. ASHOKRAJ, SHRUTIDEVI AGRAWAL AND R. PANCHAGNULA 1-4  
SWATI RAWAT, SUDHA VENGURLEKAR, B. RAKESH, S. JAIN, G. SRIKARTI 5-10

### RESEARCH PAPERS

#### *In vivo* Evaluation of Single Dose Tetanus Toxoid Vaccine Formulation with Chitosan Microspheres

R. MANIVANNAN, S. A. DHANARAJ, Y. UDAYA BHASKARA RAO, A. BALASUBRAMANIAM, N. L. GOWRISHANKAR, N. JAWAHAR AND S. JUBIE 11-15

#### Ionic Cross-linked Chitosan Beads for Extended Release of Ciprofloxacin: *In vitro* Characterization

A. SRINATHA, J. K. PANDIT AND S. SINGH 16-21

#### Design and Optimization of Diclofenac Sodium Controlled Release Solid Dispersions by Response Surface Methodology

H. N. SHIVAKUMAR, B. G. DESAI AND G. DESHMUKH 22-30

#### Evaluation of Free Radical Scavenging Activity of an Ayurvedic Formulation, *Panchvalkala*

SHEETAL ANANDJIWALA, M. S. BAGUL, M. PARABIA AND M. RAJANI 31-35

#### Validation of Different Methods of Preparation of *Adhatoda vasica* Leaf Juice by Quantification of Total Alkaloids and Vasicine

S. SONI, SHEETAL ANANDJIWALA, G. PATEL AND M. RAJANI 36-42

#### Formulation and Characterization of Mucoadhesive Buccal Films of Glipizide

MONA SEMALTY, A. SEMALTY AND G. KUMAR 43-48

#### Synthesis, Antimicrobial and Anti-inflammatory Activity of 2,5-Disubstituted-1,3,4-oxadiazoles

G. NAGALAKSHMI 49-55

#### Ascorbic Acid Inhibits Development of Tolerance and Dependence to Opiates in Mice: Possible Glutamatergic or Dopaminergic Modulation

S. K. KULKARNI, C. DESHPANDE AND A. DHIR 56-60

#### Design and *In Vitro* Characterization of Buccoadhesive Drug Delivery System of Insulin

J. SAHNI, S. RAJ, F. J. AHMAD AND R. K. KHAR 61-65

#### Development and Evaluation of a Chloramphenicol Hypertonic Ophthalmic Solution

A. V. JITHAN, C. KRISHNA MOHAN, AND M. VIMALADEVI 66-70

#### Optimization of Fast Dissolving Etoricoxib Tablets Prepared by Sublimation Technique

D. M. PATEL AND M. M. PATEL 71-76

#### Furosemide-loaded Alginate Microspheres Prepared by Ionic Cross-linking Technique: Morphology and Release Characteristics

M. K. DAS AND P. C. SENAPATI 77-84

### SHORT COMMUNICATIONS

#### Isolation of Liver Aldehyde Oxidase Containing Fractions from Different Animals and Determination of Kinetic Parameters for Benzaldehyde

R. S. KADAM AND K. R. IYER 85-88

#### Microwave-Induced Synthesis of Schiff Bases of Aminothiazolyl Bromocoumarins as Antibacterials

K. N. VENUGOPALA AND B. S. JAYASHREE 88-91

#### *In vitro* Antiviral Activity of some Novel Isatin Derivatives against HCV and SARS-CoV Viruses

P. SELVAM, N. MURGESH, M. CHANDRAMOHAN, E. DE CLERCQ, E. KEYAERTS, L. VIJGEN, P. MAES, J. NEYTS AND M. V. RANST 91-94

#### Physicochemical and Pharmacokinetic Parameters in Drug Selection and Loading for Transdermal Drug Delivery

N. S. CHANDRASHEKAR AND R. H. SHOBHA RANI 94-96

#### HPLC Estimation of berberine in *Tinospora cordifolia* and *Tinospora sinensis*

G. V. SRINIVASAN, K. P. UNNIKRISHNAN, A. B. REMA SHREE AND INDIRA BALACHANDRAN 96-99

#### Parenteral Formulation of Zopiclone

P. V. SWAMY, P. SUSHMA, G. CHIRAG, K. PRASAD, M. YOUNUS ALI AND S. A. RAJU 99-102

#### Simultaneous Spectrophotometric Determination of Lansoprazole and Domperidone in Capsule Dosage Form

A. P. SHERJE, A. V. KASTURE, K. N. GUJAR AND P. G. YEOLE 102-105

#### Novel 2-Pyrazoline Derivatives as Potential Antibacterial and Antifungal Agents

SUVARNA KINI AND A. M. GANDHI 105-108

#### Spectrophotometric Estimation of Ethamsylate and Mefenamic Acid from a Binary Mixture by Dual Wavelength and Simultaneous Equation Methods

