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SALBUTAMOL DELIVERING TRANSDERMAL DOSAGE FORM BASED ON OSMO-REGULATORY PRINCIPLE.

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ABSTRACT

A transdermal drug delivery system of Salbutamol was developed which released the drug following zero order kinetics. The designed system essentially based on trilaminated matrix concept. The delivery of drug from the system affected by osmotic phenomenon where sodium chloride was used as an osmogent. To establish the desired release rate polyethylene glycol 4000 (PEG 4000) was used as channelising agent in rate controlling membrance of cellulose acetate. The designed systems exhibiting zero-order release rate, were studied for the in-vitro skin permeation. The product which was having skin permeability rate 115 mcg/hr/cm^2 was selected for the in-vivo evaluation. The forced expiratory volume (FEV_1) and drug plasma concentration were monitored periodically. The study revealed that designed osmo-regulatory transdermal drug delivery system of Salbutamol could be used successfully with improved therapeutic response and holds promise for the clinical studies.

INTRODUCTION

Controlled release delivery system offers number of distinct advantages in therapeutics, one being the potential of designing delivery system that releases therapeutic agent at defined rate. This ability to control the rate of drug delivery minimises undesirable side effects(1). In recent years, the major advances in pharmaceuticals has been the successful development of transdermal therapeutic systems. The controlled release transdermal therapeutic system of Nitroglycerine[1-3], Scopolamine[4], Clonidine[5], and Estradiol[6] are available in market.

Present work is aimed for the development of a controlled release transdermal drug delivery system of salbutamol, based on osmo-regulatory principle. The long acting formulation of salbutamol are demanded for the treatment of all type of reversible airways obstruction as a back ground to inhalation therapy (2). A new controlled release device based on osmo-regulatory principle for oral administration of salbutamol has been discussed that provides a linear release of drug (3).

Salbutamol is reported to be metabolized by hepatic pass effect in the liver, and as a result, about half of the administered dose is recovered in the urine as an inactive sulphate metabolite (4). Considering the pharmacokinetic parameters, the need of transdermal delivery of salbutamol was realised. The osmo-regulatory controlled transdermal drug delivery system of salbutamol was designed and developed to release the drug at a defined and controlled rate over an extended period for 24 hours. The designed system was evaluated for *in vitro* drug release and permeation across the freshly excised hairless mouse skin and finally tested for its *in vivo* performance.

EXPERIMENTAL

A. Materials

Salbutamol (Ranbaxy Laboratories, Delhi, India); Cellulose acetate, Polyethylene glycol 4000, and Glycerine (Loba Chemie

Indoaustranol Co., Bombay, India); Polystyrene, M.W. 3,21,000, (Aldrich Chemical Co. Wisconsin, USA); Dibutyl phthalate (Sigma Chemical Company St. Louis, USA); other chemicals and reagents, sodium chloride, chloroform, methanol were used as obtained.

B. Drug Permeability

The drug permeability through excised hairless mouse skin was determined by placing an aqueous solution of salbutamol (5ml of 0.4 mg/ml) into the donar compartment of franz diffusion cell (supplied by Crown Glass Co. N.J., USA). The contents of donar and receptor compartment was separated by placing freshly excised hairless mouse skin in between the two compartments. The skin was mounted in such a way that stratum corneum side of the skin continuously bathed with the content of the donar compartment. The receptor compartment contained isotonic phosphate buffer of pH 7.4 (5). The sink condition was maintained by using 20% PEG 400 in the receptor compartment and the temperature of the receptor compartment at $37\pm1^{o}C$ with the use of a circulating water bath. The donar compartment was exposed to the ambient temperature.

Samples (1.0 ml) were withdrawn periodically for 14 hours and assayed for drug content spectrophotometrically using the method reported by Shigbal and Joshi (6).

C. Dose Designing

On the basis of pharmacokinetic parameters, the drug delivery rate through skin required to achieve an effective plasma concentration was calculated to be 109.42 mcg/hr (7).

D. Drug Reservoir Preparation

The designed transdermal drug delivery system was consisted of the following layers : (a) Backing membrane; (b) drug matrix; (c) rate controlling membrane. These membranes were prepared using the method described by Iyer and Vasavada using mercury substrate (8).

