DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(7), 1267-1278 (1987)

PREPARATION AND IN VITRO EVALUATION OF CONTROLLED RELEASE DOSAGE FORM OF INDOMETHACIN

Biswanath Sa*, Suranjana Roy, and Sudip K. Das

Division of Pharmaceutics
Faculty of Engineering and Technology
Department of Pharmacy
Jadavpur University, Calcutta 700 032, India

ABSTRACT

A controlled release oral drug delivery system of Indomethacin was developed using gelatin as the matrix system, which was rigidized with different concentrations of formalin, without using alcohol. The proportion of drug and gelatin as well as the concentration of formalin had the pronounced effect on the Indomethacin release rate and the patterns of which depicted that they correlated with Lang primary requirements for drug release from controlled release dosage forms. All the types of formulations showed release rate patterns that could best be described by First Order Kinetics, indicating that First Order release was mainly operative.

INTRODUCTION

The bioavailability of Indomethacin, an effective non-steroidal anti-inflammatory agent and a potent inhibitor of prostaglandin synthesis, is associated with a very low

*To whom reprint requests should be addressed.

aquous solubility (0.01 mg/ml) and hence the absorption of the drug is controlled by its rate of dissolution in the G.I. fluid (1). The controlled release of Indomethacin is an important therapeutic aspect because the instantaneous release of the drug from the dosage form produces serious gastrointestinal irritation as well as the dose dumping effect (2). In addition to this, the controlled release dosage form of Indomethacin would be capable to maintain steady plasma level of the drug and reduce the frequency of administration (3).

The present investigation envisages the development of the controlled release dosage form of Indomethacin in order to maximise the therapeutic effects and minimise the side effects. The methodology was developed by suitable modification of the micropelleting technique, using gelatin as the matrix, introduced by Tanaka et. al. (4) and later developed by Das and Gupta (5).

EXPERIMENTAL

Materials

Indomethacin B.P. - 1980 was supplied by the courtesy of Indian Drugs and Pharmaceuticals Limited, Hyderabad, India. Gelatin (Type-1, 300 Bloom, Sigma Chemical Company, St.Louis, U.S.A.), Liquid Paraffin and Light Liquid Paraffin - Indian Pharmacopoeia 1970, Formalin 35% w/v (E. Merck, India), Potassium di-hydrogen phosphate (E. Merck, India) were obtained commercially and used as received. All chemicals were of analytical grade, unless otherwise stated. The drug was sieved to yield particles in the range of 250 μ.

Preparation of Dosage Form

Indomethacin and gelatin, in the proportions of 3:10, 1: 2 and 1:1, were used to prepare the micropellets, which were rigidized with 10%, 15% and 20% w/v of formalin, in water.

10 gms. of gelatin was soaked with 30 ml of glass distilled water, warmed at 60-65°C to form an uniform gelatin sol. Sufficient amount of Indomethacin was incorporated slowly into the gelatin sol with the help of an electrical stirrer. The drug-gelatin mixture was then poured in a constant and steady stream into warm (55-60°C), 300 gms. of mixture of liquid paraffins of absolute viscosity 23.92 C.P. at 55°C, achieved by blending 40% v/v liquid paraffin - I.P.(6) and 60% v/v light liquid paraffin - I.P. (6), kept in 600 ml beaker. The system was stirred uniformly at 200 - 250 r.p.m. After 10 minutes the beaker was cooled quickly to about 5°C by placing ice mixture around the beaker, and this condition was maintained till the gelatin microdrops formed perfect gel. Since Indomethacin is soluble in isopropyl alcohol or methanol, the rigidization was achieved directly by adding formalin of known strengths, in situ without the use of alcohols. 150 ml of formalin, of known percentage of formaldehyde in water, at 5°C was added dropwise to the system while stirring. The stirring was continued for another 20 minutes and then the beaker was kept in refrigerator at -5°C for 12 hours to allow completion of rigidization.

In order to recover the micropellets, the system was stirred slightly to disperse freezed out water and the micropellets throughout the medium. The supernatant was removed, micropellets were filtered through a # 100 mesh nylon cloth and washed with glass distilled water till those were devoid of liquid paraffins and formalin. Then the newly formed micropellets were dried in vaccum desicator for 24 hours to a moisture content of about 15-20%.

Reproducibility of the methodology was evaluated by preparing replicate batches and determining the percentage of drug embedded. Sieve analysis of each batch was carried over to determine the size distribution.

