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Preparation and *in vitro* Evaluation of Indomethacin Microspheres Prepared with Eudragit RS 100 and Eudragit RL 100 by Solvent Evaporation Method

RABINDRA N. PAL*, MANAS CHAKRABORTY, BIJAN K. GUPTA†,
RABINDRA DEBNATH, ABHIJIT MAITY and RANA MAZUMDER
Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology and Allied Health Sciences, Howrah-711 316, India
E-mail: pal.rabindranath@gmail.com

The aim of the study is to prepare and evaluate Eudragit micro spheres containing indomethacin. Micro spheres were prepared by solvent evaporation method using acetone/liquid paraffin system. The influence of formulation factors (stirring speed, polymer: drug ratio, type of polymers, ratio of the combination of polymers) on particle size, encapsulation efficiency and *in vitro* release characteristics of micro spheres were investigated. The yield of preparation and the encapsulation efficiency were obtained. Mean particle size changed by changing concentration of the polymer: drug ratio or stirring speed of the system. Although indomethacin release rates from Eudragit RS micro spheres were very fast and incomplete for all formulation, drug release were very slow from micro spheres prepared with Eudragit RL100 only. When Eudragit RS 100 was added to Eudragit RL100 during preparation of micro spheres, release rates become controlled and achieved the release profile suitable for peroral administration.

Key Words: Indomethacin, Eudragit, Micro spheres, Sustained release.

INTRODUCTION

Despite tremendous advancement in the drug delivery system[1] oral route remains the preferred route for the administration of therapeutic agents and because of low cost therapy and ease of administration leads to higher level of patient compliance. Conventional oral dosage forms such as tablet, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Biodegradable polymeric micro spheres have been studied extensively during the past three decades as a formulation approach to protect encapsulated drugs from degration, enhance bioavailability and sustain drug release[2,3]. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability. Thus

†Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700 032, India.

there were continued efforts to improve the pharmaceutical formulation of indomethacin in order to achieve an optimal therapy as indomethacin has very short half life[4]. With the help of some polymeric substances such as chitoson, polyacrylate, polymethylacrylate, ethyl cellulose we can control the release of the drug by producing matrix tablets or micro spheres. Here we attempt to produce microspheres by solvent evaporation method[5,6] with Eudragit RS100 and Eudragit RL100 in combination at a fixed rotation speed. The prepared microspheres were evaluated for size distribution, drug entrapment efficiency and drug release behaviour in phosphate buffer of pH 7.4.

EXPERIMENTAL

Indomethacin was obtained as gift sample from Tablets Pvt. Ltd., Gandhinagar, Eudragit RS100 and Eudragit RL100 were received from Albert Devid Limited, Kolkata. All other chemicals used were of analytical grade.

Preparation of microspheres: Microspheres were prepared by solvent evaporation technique. The weighed quantity of Eudragit RS 100 and Eudragit RL 100 in the ratio of 1:10 dissolved in acetone and weighed quantity of the indomethacin was dissolved in small quantity of chloroform separately in small glass beakers. These two solutions were well mixed with the help of a magnetic stirrer for 5 min. This solution was added in a form of a continuous stream in the light liquid paraffin with continuous stirring. The stirring speed was kept around 400 rpm and was continued for 4 h to allow to evaporate the smell of acetone. The microspheres were filtered and washed with a portion of petroleum ether thrice. The washed micro spheres were dried in an oven at room temperature not exceeding 25 °C. In this way five batches of micro spheres namely B1, B2, B3, B4, B5 were prepared using different drug: polymers ratio (1:1, 1:2, 1:3, 1:4, 1:5) (Table-1).

TABLE-1
VARIOUS FORMULATION PARAMETERS FOR MICROSPHERES

Formulation code	Drug/polymer ratio	Yield (%)	Particle size (μ)	Drug entrapment efficiency (%)
B1	1:1	75.71	271 ± 3.3	89.35 ± 1.42
B2	1:2	88.41	331 ± 1.7	90.51 ± 1.14
B3	1:3	91.13	382 ± 1.4	90.16 ± 1.18
B4	1:4	77.14	412 ± 1.2	91.51 ± 1.17
B5	1:5	85.22	534 ± 1.6	92.07 ± 1.12

*All values are expressed as mean ± SD, n = 3.