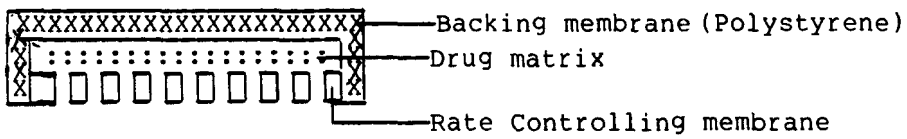

Figure 1. Designed osmo-regulatory transdermal drug delivery system.

a. Backing membrane : It was prepared using 10% w/w solution of polystyrene in chloroform and 10% w/w dibutyl phthalate (based on total polymer weight).

b. Drug matrix : On dried film of polystyrene, a 2% w/w solution of drug in methanol containing 10% w/w glycerine and 0.1% w/w sodium chloride was poured and dried at 30°C for 48 hrs.

c. Rate controlling membrane : The rate controlling membrane was casted on drug matrix using 5 ml solution of polymer containing different combinations of cellulose acetate and polyethylene glycol 4000 (PEG 4000) and 15% w/w glycerine as plasticizer. The rate controlling membrane was dried at 30°C for 48 hours.

The complete dried system was finally removed from the stainless steel ring and stored at < RH 30°. The designed system is diagramatically shown in Fig. 1 and the compositions of different transdermal preparations are shown in Table 1.

E. **In vitro** Drug Release.

In vitro drug release from different drug reservoirs was determined using Franz diffusion cell. The procedure was same as outlined above for drug skin permeation studies except that no skin sample was sandwitched between transdermal patch and receptor compartment solution. In this study, the receptor solution was completely withdrawn andreplaced with fresh isotonic phosphate buffer of pH 7.4 at each scheduled sampling time. The salbutamol

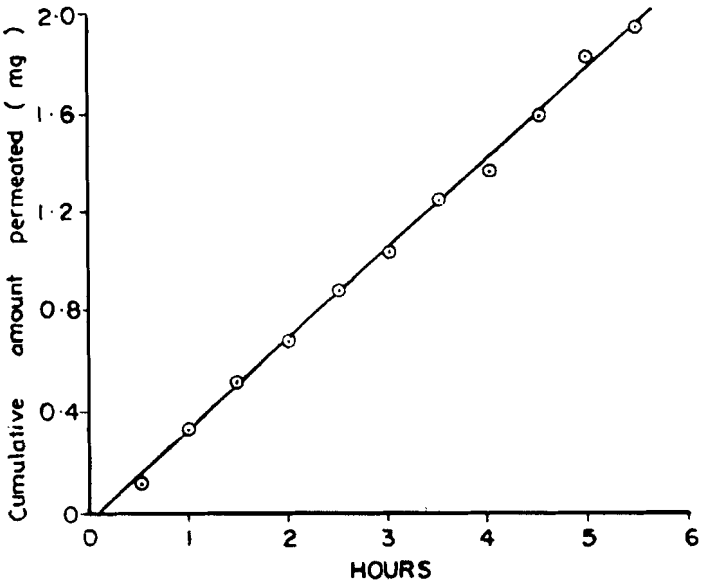

Figure 2 : Drug skin permeation profile of Salbutamol through excise hairless mouse skin.

In vivo studies were performed on twelve human subjects (Asthmatic patients), divided into two groups of six each. Subjects of one group were given 4 mg salbutamol conventional tablet (Asthaline^{R}, Cipla Laboratories, India) orally at six hours interval. To the subjects of second group, transdermal patch was applied topically at the mastoid prominence area (near intra-auricular region). Following the application of transdermal patch and oral administration of salbutamol conventional tablet, the forced expiratory volume (FEV_1) was measured periodically for 28 hours in a manner described by Walker and coworkers (9). Simultaneously, the blood samples were withdrawn and analysed for salbutamol content by high performance liquid chromatography method described by Hutchings and coworkers (10), using Shimadzu model LC-3A high performance liquid chromatograph equipped with a fluorescence spectromonitor (Shimadzu model RF 530).

TABLE I.

Composition of Drug Reservoir Patch (TDD Patch)

Layer	Polymer(s)	Per cent concentration				
		A	B	C	D	E
a. Rate Controlling membrane	Cellulose Acetate	98	96	94	92	90
	PEG 4000	02	04	06	08	10
	Glycerine	15% w/w based on total matrix wt.				
b. Drug matrix	Salbutamol	2% w/w based on total matrix wt. with 0.1% sodium chloride and 10% w/w Glycerine.				
c. Backing membrane	Polystyrene	10% w/w based on total matrix wt. with 10% w/w dibutyl phthalate.				

concentration in the samples was assayed by spectrophotometric method (6).