In Vitro Drug Release Study

In Vitro drug release was studied using on U.S.P. - XX rotating basket dissolution apparatus. 800 ml of dissolution medium of the composition of 1 part of phosphate buffer of pH 7.2 (7) and 4 parts of glass distilled water at 37 ± 1°C. The basket was rotated at 100 r.p.m. (±4%). Micropellets weighing 75 mg. of # 26 mesh were placed into the basket and a # 80 mesh nylon screen was covered the basket to prevent coming out of the beads during the progress of dissolution. 10 ml aliquots were withdrawn from the dissolution medium at an interval of 30 minutes and the same volume of fresh medium were replenished.

The dissolution samples were suitably diluted with the fresh dissolution medium and assayed for Indomethacin release, at 318 nm (8), using a Pye-Unicam UV/Vis spectrophotometer, Model SP8-300. Dissolution experiments were duplicated and were found reproducible within 5% limits.

RESULTS AND DISCUSSION

Content Uniformity and Particle Size Analysis

Indomethacin content of the micropellets was determined (8) and the results presented in Table 1, which depicts the average amount of drug contained in each of the five formulations studied. The coefficient of variability in all the cases fall within the 5% limits, that are established for most pharmaceutical preparations.

The cumulative distribution plots, depicted in Figure 1 illustrate the comparative size distribution of micropellets, in the proportions of 3:10, 1:2 and 1:1 of Indomethacin and Gelatin.

In Vitro Rate of Release of Indomethacin

The study of in Vitro release of drug from the dosage form is an important functional aspect in the design of a

TABLE - 1

Reproducibility of the Manufacturing Process

Indomethacin : Gelatin	Rigidization with Formalin w/v	mg. of Indomethacin per 0.5 gm of Micropellets Mean of Four Batches	Sample standard Deviation
3:10	10%	76.92	± 0.0135
	15%	76.46	± 0.0186
	20%	75.22	± 0.0187
1:2	15%	76.14	± 0.0219
1:1	15%	75.57	± 0.0192

Micropellets were of size of mesh ≠≠ 26.

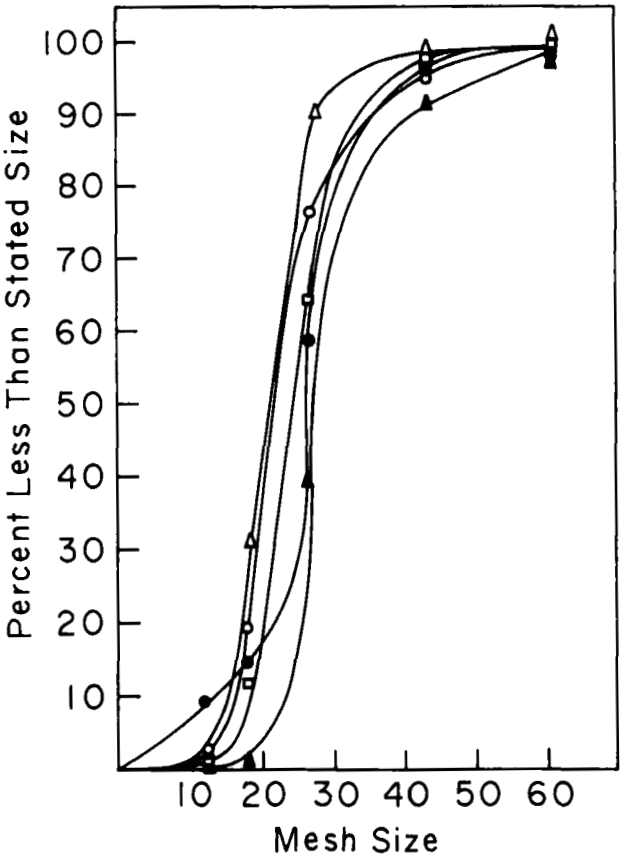

Figure 1 : Cumulative distribution plot for Indomethacin(IMC) Micropellets, key : IMC-Gelatin in 3:10 ratio, rigidized with 10% (□), 15% (▲), and 20% (●) of Formalin w/v; IMC-Gelatin in 1:2 ratio (Δ) and 1:1 ratio (○), rigidized with 15% Formalin w/v.

dosage form. A conventional set of requirements for successful sustained release preparations, based on the in Vitro rotating bottle dissolution method, described by Vora et.al. (9) with slight modifications, was suggested by Lang (10). The conditions of primary requirements for the release of drug from sustained

release tablets, suggested by Lang, depend on the conception that the minimum effective plasma concentration should be achieved within the shortest time and thereafter only the maintenance of this concentration is desired.

