DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(3), 375-386 (1994)

IN-VITRO RELEASE KINETICS OF SALBUTAMOLSULPHATE MICROCAPSULES COATED WITH BOTH EUDRAGIT RS 100 AND EUDRAGIT RL 100

R. S. Bhanja, T.K. Pal

Pharmaecutical Engineering Division
Department of Pharmaceutical Technology
Jadavpur University
Calcutta - 700032, India.

ABSTRACT

Sabutamolsulphate, a bronchodialatory drug for Asthma is encapsulated by Eudragit RS 100 and Eudragit RL 100 of varying ratios (1:1, 3:1, 1:3) using Emulsion-Solvent-Evaporation method. The experimental data obtained from the in-vitro dissolution study have been computed in the light of different kinetic models like Zero Ordr, Higuchi Matrix, First Order, Baker-Lonsdale. An extensive programming in BASIC is performed to determine the co-relation coefficient and slope for each of the functions. The diffusivity rate constant (K_{BL}) and diffusion coefficient (Da) have been evaluated with the help of Baker-Lonsdale Model.

INTRODUCTION

Microencapsulation of drugs as well as their diffusional release kinetics have been extensively reported by various authors (1,2,3,4). But limited information is available on computer simulation release kinetics data. The prime objective of this paper is to compute the drug release data, obtained from the in-vitro dissolution studies, in the light of different kinetic models according to the to the method described by Bhaja et. al (5).

An extensive programming in BASIC(6) is performed to compute the release data obtined from the dissolution studies of different microcapsules coated with varying Eudragit RS 100 and Eudragit RL 10 ratios (1:1, 3:1, 1:3) to fit the order of the equations (Zero Order Mt=f(t); First Order log (Mo-Mt)=f(t); Higuchi Matrix Mt=f($\sqrt{t}$) and Baker Lonsdale $\frac{3}{2}[1-(1-\frac{Mt}{M\alpha})^{2/3}] - \frac{Mt}{M\alpha} = f(t)$ where Mt is the amount of drug release at time t, $M\alpha$ is the amount of drug release at infinite time (α) and Mo is the initial amount of drug in the microcapsules. The co-relation coefficient analysis for linear relationship of the above equations have been determined with the help of computer program(6). The diffusion coefficient (Da) and diffusivity rate constant (K_{BL}) have been evaluated with the help of Baker-Lonsdale Model when the Matrix mechanism of release predominates over Zero Order and First Order having better co-relation coefficient for linearity.

MATERIALS AND METHODS

Salbutamolsulphate (Donated by CIPLA, India Ltd). Eudragit RS 100 Eudragit RL 100 (Donated by Rohm Pharma, Germany). All other chemicals are of analytical grade produced in India by different companies. Computer, WIPRO PC-XT (Wipro, India Ltd).

Preparation of Microcapsules

Microcapsules were prepared by solvent evaporation method using 800 ml Heavy-Liquid-Paraffin as external phase with 4 ml of Span 20 as emulsifier 1 gram of Eudragit RS 100 and 1 gm of Eudragit RL 100 was dissolved in 5 ml of methylene chloride and 0.175 gm of Aluminiumtristearate was added to it and 0.5 gm of salbutamolsulphate was dispered in the polymeric solution. Then the drug-polymer dispersion was added drop by drop into external phase and stirred at 200 RPM. The temperature of the mix ture was raised to 35°C and kept constant for 3 hours. Then the microcapsules produced were filtered off from the external phase and washed with normal hexane. Then dried and separated into size fractions using standard sieves.

The micromeritic properties of the microcapsules such as density porosity average particle size were determined and tabulated in the Table-1.

In-vitro Release Rate Study

The dissolutions of the microcapsules were carried out at medium of pH 1.2 and pH 7.2 by modified flask

TABLE I

MICROMERETIC PROPERTIES OF THE MICROCAPSULES.

Varying Eudragit RS 100 and Eudragit RL 100 ratio.

Sieve fraction	1:1			3:1			1:3		
	Size um	Density gm/cc	Porosity %	Size um	Density gm/cc	Porosity %	Size um.	Density gm/cc	Porosity %
+22	845	0.9748	23.0010	850	1.0012	23.0045	855	1.0528	24.0162
-22+44	395	1.1249	13.0168	400	1.1145	8.9845	390	1.1256	16.0215
-44+85	135	1.1387	7.9842	135	1.1204	7.0295	130	1.1472	9.2254

method (7) and the drug release was estimated by using the method of Singbal et. al (8). The data obtained from the in-vitro dissolution studies were computed in the light of different kinetic models. The slope and co-relation coefficient of ech of the funetional equations were obtained from the computer out put and are tabulated in Tables 2, 3, and 4.