F. **In vitro** Skin Permeation

In vitro drug permeation through excised hairless mouse skin from transdermal patch was studied using franz diffusion cell. A transdermal patch (drug reservoir patch, 1 cm^2) was placed in intimate contact with the skin mounted on a franz diffusion cell apparatus. The same procedure as described for drug skin permeation studies was adopted.

One ml solution was withdrawn from the receptor cell at a regular time interval for 28 hours and assayed for salbutamol content (6).

G. **In vivo** Performance

On the basis of the in vitro skin permeation studies, the formulation releasing the drug at desired rate (109.42 mcg/hr) was selected for in vivo evaluations.

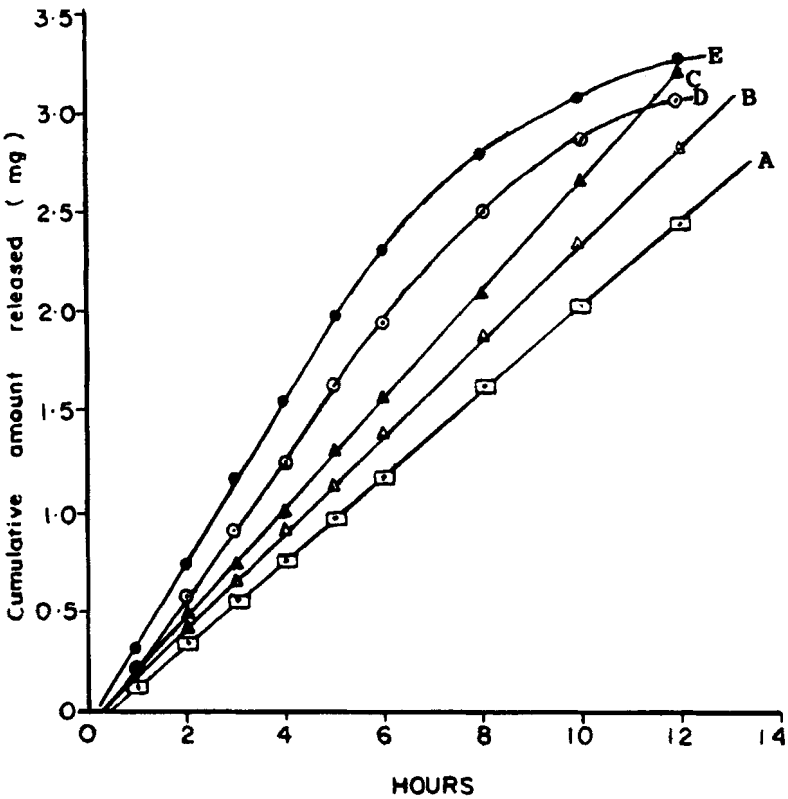

Figure 3 : In vitro drug release profile of Salbutamol from drug reservoir patches.

RESULT AND DISCUSSION

The drug permeability through excised hairless mouse skin determined to be 4.0×10^{-4} gm/hr/cm^2 was indicative of good permeant nature of the drug across the skin (Fig. 2).

Different drug reservoirs were prepared which consisted of backing membrane, drug matrix and rate controlling membrane. The rate controlling membranes of different combinations of cellulose acetate and PEG 4000 were prepared. These drug reservoirs (transdermal patches) were studied for their in vitro drug release. Figure 3 shows that the salbutamol released from these drug reser-

TABLE - II

Release rate and Permeability rate constant of different products.

PRODUCT	Release rate constant mcg/hr/cm^2	Permeability rate constant mcg/hr/cm^2
A	212.5	85
B	237.5	95
C	275.0	115
D	337.5	--
E	412.5	--

voir patches at a constant rate approximating a zero-order kinetics. It was also observed, that on increasing the concentration of PEG 4000 from 2 to 10 per cent in the total polymer matrix, the release rate of the drug increased from 212.5 to 412.5 mcg/hr/cm^2. (Table II).