Table 2 shows the comparison of the reported primary requirements for the drug release from sustained release dosage forms with the experimental results and on the basis of which the following conclusions could be drawn :

a) Increasing the formalin concentration significantly decreased the release of Indomethacin from the gelatin matrix systems. The extent of release of Indomethacin from 3:10 drug-gelatin matrix and with 20% formalin was only 58.2%, whereas as per Lang primary requirements 70-90% of the drug may be released after 6.5 hours.

b) Increase in the drug-gelatin ratio, keeping the formalin concentration same, as evidenced from formulation (2) & (4) in Table 2, retards drug release from matrix which indicates optimum drug-gelatin ratio would be very much effective. The formulation having drug-gelatin ratio of 1:1, rigidized with 15% formalin w/v, showed uniform release, which correlate very well within the Lang primary requirements.

It could, therefore, be concluded that the release rate of drug from the matrix system is dependent both on the drug-gelatin ratio and the formalin concentration.

Kinetics of Indomethacin Release from the Matrix

The release of indomethacin from the micropellets may be either first order or a diffusion controlled process (11).

From the data of Indomethacin release from the micropellets, the logarithm of the percent of Indomethacin remaining

TABLE - 2

Comparison of Experimental Results (g) with the Reported Release Values

Time (hr)	Cumulative Percent Release					
	Reported values	Experimental Values Formulations				
		(1)[a]	(2)[b]	(3)[c]	(4)[d]	(5)[e]
1.0	25 - 50	48.41	39.34	16.78	31.98	25.99
2.0	40 - 60	73.27	63.81	30.54	54.32	47.30
3.5	52 - 72	90.14	82.21	42.16	76.72	65.30
5.0	60 - 80	96.59[f]	92.24[f]	50.69	86.08	74.98
6.5	70 - 90	****	****	58.20	92.24	84.13

Indomethacin and Gelatin in 3:10 ratio, rigidized with 10% (a), 15% (b) and 20% (c) of Formalin w/v.

d. Indomethacin and Gelatin in 1:2 ratio, rigidized with 15% Formalin w/v.

e. Indomethacin and Gelatin in 1:1 ratio, rigidized with 15% Formalin w/v.

f. After the specified time the release was insignificant.

g. In vitro drug release study of micropellets of mesh # 26.

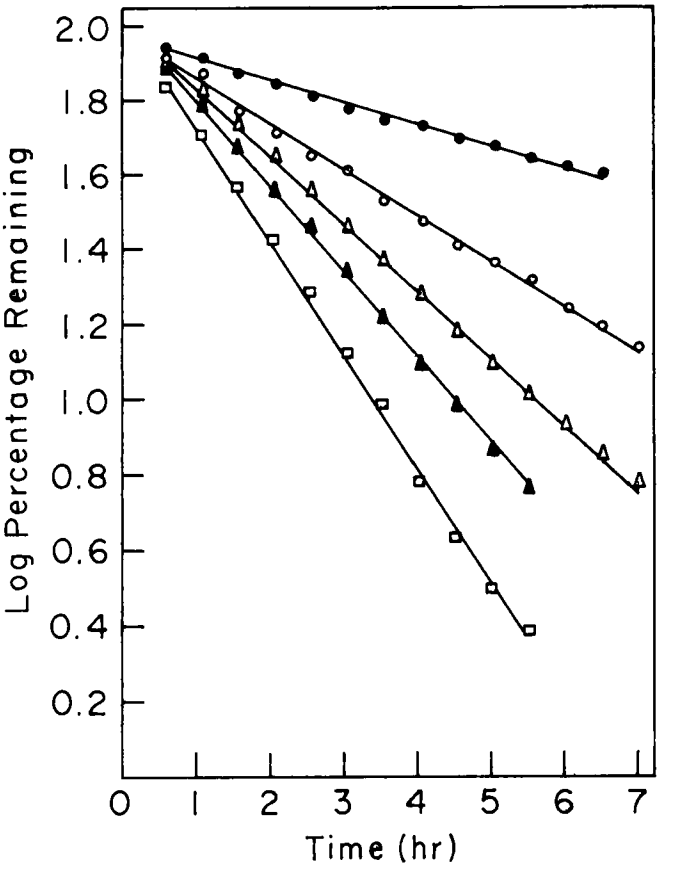

Figure 2 : Release profiles of Indeomethacin (IMC) from Micropellets plotted according to first-order kinetics, key : IMC-Gelatin in 3:10 ratio, rigidized with 10% (□), 15% (▲) and 20% (●) of Formalin w/v; IMC-Gelatin in 1:2 ratio (Δ) and 1:1 ratio (○), rigidized with 15% Formalin w/v.

to be released from the micropellets was plotted as a function of time as predicted by first order kinetics (12).

A true linear relationship, Figure 2, indicating a first order release, was obtained for the total time of experimentation.

