International Journal of Medical, Medicine and Health Sciences
ISSN: 2517-9969
Vol:6, No:7, 2012

Salbutamol Sulphate-Ethylcellulose Tabletted Microcapsules: Pharmacokinetic Study using Convolution Approach

Ghulam Murtaza, Kalsoom Farzana

***Abstract*—**The aim of this article is to narrate the utility of novel simulation approach i.e. convolution method to predict blood concentration of drug utilizing dissolution data of salbutamol sulphate microparticulate formulations with different release patterns (1:1, 1:2 and 1:3, drug:polymer). Dissolution apparatus II USP 2007 and 900 ml double distilled water stirrd at 50 rpm was employed for dissolution analysis. From dissolution data, blood drug concentration was determined, and in return predicted blood drug concentration data was used to calculate the pharmacokinetic parameters i.e. C_{max}, T_{max}, and AUC. Convolution is a good biwaiver technique; however its better utility needs it application in the conditions where biorelevant dissolution media are used.

Salbutamol sulphate

***Keywords*—**Convolution, Dissolution, Pharmacokinetics,

I. Introduction

THE efficient perception of *in vitro* as well as *in vivo* activity and their mutual correlation (IVIVC) is necessary for formulation development, especially in short period of time [1]. To make a new formulation, IVIVC supports the utility of *in vitro* dissolution tests instead of the involvement of human, named as biowaiver [2]. Thus the estimation of drug concentration in blood is the useful objective of *in vitro* dissolution testing i.e. *in vitro* dissolution testing serves as a tool that surrogates the bioavailability studies, a multifarious process. It necessitates the development of suitable dissolution methods for the estimation of *in vivo* data [3]. Out of many mathematical approaches, convolution method is one of them which is very efficiently employed to extract drug concentration in blood from *in vitro* dissolution profiles [4].

Using suitable compartment model, the obtained blood drug concentration data is then analyzed to estimate various pharmacokinetic parameters like AUC (area under the blood drug concentration versus time curve), C_{max} (maximum blood drug concentration), and T_{max} (time taken by drug to reach C_{max}). These pharmacokinetic parameters can be used to calculate bioavailability of a drug product and/or bioequivalence of different drug products containing same drug. The objective of this article is to signify the methodology how to convolve the dissolution data for the estimation of pharmacokinetics. To achieve this goal, salbutamol sulphate is taken as a model drug that belongs to BCS class I. Here, the dissolution data of salbutamol sulphate in its encapsulated from is employed to derive plasma drug levels. The polymer used for microencapsulation is ethylcellulose.

Ghulam Murtaza is with the Department of Pharmaceutical Sciences, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan (phone: 92-314-2082826; fax: 92-992-383441; e-mail: gmdogar356@ gmail.com).

Kalsoom Farzana was with Department of Pharmacy, Women Institute of Learning, Abbottabad 22060, Pakistan. (e-mail: kalsoom_farzana@ hotmail.com).

II. Materials and Methods

A. Materials

Salbutamol sulphate (SS, 99.6% pure) was got as gift sample from Xenex Pharmaceuticals, Lahore, Pakistan. Ethylcellulose (EC, 26 cps, Sigma-USA) and other analytical grade chemicals were purchased through traders.

B. Microencapsulation, Tabletting and the analysis of tablets

The SS loaded EC tabletted microparticles with drug:polymer as 1:1, 1:2 and 1:3 (and the prepared tablets were named as T1, T2 and T3, respectively) were prepared by temperature change coacervation technique, followed by compression into tablets as narrated previously [5]. Each tablet contained salbutamol equivalent to 8 mg.

The prepared tablets were assessed for their physico-chemical properties and the results showed that the studied parameters for all tablets were within permitted range of USP 2007 [5,6]. In order to find out whether SS is compatible with EC or not, various compatibility analysis like FTIR, DSC and XRD were made and was observed that SS was compatible with EC and the employed microencapsulation technique exerts no adverse effect to drug [5].