Yield of microspheres[7]: The prepared microspheres were collected after appropriate drying and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microsphers.

% Yield = (Actual weight of product/Total weight of excipient and drug) × 100.

Particle size analysis: Size distribution was determined by sieving the microspheres using a nest of standard BSS sieves as well as by optical microscopy. The microspheres were separated by shaking by a mechanical sieve shaker for 10 min (Table-2).

TABLE-2
IN VITRO DRUG RELEASE PROFILE DATA
Cumulative % drug release of coded formulation; In phosphate buffer at pH 7.4

Time (h)	B1	B2	B3	B4	B5
1	38.12 ± 1.11	25.16 ± 1.12	24.11 ± 1.88	23.17 ± 1.14	21.13 ± 1.17
2	42.31 ± 1.49	37.11 ± 1.33	32.16 ± 1.18	29.07 ± 1.18	27.21 ± 1.15
3	47.41 ± 1.62	41.39 ± 1.23	39.54 ± 2.57	33.51 ± 2.13	31.03 ± 1.73
4	53.21 ± 1.47	58.32 ± 2.34	54.21 ± 1.46	41.25 ± 2.22	39.17 ± 1.13
5	66.32 ± 1.98	64.17 ± 1.87	57.17 ± 1.23	49.67 ± 2.43	47.52 ± 1.02
6	67.52 ± 2.66	68.33 ± 1.53	67.34 ± 1.42	56.21 ± 2.43	54.77 ± 1.11
7	76.15 ± 1.13	73.33 ± 2.21	71.63 ± 2.53	59.31 ± 2.41	57.87 ± 1.78
8	87.21 ± 1.12	77.41 ± 2.53	73.44 ± 1.78	67.75 ± 2.31	59.18 ± 1.05
9	89.08 ± 1.17	87.15 ± 1.77	75.16 ± 2.13	69.19 ± 2.17	64.63 ± 1.88
10	91.57 ± 2.56	94.55 ± 1.21	81.33 ± 2.13	77.21 ± 1.98	67.22 ± 1.09

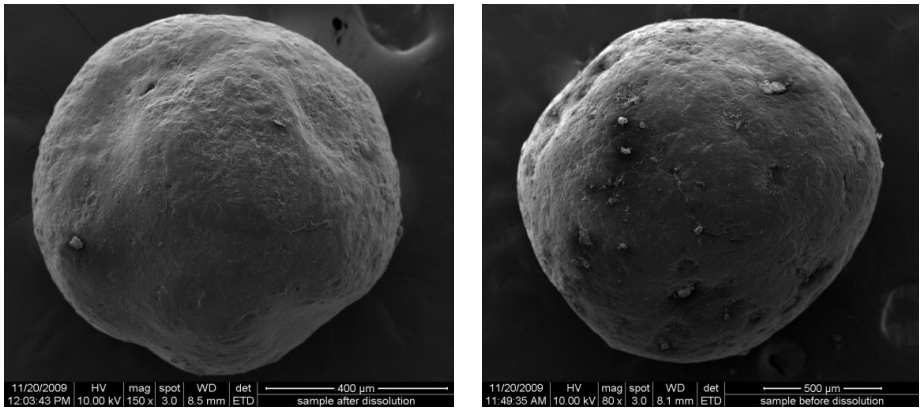
*All values are expressed as mean ± SD, n = 3.

Drug entrapment efficiency: Microspheres equivalent to 100 mg of pure drug were crushed and added to 50 mL of phosphate buffer (pH 7.4). The resulting mixture was shaken in a mechanical shaker for 3 h to completely extract the drug. The solution was filtered with Whatman filter paper. 1 mL of this filtrate was further diluted to 25 mL using phosphate buffer and analyzed spectrophotometrically at 318 nm[8] using UV-visible double beam spectrophotometer (1700, Shimadzu, Japan) (Table-3).