The diffusion coefficient and diffusivity rate constant were evaluated upto 50% of the drug release with the help of Baker-Lonsdale Model and tabulated in Tables 5 and 6.

RESULTS AND DISSCUSSION

It is evident from the in-vitro dissoltuon profiles that the release of the drug increases as the size of the microcapsules decreases. The release of drug increases as the amount of Eudragit RL 100 increases in the polymeric coating material for both the pH-values 1.2 and 7.2. This is due to the fact that Eudragit RL 100 which contains more cataionic centres than Eudragit RS 100 gives the microcapsules membrane a more open structure (9). More over Eudgragit RL 100 is strongly hydrophilic which promotes the penetration of the aqueous buffers and hence good leaching of the drug so due to strong permeability and greater porosity of Eudragit RL 100 the release of the drug increases as the amount of Eudragit RL 100 increases in the polymeric coating materials. The release of the drug for a particular size of the microcapsules is more controlled and sustained at pH 7.2 than pH 1.2. This is due to the

TABLE 2

CORELATION COEFFICIENT AND SLOPE OF KINETIC EQUATIONS UPTO 50% OF DRUG RELEASE.

	EUDRAGIT RS 100AND EUDRAGIT RL-100 RATIO 1 : 1							
Sieve fraction	Zero Order	Higuchi Matrix	First Order	Baker Lonsdale	Zero order	Higuchi Matrix	First Order	Baker Lonsdale
	p^H 1,2					pH 7.2		
+22	0.9904	0.9996	0.9967	0.9980	0.9727	0.9949	0.9873	0.9979
	(0.3236)*	(1.5090)	(0.0499)	(0.9942)	(0.1430)	(1.0252)	(0.0337)	(0.0020)
-22+44	0.9242	0.9711	0.9445	0.9761	0.9862	0.9958	0.9937	0.9924
	(0.1734)	(1.0958)	(0.0250)	(0.0023)	(0.1841)	(1.1181)	(0.0253)	(0.0017)
-44+85	0.9930	1.0000	0.9983	0.9998	0.9519	0.9819	0.9643	0.9797
	(0.3061)	(1.4244)	(0.0525)	(0.0056)	(0.1487)	(0.9923)	(0.0243)	(0.0023)

* Slope

TABLE 3

CORELATION COEFFICIENT AND SLOPE OF KINETIC EQUATIONS UPTO 50% OF DRUG RELEASE

	EUDRAGIT RS 100 AND EUDRAGIT RL-100 RATIO 3 : 1							
Sieve fraction	Zero Order	Higuchi Matrix	First Order	Baker Lonsdale	Zero Order	Higuchi Matrix	First Order	Baker Lonsdale
	pH 1.2				pH 7.2			
+22	0.9671	0.9946	0.9787	0.9913	0.9857	0.9976	0.9937	0.9955
	(0.1099)*	(0.6797)	(0.0183)	(0.0019)	(0.0500)	(0.5073)	(0.0075)	(0.0006)
-22+44	0.9908	0.9996	0.9949	0.9984	0.9289	0.9747	0.9439	0.9701
	(0.1725)	(0.8044)	(0.0298)	(0.0033)	(0.0677)	(0.4984)	(0.0102)	(0.0009)
-44+85	0.9903	0.9995	0.9946	0.9982	0.9702	0.9908	0.9850	0.9991
	(0.1717)	(0.8010)	(0.0306)	(0.0034)	(0.3811)	(0.7984)	(0.0612)	(0.0058)

* Slope

TABLE 4

CORELATION COEFICIENT AND SLOPE OF KINETIC EQUATIONS UPTO 40% OF DRUG RELEASE

	EUDRAGIT RS 100 AND EUDRAGIT RL - 100 RATIO 1 : 3							
Sieve fraction	Zero Order	Higuchi Matrix	First Order	Baker Lonsdale	Zero Order	Higuchi Matrix	First Order	Baker Lonsdale
	pH 1.2				pH 7.2			
+22	0.9671 (0.1099)*	0.9946 (0.6796)	0.9779 (0.0168)	0.9910 (0.0018)	0.9837 (0.0840)	0.9979 (0.6694)	0.9926 (0.0118)	0.9950 (0.0011)
-22+44	0.9496 (0.2436)	0.9708 (0.1564)	0.9619 (0.0383)	0.9782 (0.0039)	0.9838 (0.0840)	0.9979 (0.6695)	0.9926 (0.0123)	0.9950 (0.0011)
-44+85	0.9609 (0.1230)	0.9853 (0.5829)	0.9675 (0.0219)	0.9737 (0.0027)	0.9856 (0.2915)	0.9981 (1.3643)	0.9936 (0.0484)	0.9994 (0.0054)

* Slope.

