RESEARCH PAPER

Accepted 29 January 2005
Revised 19 August 2004
Received 8 July 2003
Indian J. Pharm. Sci., 2005, 67(1): 66-69

Melt Extrusion Bioadhesive Drug Delivery: A Case of Diclofenac Contained in Carbopol 940 Matrices

A. A. ATTAMA* AND PETRA O. NNAMANI
Drug Delivery Research Unit, Department of Pharmaceutics,
Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka 410001, Nigeria

Carbopol 940 and theobroma oil were used to formulate melt extrusion bioadhesive tablets of diclofenac. Different batches of the tablets were formulated using different quantities of Carbopol 940 granules containing diclofenac and theobroma oil in a plastic mould by pour moulding. The bioadhesion of the tablets were measured by determining the bioadhesive strength generated when the tablet interacted with the mucus on everted hog jejunum on a tensiometer adapted for that purpose. The tablets were evaluated using weight uniformity, resistance to rupture and liquefaction time. Release of diclofenac from the tablets was studied in simulated intestinal fluid (pH 7.2) without pancreatin. The tablets had low liquefaction times and were highly bioadhesive. Result of the study indicated that theobroma oil could be used to formulate melt extrusion bioadhesive tablets of diclofenac. All the tablets evaluated conformed to pharmacopoeial specifications.

The oral route of drug delivery is the most frequently used and is very convenient, safe and simple[1]. The most common dosage forms available for oral administration include tablets, capsules, solutions, suspensions, emulsions and syrups. There are however more specialised groups of *per oral* dosage forms commonly referred to as sustained release, long acting, gradual release, slow release or prolonged release dosage forms[2]. Site-specific delivery is achieved by enteric coating that provides a means of delaying the release of a drug until the dosage form reaches the small intestine. Colon-selective drug delivery is achieved by both the use of polymers specifically degradable by colonic bacteria and by the use of pH-dependent drug delivery systems[3], where rate of drug release is dependent on the rate of polymer hydrolysis at the prevailing pH[4]. Bioadhesive polymers have also been utilized in controlled release and site-specific delivery of some drugs, including proteins and peptides[5-7]. This study aimed at devising a method for the delivery of diclofenac a non-steroidal antiinflammatory drug into the jejunum by a combination of melt extrusion and bioadhesion. This is quite different from conventional tablets because the drug will be released after melting of the theobroma oil and subsequent bioadhesion and hydration of the granules containing the drug. Delivery of drugs via melt extrusion process was studied by Sprockel *et al.*[8]. However, these workers prepared melt extrusion matrices by compression as in conventional tablet manufacture. This work is a preliminary report on the bioadhesive melt extrusion delivery as a novel drug delivery system.

*For correspondence
E-mail: aaattama@yahoo.com

MATERIALS AND METHODS

The following materials were used as procured without further purification: diclofenac (Ciba), Carbopol 940 (B. F. Goodrich), diclofenac retard tablets (Supreme Pharma) and theobroma oil (Golden oil). All other reagents and solvents were of analytical grade and were used as supplied. Distilled water was freshly obtained from a glass still.

Preparation of drug containing granules and melt extrusion bioadhesive tablets:

Diclofenac powder was granulated with Carbopol 940 by solvent granulation method[9] such that the particles are embedded in the matrix of the polymer. For each batch, the

TABLE 1: QUANTITIES OF MATERIALS USED FOR THE PREPARATION OF MELT EXTRUSION BIOADHESIVE TABLETS

Batch	Theobroma oil (mg)	Carbopol 940 (mg)	Ratio	Diclofenac (mg)
A	150	150	1:1	50
B	200	100	2:1	50
C	100	200	1:2	50
D	180	120	3:2	50
E	120	180	2:3	50
F	300	000	1:0	50

polymer was mixed thoroughly with the drug in a dry mortar and wetted with water. The wet mass was screened through a mesh of 1.5 mm aperture and dried in an oven (model OV110) at 40°, and later dry-screened through a mesh of 1 mm aperture. The quantities of the drug and Carbopol 940 used for the granule preparation are presented in Table 1. For each batch of the tablets, appropriate quantities of the granules were added to molten theobroma oil and the mixture was stirred until it was about to solidify. The mixture was poured into a plastic mould and allowed to set at 0° for 30 min. The tablets were thereafter removed and stored in a cool place.

Weight uniformity:

Twenty tablets from each batch were randomly selected, weighed together and then individually in an analytical balance (Sauter KGD 7470, W. Germany). The mean and coefficient of variation were calculated for each batch of tablets.

Resistance to rupture:

This was determined as described for suppositories in European Pharmacopoeia[10]. The tablets were maintained for 24 h at 28°. In each case, the tablet was placed vertically between the jaws in the sample holder. The top pressure block of the suspension-loading rod was carefully positioned. A 200 g disc was added and 1 min was allowed to pass and further weights added in 200 g units. The total added weights required to crush the tablet was recorded. Ten determinations were done for each batch and the mean and standard deviation calculated.