ANJU GOYAL AND I. SINGHVI 108-111

#### Novel Colon Targeted Drug Delivery System Using Natural Polymers

V. RAVI, T. M. PRAMOD KUMAR AND SIDDARAMAIAH 111-113

#### Effect of Some Clinically Used Proteolytic Enzymes on Inflammation in Rats

A. H. M. VISWANATHA SWAMY AND P. A. PATIL 114-117

#### Synthesis and Pharmacological Evaluation of (6-Substituted 4-Oxo-4H-chromene-3 yl) methyl N-substituted Aminoacetates

ASMITA GAJBHIYE, V. MALLAREDDY AND G. ACHAIHAH 118-120

#### Development and *In Vitro* Evaluation of Buccoadhesive Tablets of Metoprolol Tartrate

P. D. NAKHAT, A. A. KONDAWAR, L. G. RATHI AND P. G. YEOLE 121-124

#### RP-HPLC Estimation of Venlafaxine Hydrochloride in Tablet Dosage Forms

S. L. BALDANIA, K. K. BHATT, R. S. MEHTA, D. A. SHAH AND TEJAL R. GANDHI 124-128

#### Simultaneous Estimation of Esomeprazole and Domperidone by UV Spectrophotometric Method

S. LAKSHMANA PRABU, A. SHIRWAIKAR, ANNIE SHIRWAIKAR, C. DINESH KUMAR, A. JOSEPH AND R. KUMAR 128-131

#### *In Vitro* Anthelmintic Activity of *Baliospermum montanum* Muell. Arg roots

R. G. MALI AND R. R. WADEKAR 131-133

#### REFEREES FOR INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES DURING 2006 & 2007

134-134

# Physicochemical and Pharmacokinetic Parameters in Drug Selection and Loading for Transdermal Drug Delivery

N. S. CHANDRASHEKAR\* AND R. H. SHOBHA RANI

Department of Pharmaceutics, Al-Ameen College of Pharmacy, Hosur Road, Bangalore - 560 027, India

## Chandrashekar, *et al.*: Physicochemical and Pharmacokinetic Parameters for Transdermal Drug Delivery

**Skin of an average adult body covers a surface of approximately 2 m<sup>2</sup> and receives about one-third of the blood circulating through the body. The transdermal route of administration cannot be employed for a large number of drugs. The rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug are the important factors to be considered for deciding its suitability of drug for delivery by transdermal route.**

**Key words:** Transdermal delivery, Physicochemical, Pharmacokinetics

Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action. Skin of an average adult body covers a surface of approximately 2 m<sup>2</sup> and receives about one-third of the blood circulating through the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface

is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area<sup>1</sup>. It is one of the most readily accessible organs of the human body. The potential of using the intact skin as the port of drug administration to the human body has been recognised for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time<sup>2</sup>.

The transdermal route of administration cannot be employed for a large number of drugs. The objective of this paper is to focus on the rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug. Physicochemical factors such as solubility, crystallinity, molecular weight <400, polarity, melting point <200, partition coefficient Log P (octanol-water) between -1.0 to 4 must be considered<sup>3</sup> (Table 1). Biological factor should also be considered such as skin irritation, site of application of the patch e.g. scopolamine patch for motion sickness is applied

---

**\*For correspondence:**

E-mail: nschandrashekar@gmail.com

**TABLE 1: FACTORS TO BE CONSIDERED FOR TRANSDERMAL DOSE CALCULATION**

Physiochemical	Pharmacokinetic	Biological
<ul style="list-style-type: none"> <li>• Solubility</li> <li>• Crystallinity</li> <li>• Molecular weight</li> <li>• Polarity</li> <li>• Melting point</li> </ul>	<ul style="list-style-type: none"> <li>• Half-life</li> <li>• Volume of distribution</li> <li>• Total body clearance</li> <li>• Therapeutic plasma concentration</li> <li>• Bioavailable factor</li> </ul>	<ul style="list-style-type: none"> <li>• Skin toxicity</li> <li>• Site of application</li> <li>• Allergic reactions</li> <li>• Skin metabolism</li> <li>• Skin permeability</li> </ul>

**TABLE 2: IDEAL PROPERTIES OF DRUG CANDIDATE FOR TRANSDERMAL DRUG DELIVERY**

Parameter	Properties
Dose	Should be low (<20 mg/day)
Half-life in h	10 or less
Molecular weight	<400
Partition coefficient	Log P (octanol-water) between-1.0 and 4
Skin permeability coefficient	>0.5 X 10 <sup>-3</sup> cm/h
Skin reaction	Non irritating and non-sensitizing
Oral bioavailability	Low
Therapeutic index	Low

backside of the ear and Transderm-Nitro is applied on the chest. When a pharmacologically active material has to be presented to the skin, an occlusive or allergic response is significant, limits have to be determined for the acceptability of the undesired effect<sup>4</sup>. The pharmacokinetic information of the drug is a critical factor in deciding its suitability for delivery by the transdermal route as it is suitable only for drugs whose daily dose is in few milligrams. The resulting plasma concentration of active agent depends on the clearance; however, if one assumes a small volume of distribution and relatively long half-life, plasma level in excess of few micrograms per milliliter is very unlikely. Another important factor is the half-life, (e.g., nitroglycerin  $t_{1/2}$  is 3 min) which provides information on the disposition of a drug in our body other parameters such as effective plasma level; also determine whether a transdermal delivery can be developed or not (Table 2).