Additionally, it was also observed that as the concentration of PEG 4000 increases above 6% w/w, the release pattern deviate from zero-order kinetics. The zero-order release upto 6% PEG 4000 concentration could be ascribed to the osmo-regulatory release of drug from such system(s). PEG 4000 forms channels in the rate controlling membrane when it comes in contact with the content of receptor cell, whilst above 6% w/w PEG 4000 concentration, it could be hydrated to impart a gel like diffusion barrier to the drug matrix. Below 6% w/w PEG 4000 concentration could have dissolved in the fluid of receptor cell to form channels and the incorporated osmogent (sodium chloride) in the drug matrix facilitated the drug release through these channels.

The product A to C were selected for *in vitro* skin permeation studies as the drug release from these products follows zero-order

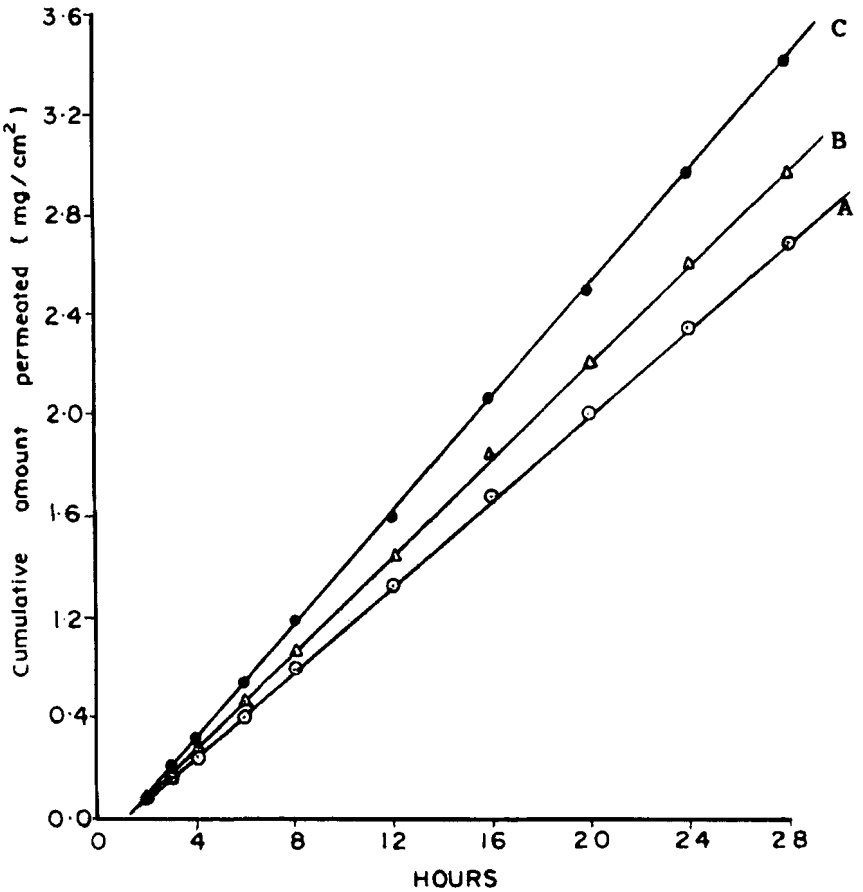

Figure 4 : In vitro drug permeation profile through excised hairless mouse skin of salbutamol from Drug reservoir patches.

kinetics. Fig. 4 indicates that salbutamol penetrated through the excised abdominal skin of the hairless mouse at a rate that follows zero-order kinetics. The skin permeation rate constant was calculated to be 85,95 & 115 mcg/hr/cm^2 for product A, B & C respectively. (Table II).

On the basis of in vitro skin permeation studies, the product C was selected for in vivo studies as its permeability rate