The obtained microcapsules were also tested for their drug release behaviors in 900 ml double distilled water using USP II (rotating paddle) method. The pH and temperature of medium was 6.9 and 37 ± 0.5°C, respectively. The stirring speed of medium was 50 rpm. In order to find, the mode of drug release from tablets, 5 ml as dissolution samples were collected at pre-defined time points. The collected samples were then analyzed using UV spectrophotometer (1601, Shmadzu, Japan) at 276 nm without prior dilution [5,6]. After preparing suitable dilutions of stock solution, calibration curve was also made to determine drug concentration in each dissolution sample. The experimentation was repeated three times. The obtained dissolution data was tested by applying various kinetic models like zero-order equation, first-order equation, Higuchi model and Korsmeyer–Peppas cube root equation. From this kinetic analysis, it was observed that the dissolution data was best fit to the Higuchi model [5].

Based on a previous study [5], the *in vivo* evaluation of the prepared tablets was also carried out and the obtained plasma drug concentration vs. time profiles for all tablets are described in Figure 1. Using this *in vivo* data, different pharmacokinetic parameters were calculated as given in Table 1.

C. Convolution approach

The novel part of this article is the application of convolution model to the dissolution data to directly estimate the blood drug concentration. In this context, equation-1 was derived from the numerical method and then applied to the dissolution data.

TABLE I
PHARMACOKINETIC PARAMETERS FOR ALL TABLETS OBTAINED FROM IN VIVO EXPERIMENTS AND CONVOLUTION METHOD

Parameters	Approach	Ventolin® 8 mg	T1	T2	T3
t_{max} (h)	*In vivo*	3 ± 0.20	3 ± 0.17	3 ± 0.27	3 ± 0.12
	Convolution	8 ± 0.23	7 ± 0.18	8 ± 0.16	8 ± 0.25
C_{max} (ng/ml)	*In vivo*	35.74 ± 1.03	36.06 ± 1.83	33.63 ± 0.93	28.43 ± 1.32
	Convolution	8.09 ± 3.27	7.47 ± 5.01	7.84 ± 6.37	6.77 ± 3.58
$AUC_{0-\infty}$ (ng.h/ml)	*In vivo*	215.69 ± 5.72	210.70 ± 6.83	208.75 ± 7.93	238.71 ± 8.36
	Convolution	104.23 ± 4.14	108.05 ± 6.37	104.53 ± 4.57	80.47 ± 5.94

$$C(t) = \int_0^t C_\delta\,(t-u)X'_{vitro}(u)du \qquad (1)$$

Single entity inclination retort (C_δ) and contributing rate of *in vitro* (X'_{vitro}) dissolution process for the studied drug products are successfully used parameters for determining the concentration of drug in blood c(t) through convolution approach. In equation 1, C_δ is characteristically established from the data obtained after the administration of single large intravenous dose of drug. The functions *c(t)*, X'_{vitro} and *u* indicate the blood drug level vs. time of the designed formulations, drug administration rate via oral route and variable of assimilation, correspondingly [1]. In addition, the prediction error of this new predicting approach was also determined using below given equation:

$$Prediction\ error\ (\%)_{C_{max}} = \frac{C_{max_{Observed}} - C_{max_{Predicted}}}{C_{max_{Observed}}} \times 100 \qquad (2)$$

D.Statistical Analysis

The obtained data was narrated as average ± SD. One way analysis of variance was applied to elaborate the significance of difference employing a most commonly used software, SPSS version 15.0. The significance echelon was located at 0.05.

III. Results And Discussion

The pharmacokinetic study is tremendously erratic effort as enormous physiological variables possess tremendous capability to influence the *in vivo* dissolution testing and the absorption profiles. On the contrary, *in vitro* outcomes do not exhibit such type of unevenness, as the *in vitro* drug dissolution testing is in general conducted under virtually constant environment [1]. Convolution formula has been narrated in this article with its application on an experimental data performed in our laboratory. It involves the direct prediction of blood drug concentration from the *in vitro* dissolution profiles [4].