Liquefaction time determination:

The procedure described by Setnikar and Fantelli[11] for suppositories was adopted with little modification. In each case, one tablet from each batch was carefully wrapped with a semi-permeable and transparent cellophane dialyzer, tied with a thermostable and inextensible string and suspended in SIF (pH 7.2), thermo-regulated at 37±0.5°. The time taken for the tablet to melt and release the granules completely at that temperature was recorded. Average of twenty determinations for each batch was taken as the liquefaction time.

Bioadhesive strength determination:

The Lecomte Du Nouy tensiometer (A. Kruss, model No. Nr 3124, Germany) was used for this study. A freshly excised hog jejunum with a diameter of 2 cm and length of 5 cm was used. The mucus surface was exposed, freed of intestinal waste and used immediately for the test. The tissue was pinned onto a cork and placed on the platform of the tensiometer. On the lever arm of the tensiometer was a flexible wire onto which a plastic plate (0.5 cm×2.0 cm) was attached. The instrument was properly zeroed. For the tablet studies, a tablet from each batch was glued to the plastic plate using a cyanoacrylate adhesive. The everted tissue pinned on a cork was then raised by means of a screw so that it established contact with the glued tablet. A time interval of 1 min was allowed for tablet-mucus interaction. The plate was then raised by means of a screw until the tablet just detached from the surface of the mucus layer. The force required for the tablet removal was read off from the tensiometer scale in degrees. The procedure was repeated twenty times for each tablet batch. The values were thereafter converted to tensions equivalent to bioadhesive strengths using the modified equation of Harkins and Jordan[12]. $T=(Mg/2L)\times F$ and $L=2\pi r$ or πD, therefore, $T=(Mg/2\pi D)\times F= (Mg/2D)\times F'$ (1). where T is the tension equivalent to bioadhesive strength, M is the mass required to return the lever to its original position, g is the acceleration due to gravity, L is the area of the surface in contact with the tissue mucus and F is Harkins and Jordan constant[12]. A circular flat-faced tablet was used thus L becomes the area of one side of the tablet, $F'=Fx7/22$ and D is the average diameter of the tablet.

TABLE 2: PHYSICAL PROPERTIES OF THE MELT EXTRUSION BIOADHESIVE TABLETS

Batch	Mean mass (mg ± SD)	Liquefaction time (min ± SD)	Bioadhesive strength (Nm^{-1} ± SD)	Resistant to rupture (kg ± SD)
A	357±1.4	9.2±1.3	167±7.8	3.5±0.1
B	353±1.7	11.7±2.1	148±5.4	3.2±0.3
C	347±2.3	7.5±1.5	251±7.5	4.1±0.1
D	350±2.1	10.8±2.3	161±4.7	3.6±0.2
E	354±1.3	8.9±2.2	172±5.2	3.9±0.1
F	342±2.4	12.5±1.9	2.9±1.5	2.9±0.1

SD represents the standard deviation for each batch (n=20)

Release studies:

The release studies were carried out in a dissolution apparatus (DTD, Erweka Germany). The dissolution medium consisted of 500 ml of SIF maintained at 37±1°, while agitation was maintained at 100 rpm. In each case, a tablet from each batch was placed in the appropriate chamber of the release apparatus and samples were withdrawn at predetermined time intervals for a period of 8 h and analyzed for diclofenac spectrophotometrically at 272 nm using a spectrophotometer (SP6 450, UV/Vis, Pye Unicam). Equal volume of fresh dissolution medium was used to replace the sample withdrawn at each time interval. Triplicate determinations were made.

RESULTS AND DISCUSSION

The result of the weight uniformity test carried out on the melt extrusion bioadhesive tablets is presented in Table 2. The result indicated that the tablets were uniform. The mean tablet weights had low coefficients of variations. This confirmed the reproducibility of this method of tablet manufacture. Tablets could thus be formed without sophisticated machinery and rigorous unit operations in conventional compressed tablet manufacture. All the tablets conformed to pharmacopoeial specifications in terms of weight uniformity[10]. The results of the resistance to rupture showed that the tablets could withstand the shock of handling and transportation and are presented in Table 2. Theobroma oil forms strong compact on cooling provided no overheating occurred during the melting stage. The result of the liquefaction time determination is presented in Table 2. This parameter resembles the disintegration time of compressed uncoated tablets. Liquefaction exposes the granules for bioadhesive interaction, hydration and release of incorporated drug. Otherwise, only the granules at the surface would interact with the mucus. In melt extrusion delivery systems, the type of base or matrix forming material determines the rate of drug release[13]. The liquefaction time of the dosage forms at 37±0.5° varied. The variation depended on the quantity of Carbopol 940 present. Higher quantity produced tablets that had shorter liquefaction times (Table 2). This may be as a result of the combined action of swelling of the bioadhesive polymer and melting of the matrix forming material. Tablets containing no Carbopol 940 had longer liquefaction time. The liquefaction was solely based on the melting of the matrix.