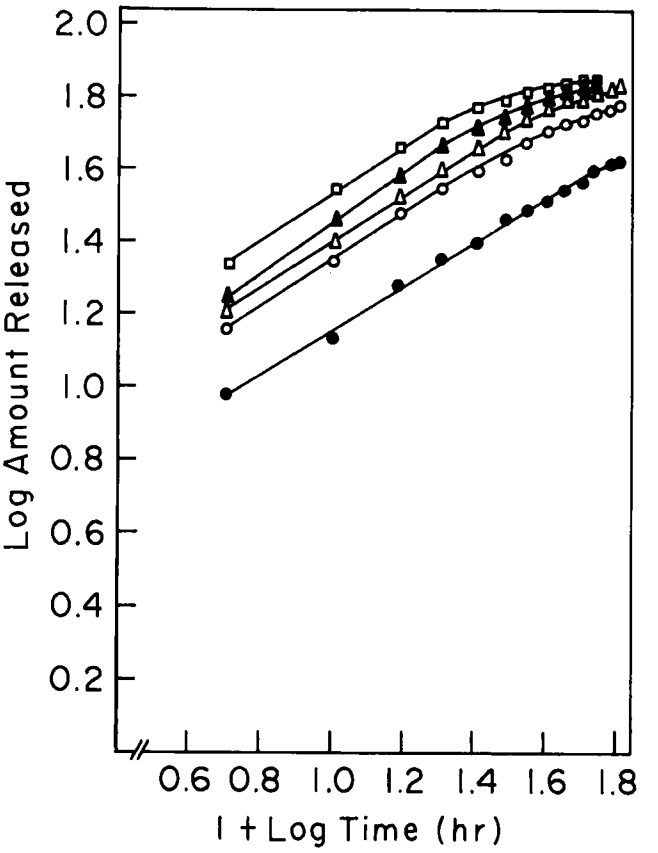

Figure 3 : Plot of the Log of the amount of Indomethacin(IMC) released from Micropellets against the Log of time, key : IMC-Gelatin in 3:10 ratio, rigidized with 10% (□), 15% (▲), and 20% (●) of Formalin w/v; IMC-Gelatin in 1:2 ratio (Δ) and 1:1 ratio (○), rigidized with 15% Formalin w/v.

In order to strictly identify between the first order and diffusion controlled drug release, a plot of Log of the amount released versus Log of the time, was shown in Figure 3.

By taking the logs of Higuchi Equation (13), $Q = Kt^{1/2}$

$\text{Log } Q = \text{Log } K + 0.5 \text{ Log } t$

where Q = the amount of drug released after time t per unit exposed area.

K = Higuchi Constant.

This shows that the plot of Log Q versus Log t should not only give straight line, but also should have the slope of 0.5, indicating diffusion controlled mechanism is operative. Figure 3 depicts plots according to Log of Higuchi equation, which indicates deviations from the diffusion controlled behaviour, slopes in neither cases were 0.5 as well as the plots were not linear rather hyperbolic in nature.

The present method of preparation of matrix type of drug delivery systems, having the advantages of incorporation of alcohol soluble drugs, was proved to be efficient in releasing drug in conformity with the requirements of sustained release preparation, following first order kinetics of drug release.

ACKNOWLEDGEMENTS

The authors thank Jadavpur University authorities for providing necessary facilities and the University Grants Commission of India for the research grant.

REFERENCES

1. S.A. Kaplan, in "Dosage Form Design and Bioavailability", J. Swarbrick, ed., Lea and Febiger, Philadelphia, 1973, p.20.

2. P.L. Boardman and F. Dudley Hart, Ann. rheum. Dis., 26, 127 (1967).

3. P. De Haan and C.F. Lerk, Pharm. Weekbl (Sci)., 6, 57 (1984).

4. N. Tanaka, S. Takino, and I. Utsumi, J. Pharm. Sci., 62, 664 (1963).

5. S.K. Das and B.K. Gupta, Drug Dev. Ind. Pharm., 11, No.8 (1985) (in press).

6. Pharmacopoeia of India - 1966 (1970), Ministry of Health, Govt. of India, 2nd edn., Manager of Publication, Delhi, India, P.740.

7. The United States Pharmacopeia, 20th rev., The United States Pharmacopeial Convention, Rockville, MD, p. 1101 (1980).

8. Ibid., pp. 400 - 401.

9. M.S. Vora, A.J. Zimmer and P.V. Maney, J. Pharm. Sci., 53, 487 (1964).

10. B. Lang, Pharmazie, 26, 661 (1971).

11. J.B. Schwartz, A.P. Simonelli and W.I. Higuchi, J. Pharm. Sci., 57, 274 (1968).

12. M. Gibaldi and S. Feldman, J. Pharm. Sci., 56, 1238 (1967).

13. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).