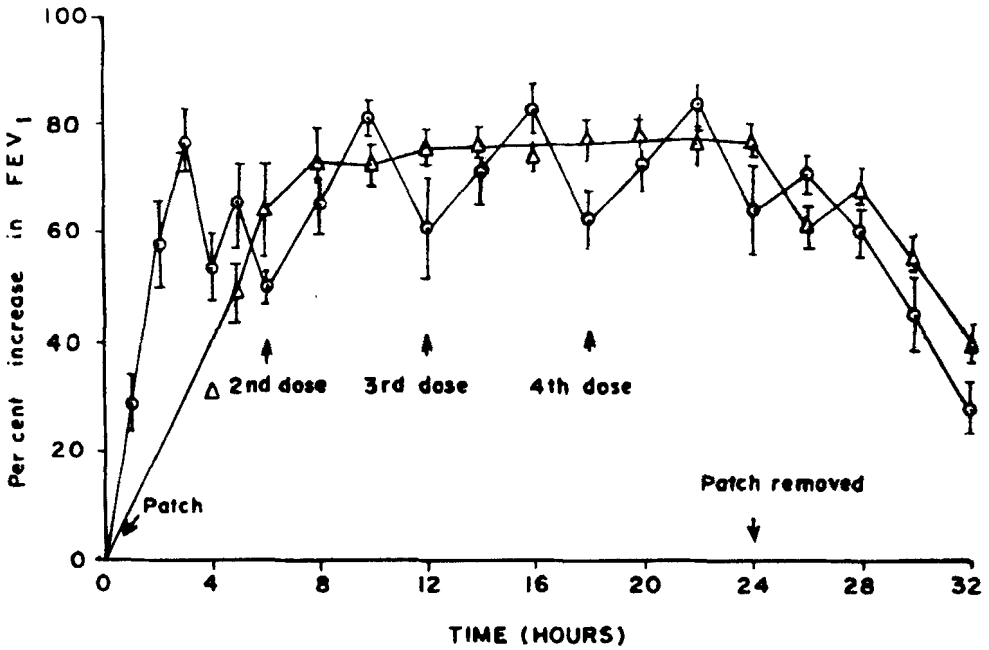

Figure 5 : Percent increase in FEV_1 vs time plot following oral administration of conventional tablet and TDD patch application. O-O : Oral administration; Δ—Δ : TDD patch.

constant (115 mcg/hr/cm^2) is close to the required permeation rate (i.e. 109.42 mcg/hr/cm^2) to achieve the effective drug plasma concentration. The in vivo performance of the transdermal product was compared with orally administered conventional tablet, Asthaline^R (Cipla Laboratories, India). The drug plasma levels as well as forced expiratory volume (FEV_1) were measured in asthmatic patients. Following oral dose of 4 mg of salbutamol to six patients, the peak plasma level 12.34 ng/ml was recorded within three hours after the administration whilst, in the case of transdermal application the peak plasma concentration (10.64 ng/ml) reached within six hours which however, remained constant for 24 hours (Fig. 5).

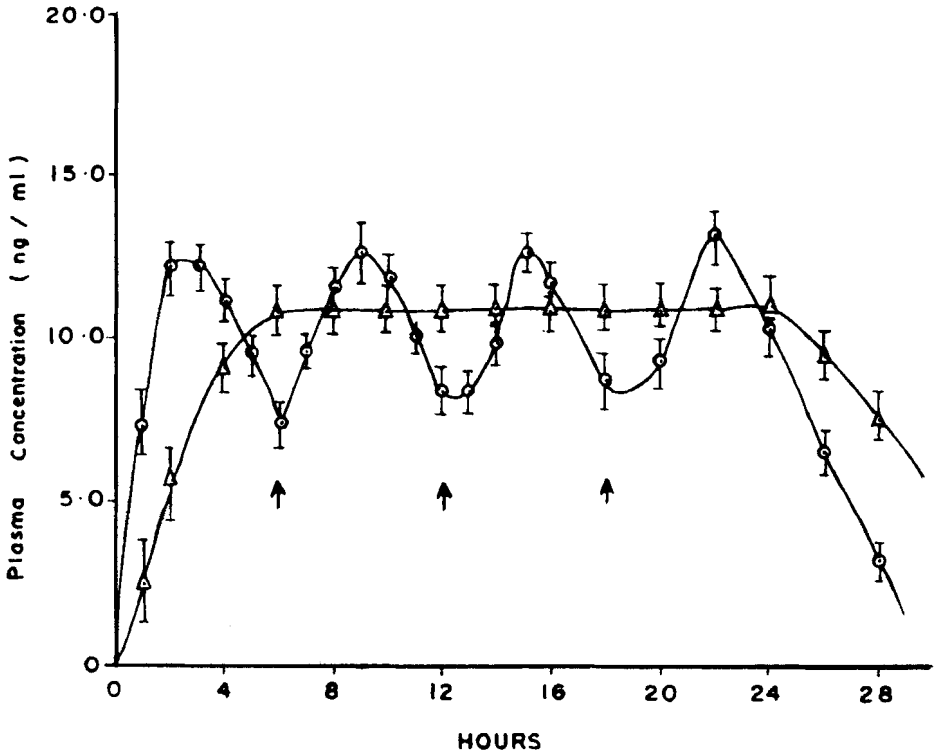

Figure 6 : Drug plasma profile of Salbutamol following oral administration of conventional tablet and TDD patch application. O-O : Oral administration; Δ—Δ : TDD patch.