The results of the bioadhesive strength indicated a linear relationship between the quantity of Carbopol 940 and the bioadhesive strength (Table 2). This was so because in those tablets that contained higher quantity of Carbopol 940, there was a higher surface area available for bioadhesion created by more granules of Carbopol 940 on the surface of the tablet. Carbopol 940 has been shown to be highly bioadhesive[14]. The aim of this melt extrusion bioadhesive delivery was to achieve maximum bioadhesion and release of the incorporated drug since the tablet matrix easily melts to release the bioadhesive granules, thus increasing the surface area for bioadhesion and drug release. The advantages of this form of drug delivery system include ease of preparation, simplicity, non-involvement of sophisticated equipment and manufacturing steps and the possibility of increasing the solubility and absorption of hydrophobic drugs.

Fig. 1 shows the release profile of diclofenac from different batches of the tablets. A general prolonged effect was exhibited by all the batches. However, the degree of

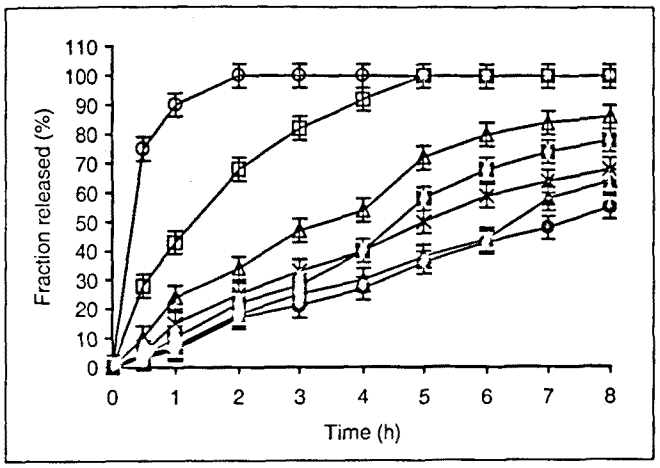

Fig. 1: Release profile of diclofenac from the melt extrusion bioadhesive tablets in SIF.

▪ Batch A, □ Batch B, ▲ Batch C, △ Batch D, ● Batch E, ○ Batch F and x Diclofenac retard tablet

prolongation varied. The prolongation of diclofenac release may be as a result of the hydrophobic nature of theobroma oil and the polymeric nature of Carbopol 940[15]. Batches B and F tablets did not prolong the release of diclofenac as other batches, reaching maximum release after 5 h and 2 h, respectively (fig. 1). This may be because of the quantity of Carbopol 940 present or solubility of diclofenac in the base since batch F contained no polymer. The remaining batches did not reach maximum release after 8 h. This indicated that they could be useful in formulating melt extrusion bioadhesive tablets intended for prolonged release of diclofenac. All other batches exhibited the same pattern of release with the commercial tablet dosage form (Diclofenac retard®). Analysis of the release result was done using Higuchi's square root plot[16]. This plot revealed that diffusion was the predominant process of release in all the tablets (fig. 2). Result of the study showed that melt extrusion bioadhesive tablets prepared with theobroma oil and Carbopol 940 could be used for prolonged release of diclofenac. Melt extrusion bioadhesive tablets of batches C and E gave better result than others in terms of prolongation of drug release. However, the tablets containing 1:2 ratio of theobroma oil and Carbopol 941 (batch C) had the highest bioadhesive strength. This batch would be adjudged to be the best since the aim of the work was to achieve prolongation of release using bioadhesive approach.

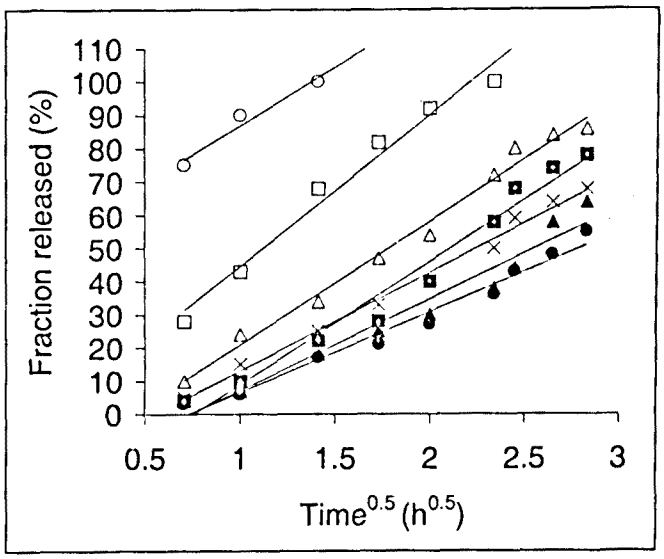

Fig. 2: Higuchi's plot of the amount of diclofenac released.

▪ Batch A, □ Batch B, ▲ Batch C, △ Batch D, ● Batch E, ○ Batch F and x Diclofenac retard tablet

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