TABLE - 5

DIFFUSION COEFFICIENT AND DIFFUSIVITY RATE CONSTANT OF SALBUTAMOL SULPHATE FROM MICROCAPSULES AT pH 1.2

Varying Eudragit RS 100 & Eudragit RL 100 Ratio						
Sieve fraction	Eudragit RS 100 : Eudragit RL 100 1:1		Eudragit RS 100 : Eudragit RL 100 3:1		Eudragit RS 100 : Eudragit RL 100 1:3	
	$D_a \times 10^9$	$K_{BL} \times 10^4$	$D_a \times 10^9$	$K_{BL} \times 10^4$	$D_a \times 10^9$	$K_{BL} \times 10^4$
	$cm^2\ Sec^{-1}$	Min^{-1}	$cm^2\ Sec^{-1}$	Min^{-1}	$cm^2\ Sec^{-1}$	Min^{-1}
+ 22	22.1078	42	10.8241	19	11.2240	18
- 22 + 44	3.2308	23	4.6329	33	5.1345	39
- 44 + 85	0.9211	56	0.5366	34	0.4240	47

TABLE - 6

DIFFUSION COEFFICIENT AND DIFFUSIVITY RATE CONSTANT OF SALBUTAMOL SULPHATE FROM MICROCAPSULES AT pH 7.2

	Varying Eudragit RS 100 & Rudragit RL 100 Ratio					
Sieve fraction	Eudragit RS 100 : Eudragit RL 100 1 : 1		Eudragit RS 100 : Eudragit RL 100 3 : 1		Eudragit RS 100 : Eudragit RL 100 1 : 3	
	$D_a \times 10^9$	$K_{BL} \times 10^4$	$D_a \times 10^9$	$K_{BL} \times 10^4$	$D_a \times 10^9$	$K_{BL} \times 10^4$
	$cm^2\ Sec^{-1}$	Min^{-1}	$cm^2\ Sec^{-1}$	Min^{-1}	$cm^2\ Sec^{-1}$	Min^{-1}
+ 22	16.8347	20	5.4662	6	10.9684	11
- 22 + 44	3.9172	17	2.0020	9	2.3158	11
- 44 + 85	0.6049	23	1.4624	58	1.3563	54

fact that salbutamilsulphate which is a salt of weak base, the solubility of the drug decreases as the pH of the medium increases (10), but the stability of the drug decreases with increase of the pH of the medium.

It is observed from the in-vitro release kinetic study that the Higuchi-Matrix mechanism predominates over First Order and Zero Order mechasnism having better co-relation coefficient for linearity upto fifty percent of drug release.

It is evident from the diffusional studies, with the help of Baker-Lonsdale model, the diffusion coefficient has a trend of increasing as the size of the microcapsules increases, while the diffusivity rate constant (K_{BL}) increases as the size of the microcapsule decreases. These results are in good agreement with Vidmar et. al (11).

ACKNOWLEDGEMENT

The authors are grateful to Indian Council of Medical Research (New Delhi, India) for their financial support to carry on this research work.

REFERENCES

1. S. Benita. H. Hoffman, M.J. Donbrow, J. Microencapsulation, 2, 207, (1985).
2. V. Vidmar, I. Jalsenjak, Acta Pharmaceutica Technologica, 28, 78, (1982).
3. R.G. Gupta, B.C. Rao, Drug Dev & Indus Pharm, 11, 41, (1985).

4. H.P. Merkle, S. Speiser, J. Pharm. Sci., 82, 1444, (1985).

5. R.S. Bhanja, T.K. Pal, Bulletino Chemico Farmaceutico, 128, 281, (1989).

6. R.S. Bhanja, A. Nandy, T. Roychowdhury, T.K. Pal, Indian J. Pharm. Sci, 52 233, (1990).

7. P. L. Madan, R.K. Jani, A.J. Barticuer, J. Pharm Sci, 67, 409, (1978).

8. D.N. Shingbal, R.R. Naik, Indian Drugs, 25, 273, (1985).

9. R. S. Okor, Int. J. Pharm, 11, 1, (1982).

10. N. Udupa, S.V. Tatwadi, K.D. Gode, Indian Drugs, 23, 221, (1986).

11. V. Vidmar, I. Jalsenk, T. Kondo, J. Pharm. Pharmacol, 34, 411, (1982).