TABLE-3
KINETIC EVALUATION OF DRUG RELEASE DATA
FOR MICRO SPHERES FORMULATIONS

Formulation code	Zero order		1st order		Higuchi model		Korsemeyer pappas model	
	R^2	k_0	R^2	k_1	R^2	k_H	R^2	n
B1	0.7503	6.62	0.9363	0.063	0.9334	20.49	0.8421	0.031
B2	0.9701	6.02	0.9871	0.043	0.9711	22.12	0.9293	0.042
B3	0.8085	6.16	0.9795	0.051	0.9742	22.31	0.8942	0.052
B4	0.9671	6.18	0.9661	0.072	0.9762	17.52	0.8714	0.033
B5	0.8173	6.28	0.9542	0.072	0.9755	21.02	0.8824	0.066

Scanning electron microscopy: For morphology and surface characteristics[9], prepared microspheres were coated with gold in an argon atmosphere. The surface morphology were then studied by scanning electron microscope (Hitchi S-3600n Scanning Electron Microscope, Japan) (Fig. 1).



(a) (b)

Fig. 1. (a) After dissolution (b) before dissolution

Fourier transform infrared spectroscopy (FT-IR): Drug-polymer interaction were studied by FR-IR spectroscopy[9]. The spectra were recorded for pure drug and drug loaded microspheres using FT-IR (Perkin-Elmer Model No 883). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 4000-400 cm^{-1} (Fig. 2).

***In vitro* drug release study:** The *in vitro* drug release[10,11] were carried out for all products in USP type II fitted with six rotatory basket (Camble Electronics, Mumbai, India) dissolution test apparatus. The microspheres were evaluated for