One can estimate the skin input rate of a drug required from its transdermal system based on volume of distribution (Vd), total body clearance ( $CL_T$ ) and steady state or therapeutic concentration (CPss) under steady state conditions, the drug input rate from its transdermal system is expected to be equal to its output rate, determined by total body clearance multiplied by the therapeutic plasma concentration. This relationship can be expressed using following mass balance equation; input rate = dosing rate  $\times$  bioavailable factor (F), output rate = total body clearance  $\times$  steady state plasma concentration and input rate = output rate

or  $F \times \text{dosing rate} = CL_T \times CP_{ss} \dots 1$ , where  $CL_T$  is total body clearance,  $CP_{ss}$  is average target plasma concentration. Since epidermis is metabolically inert,  $F = 1$ . For most drug compounds, total body clearance is the product of volume of distribution and total elimination rate ( $K_E$ ),  $CL_T = K_E \times V_d \dots 2$ . Thus the required flux from a transdermal patch can be calculated by normalizing the dosing rate Eqn. 1 for the surface area (A, cm<sup>2</sup>); Flux,  $J_{ss} = CL_T \times CP_{ss} / A \dots 3$ .

Here is an example to determine the feasibility of the anticonvulsant drug, primidone for 10 cm<sup>2</sup> transdermal patch, currently administered 750 mg/day as a tablet. The required flux ( $J_{ss}$ ) or input rate can be calculated from the pharmacokinetic properties of the drug, therapeutic concentration 10  $\mu\text{g/ml}$ , total body clearance and elimination half-life which was determined to be 0.78 ml/kg/min and 4 h, respectively, permeability coefficient is  $5 \times 10^{-3}$  and saturation solubility is 1 mg/ml<sup>5</sup>.

Since the drug is absorbed completely,  $F = 1$ , the required output rate of primidone can be calculated from Eqn. 3;  $CL = 0.78 \text{ ml/kg/min} \times 70 \text{ kg}$  (normal body weight) = 54.6 ml/min = 3276 ml/h. Output rate =  $(3276 \text{ ml/h} \times 10 \text{ } \mu\text{g/h}) \div 0 \text{ cm}^2 = 3276 \text{ } \mu\text{g/cm}^2/\text{h}$ . The input rate, transdermal flux in this case, is 3.3 mg/cm<sup>2</sup>/h is required from the transdermal patch of primidone. The mass of drug that can be delivered across the skin is  $M = P_{\text{estimate}} \times Cs = 5 \times 10^{-3} \times 1 = 5 \text{ } \mu\text{g/cm}^2/\text{h}$  the area of the patch required to deliver therapeutic plasma level of primidone is  $J_{ss} \div M = 3300 \text{ } \mu\text{g/h} \div 5 \text{ } \mu\text{g/cm}^2/\text{h} = 660 \text{ cm}^2$

From the above calculations, it is seen that a large area of the body viz. 600 cm<sup>2</sup> is required to deliver the therapeutic dose of primidone from the transdermal patch which is not desirable. Thus transdermal patch of 10 cm<sup>2</sup> would not be feasible for primidone. This paper makes an attempt to give information about the suitability of the drug(s) for the transdermal drug delivery systems based on their physiochemical and pharmacokinetic parameters.

## ACKNOWLEDGMENTS

We are highly thankful to Prof. B.G. Shivananda, Principal, Al-Ameen College of Pharmacy for his continuous encouragement, Indian Pharmaceutical Association for IPA-IRF scholarship, 3M India and 3M USA for their support in research work.

## REFERENCES

1. Torotora G. Principles of Anatomy and Physiology. 10th ed. New York: John Wiely and sons; 2003.
2. Chein YW. Novel Drug Delivery Systems Revised and expanded. 2nd ed. New York: Marcel Dekker Inc; 2005.
3. Panchagnula R. Transdermal delivery of drugs. *Indian J Pharmacol* 1997;29:140-56.
4. Naik A, Kalia YN, Guy RH. Transdermal: overcoming the skin's barrier function. *PSTT* 2000;3:318-26.
5. Jasti BR, Abraham W, Ghosh TK. Transdermal and Topical drug delivery systems. *In: Ghosh TK, Jasti BR, editors. Theory and Practice of Contemporary Pharmaceutics*. 1st ed. Florida: CRC Press; 2005. p. 423-53.

**AAccepted 30 January 2008**

**Revised 26 July 2007**

**Received 3 October 2006**

**Indian J. Pharm. Sci., 2008, 70 (1): 94-96**