Similarly, the maximum increased in FEV_1, 66 to 78 per cent over resting FEV_1 in all the subjects was recorded (Fig. 6). The maximum increase in FEV_1 were noted at 3-4 hours after oral dose. The recorded response could be correlated with the peak plasma drug concentration (9). A decrease in FEV_1 between 4 to 6 hours followed by an increase on second dose administration was noted. In case of transdermal drug delivery patch, the maximum increase in FEV_1 was observed to be 78 ± 10 per cent, which was maximum at 8 hours and remained approximately constant over a period of 24 hours. The FEV_1 decreased gradually on removal of the patch,

while the plasma concentration dropped rapidly. This could be attributed to the controlled release of the drug from the drug reservoir patch and constant skin permeation throughout the period of its application, which could have maintained the steady level of the salbutamol in the blood.

CONCLUSION

Salbutamol can successfully be administered via dermal route. The designed osmo-regulatory transdermal device, delivered the drug following zero-order kinetics. The blood salbutamol level thus, could have maintained a constant level as reflected in FEV_1 measurements, which remained almost constant for 24 hours. The performance is indicative of satisfactory pharmacological action of the drug for a prolonged time and better than conventional multiple oral dose which produced trough and peak in drug plasma levels particularly between the two doses. Thus salbutamol possesses potentiality for transdermal application and holds promise for clinical studies which are under progress.

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FOOTNOTE

1. Nitro-Dur® is the trademark for nitroglycerine, Key Pharm.Inc.
2. Nitro-disc® is the trademark for nitroglycerine, Searle Pharm. Lab.

3. Transderm-Nitro[R] is the trademark for nitroglycerine, CIBA Pharm.Co.
4. Transderm-Scop[R] is the trademark for scopolamine, CIBA Pharm.Co.
5. Catapres[R] is the trademark for clonidine, Boehringer Ingethsin, Ltd.
6. Estraderm[R] is the trademark for estradiol, CIBA Pharm. Co.

REFERENCES

1. J.E. Shaw and S.K. Chandrasekaran, Controlled topical delivery of drugs for systemic action, **Drug Metab.Rev., 8,** 223 (1978).
2. L.S. Alfredsan and S.E. Norell, Spacing between doses in a thrice daily regimen. **Br. Med. J., 282,** 1036 (1981).
3. P. DeHaan and C.L. Lerk, Oral controlled release dosage forms: A review, **Pharmacol. Week bl. (Sci. Ed.), 6,** 57 (1984).
4. D.A. Goldstein, Y.K. Tan and S.J. Soldin, Pharmacokinetics and absolute bioavailability of salbutamol in healthy adult volunteers, **Eur. J. Clin. Pharmacol., 36,** 631 (1987).
5. British Pharmacopoeia, vol.II, Ministry of Health and Social Sciences for Northern Ireland, 1980, p. A-53.
6. D.M. Shigbal and S.V. Joshi, Spectrocolorimetric Estimation of salbutamol sulphate and its pharmaceutical formulations **Indian Drugs, 21,** 398 (1984).
7. D.R. Sanvordekar, J.G. Cooney and R.C. Wester, Transdermal nitroglycerine pad. U.S. Patent No.4, 336, 243, June 22, 1982.
8. B.V. Iyer and R.C. Vasavada, Evaluation of lanolin alcohol film and kinetics of triancinolone acetomide release, **J. Pharm. Sci., 68,** 783 (1979).
9. S.R. Walker, M.E. Evans, A.J. Richardson and J.W. Paterson. The clinical pharmacology of oral and inhaled salbutamol. **Clin. Pharmacol. Therp., 13,** 861 (1972).
10. M.J. Hutchings, J.D. Pault and D.J. Morgan, Determination of salbutamol in plasma by high performance liquid chromatography with fluorescence detection. **J. Chromatogr., 277,** 423 (1983).