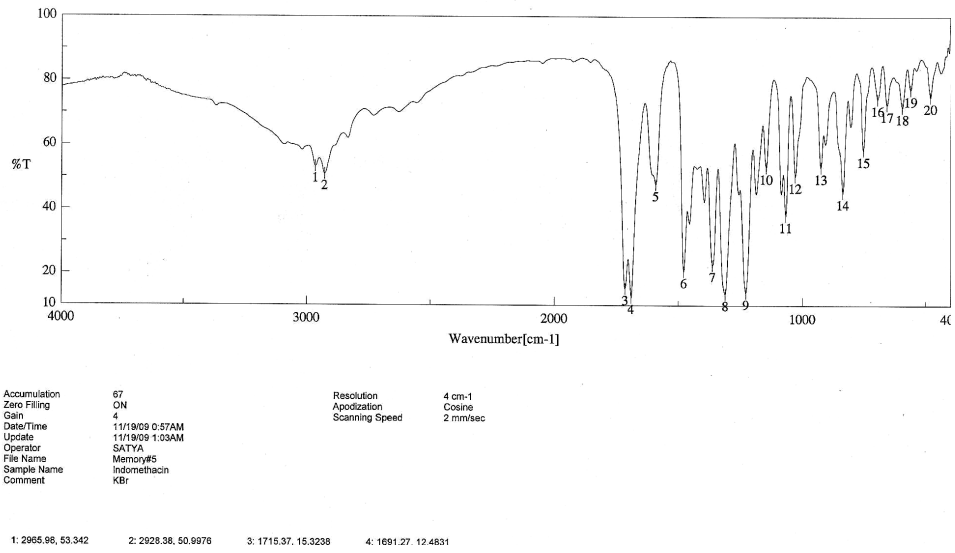


Fig. 2a. FT-IR of drug

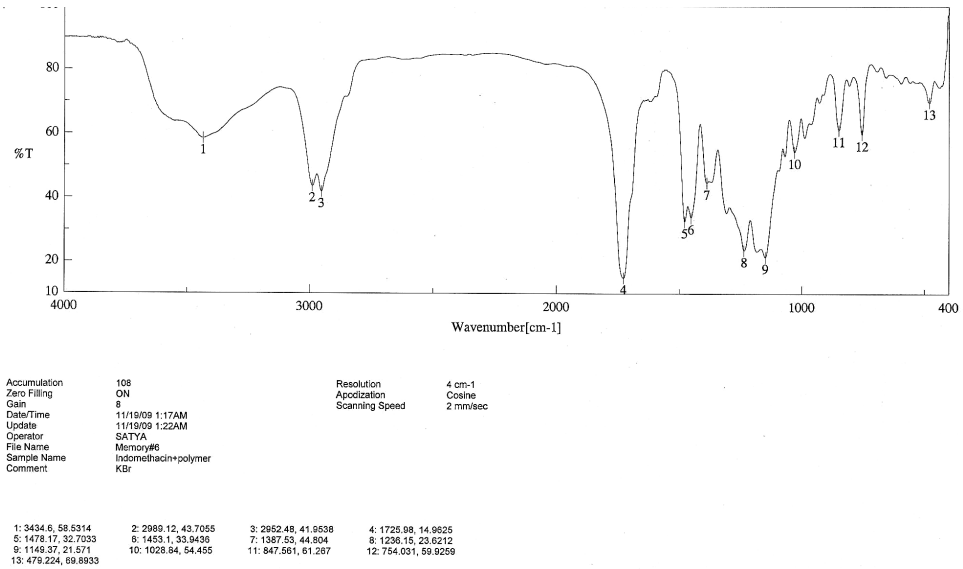


Fig. 2b. FT-IR of drug with polymer

drug release using 900 mL of phosphate buffer (pH 7.4) for 10 h maintained at 37 ± 1 ºC temperature and stirring at 100 rpm. 2 mL of the aliquots were withdrawn at different time interval and an equivalent volume of the medium prewarmed at 37 °C was added to maintained sink condition. Withdrawn samples were analyzed spectrophotometrically at 318 nm after appropriate dilution against reference using phosphate buffer (pH 7.4) black (Table-2).

Kinetic assessment: Drug release data were kinetically evaluated to fit to zero order, first order, Higuchi kinetic and Korsemayer-peppas model[12,13] (Table-3).

RESULTS AND DISCUSSION

The present study is aimed at not only to improve the free flowing property of microspheres but also to release the drug in controlled fashion. The polymers used in the fabrication of microspheres were well established polymers for the said dosage forms. The two polymers were selected in such a way that one will give bursting release (Eudragit RS100) which is essential from therapeutic point of view while other one (Eudragit RL100) will control the drug release by enhancing the binding strength in the microspheres.

The particle size of the microspheres prepared using Eudragit RS100 and Eudragit RL100 in the ratio 1:10 in all the cases which will achieve the aimed target. There were formation of microsphere with larger irregular sizes when the drug to polymer ratio were at increasing order due to increasing in solution viscosity of polymers. Hence, higher agitation speed was required to prepare microspheres of same sizes (Table-1).

No significant differences in drug loading for microspheres made of different polymer solution viscosity were noted. However, the drug loading increases as the concentration of polymers were increased. The analysis of drug content showed maximum entrapment efficiency (85-90 %) at the drug polymer ratio 1:5 in B5 (Table-1).

SEM study showed that particles made of Eudragit RL100 and Eudragit RS100 were spherical. The surface of the drug loaded microspheres manifested the presence of drug particles, clearly visible from outside. Presence of pores were detected on the microspheres surfaces which increases in size and number after dissolution indicating leaches of the drug through these channels (Fig. 1a and b).

FT-IR spectrum revealed that there was no such interaction between the drug and polymers used for microspheres formulations (Fig. 2a and b).

In vitro dissolution studies of all batches of microspheres were shown in Table-2. Microspheres made with increased concentration of polymers showed better flow property but have slower *in vitro* drug release rate. B1, B2 and B3 batches of microspheres showed 81-94 % of drug release in 10 h whereas B4 and B5 showed only 670-775 of drug release in 10 h in phosphate buffer (pH 7.4) (Table-2 and Fig. 2). The thick polymeric barrier slowed the entry of surrounding dissolution medium into the microspheres and hence less quantity of drug leaches out from the highly concentrated polymer matrices of the microspheres exhibiting extended release. The combination polymer helped to leach out the drug from its matrices and exhibit an initial rapid drug release for the first 2 to 3 h and then slower drug release which could be best explained by Higuchi's spherical matrix release (Table-3).

In order to describe the kinetics of the release process of drug from microspheres preparation, the data were fitted with diffusion kinetic models. From the kinetic table it could be observed that the release of indomethacin from microspheres exhibit diffusible characteristics and highly correlated with Higuchi spherical matrix release followed by 1st order and zero order release (Table-3).

Conclusion

The present investigation of microspheres of indomethacin was successfully prepared by using two polymers of different characteristics. Microspheres prepared with Eudragit RS100 and Eudragit RL100 at 1:2 ratio exhibit satisfactory drug release pattern, as it released the drug in controlled fashion for extended period of time in 10 h *ca.* 94 %.The size uniformity in this batch was satisfactory and almost spherical in shape.

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