As described in the "experimental", three different drug products (T1, T2 and T3) with different release behavior were produced, and then the dissolution testing was performed for these formulations with an aim to estimate the blood drug levels release in human. Then PKSolver software (menu-driven program using Microsoft Excel used for the calculation of pharmacokinetics) was used for the evaluation of pharmacokinetics utilizing the predicted *in vivo* data. In this context, three pharmacokinetic parameters i.e. C_{max}, AUC and T_{max}, as given in Table 1, were determined. The experimentally observed *in vitro* drug dissolution profiles and subsequently estimated blood drug concentrations of all developed formulations (T1, T2 and T3) as well as control tablets (Ventolin® 8 mg SR) are explained in the Figure 1.

In addition, the percentage prediction error was also greater than 10 which elaborates that there are some variables which affect the data obtained from *in vivo* source. Those variables are unquestionably gastrointestinal environment including pH, enzymes, peristalsis etc.

It is evident from the results, as given in Table 1, that the pharmacokinetics of all drug products obtained via convolution application was found significantly ($p<0.05$) unlike from the *in vivo* experimental data. This difference in the obtained data shows unlikeliness between the employed drug dissolution data and the tangible physiological environment of gastrointestinal tract. This situation necessitates the use of biorelevant dissolution media for *in vitro* dissolution studies so that this test may represent the normal physiological conditions, and ultimately the percentage prediction error will also be low.

The predicted pharmacokinetic parameters however, showed same trend of results as found in experimental results. The results show the higher value of C_{max} as well as lower value of AUC compared to that of T3. This trend in results exhibit the use of higher concentration of polymer in T3 compared to T1 which is also supported by the previous results [5].

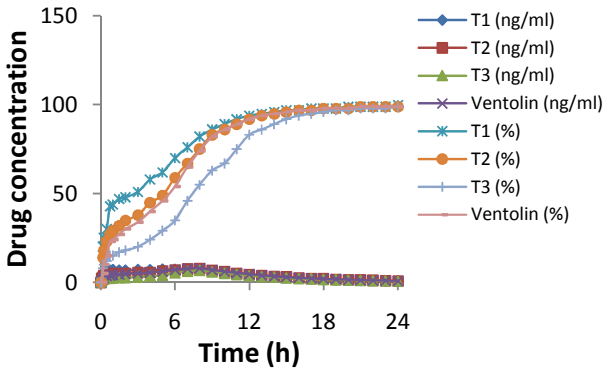

Fig. 1 Predicted plasma drug concentration and dissolution profiles

IV. Conclusion

Convolution is a good biwaiver technique; however its better utility needs it application in the conditions where biorelevant dissolution media are used.

Acknowledgment

Authors thank the Islamia University of Bahawalpur, Pakistan for the provision of facilities to conduct research.

REFERENCES

[1] J. Emami, "*In vitro - in vivo* correlation: from theory to applications", *J. Pharm. Pharm. Sci.*, vol. 9, no. 34, pp. 169-89, April 2006.
[2] S. A. Qureshi, "Choice of rotation speed (rpm) for biorelevant drug dissolution testing using a crescent-shaped spindle", *Eur. J. Pharm. Sci.*, vol. 23, no. 65, pp. 271–275, Aug. 2004.
[3] M. C. Meyer, A. B. Straughn, R. M. Mhatre, V. P. Shah, R. L., Williams, and L. J. Lesko, "Lack of *in vivo*/*in vitro* correlations for 50 mg and 250 mg primidone tablets", Pharm. Res., vol. 15, no. 19, pp. 1085-1089, July 1998.
[4] S. Riegelman, and P. Collier, "The application of statistical moment theory to the evaluation of *in vivo* dissolution time an absorption time", J. Pharm. Biopharm., vol. 8, no. 5, pp. 509-534, Sep. 1980.
[5] G. Murtaza, M. Ahmad, and N. Akhtar, "Biowaiver study of oral tabletted ethylcellulose microcapsules of a BCS class I drug", *Bull. Chem. Soc. Ethiop*. Vol. 23, no. 2, pp. 175-186, Feb. 2009.
[6] USP 2007. The United States Pharmacopoeial Convention, Inc., Rockville, MD, p. 323.