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Development and Evaluation of Lipospheres of Diclofenac Sodium

M.C. GOHEL AND AVANI AMIN
Dept. of Pharmaceutics and Pharmaceutical Technology, L.M. College of Pharmacy, Ahmedabad - 380 009.
Received 17 June 1996
Accepted 2 March 1997

Lipospheres of diclofenac sodium were prepared by melt dispersion technique using triple pressed stearic acid. Free flowing lipospheres were obtained by congealing the microemulsion. The amount of water, Tween 20 (surfactant) and butyl alcohol (co- surfactant) were identified as the key variables affecting the formation of discrete spherical lipospheres. More than 70% of the isolated lipospheres were of the size range 180-250 μ. The amount of drug entrapped in the lipospheres was found to be dependent on the lipid to drug ratio and the drug loading was further increased by using caranuba wax coated particles of diclofenac sodium. The *in vitro* drug release study was conducted in phosphate buffer (pH 7.2). Dissolution of the entrapped drug was greatly retarded. The results of the F-statistics revealed that the drug was released by anomalous diffusion.

DICLOFENAC sodium is frequently prescribed for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Its biological half-life has been reported as 1-2 h. Gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen[1]. Thus, a controlled release dosage form of diclofenac sodium is required to be formulated to minimize the damage to the gastro-intestinal mucosa and to reduce the frequency of dosing.

A survey of the lipid materials contained in drug products marketed in the United States showed that stearic acid or its salts are widely used in dosage forms[2]. The low cost, low toxicity and ease of fabrication have been stated as the major advantages of lipids by Kabwvichii[3]. Studies have been reported on the formulation development and dissolution testing of wax microspheres of different drugs[4-7]. The aim of the present investigation was to develop controlled release lipospheres of diclofenac sodium using melt dispersion technique, which does not require organic solvents.

Diclofenac sodium (J.P.) was received as a gift sample from Sharda Drugs. Triple pressed stearic acid, Tween 20 and butyl alcohol were purchased from local market.

Lipospheres were prepared from microemulsions as reported by Dino and co-workers[8]. The formulation of different batches is depicted in Table 1. Briefly, triple pressed stearic acid was melted on a water bath maintained at 70-72°. Finely powdered drug particles (90#) were dispersed in the molten wax. Aqueous phase was prepared by heating a blend of water and Tween 20 (surfactant, HLB 16.7) to 70-72°. Butyl alcohol (co- surfactant) was

Table-1 : Formulation Variables and Drug Content of Lipospheres

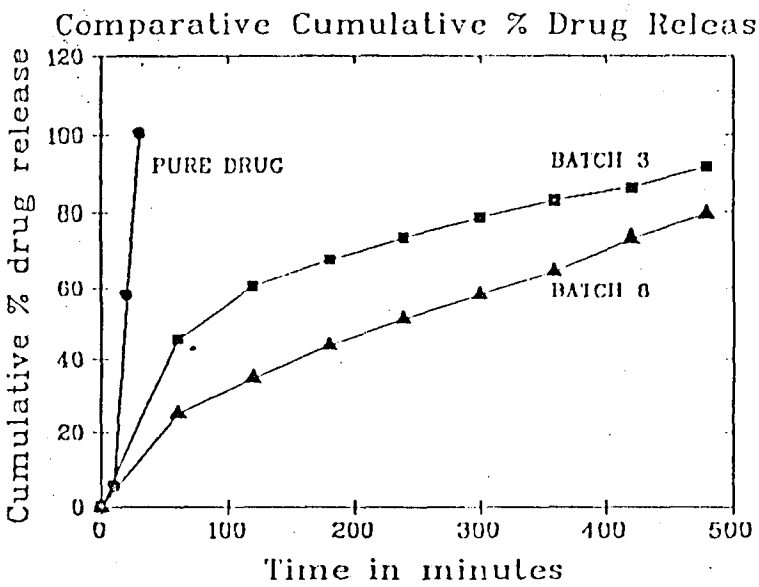
Batch No.	Butyl Alcohol (ml)	Drug (mg)	Water (ml)	Drug Content (%)	Appearance
B1	0.6	--	60	--	AP
B2	0.8	--	60	--	AP
B3	1.0	--	60	--	AP
B4	1.2	--	60	--	AP
B5	1.5	--	60	--	DP
B6	5.0	--	60	--	DP
B7	10.0	--	60	--	DP
1	1.5	500	60	5.8	DP
2	1.5	750	60	11.7	DP
3	1.5	1000	60	17.5	DP
4	1.5	500	60	5.5	DP
5	1.5	500	60	12.7	DP
6	1.5	1000	60	27.6	DP
7	1.5	1000	60	27.4	DP
8	1.5	500	40	9.9	DP
9	1.5	500	20	11.8	AP
10	1.5	500	10	13.4	AP

Note: Two % Tween 20 was used as a surfactant except in Batch 7, where 5% Polaxomer was used, All batches were prepared using 2 gm of triple pressed stearic acid, AP = Aggregated Product, DP = Discrete Product.

added to the hot aqueous phase. The aqueous phase was added to the oily phase and emulsification was assisted by stirring the contents on a magnetic stirrer. The hot microemulsion was carefully added to cold water to yield congealed lipospheres. The lipospheres were then washed with water to remove untrapped drug and residue of butyl alcohol. The product was dried under vacuum at a temperature less than 45° for 2 h. The particle size analysis was carried out using a mechanical sieve shaker. The sieves were shaken for a period of 15 min.

Hot water was added to the finely powdered lipospheres (100 mg) and the resultant dispersions were exposed to ultrasonic treatment (Vibronics, Bombay) for 20 min. The ultrasonic treatment was repeated thrice with a resting period of 30 min. between treatments. The absorbance measurements were done on a Hitachi double beam UV/VIS spectrophotometer at 276 nm[9]. Corresponding concentrations in the samples were calculated from the standard plot generated by fitting weighted linear regression model[10]. The results of the analysis are depicted in Table 1.

Comparative Cumulative % Drug Release



Lipospheres containing 100 mg of diclofenac sodium were filled in hard gelatin capsules and evaluated for *in vitro* dissolution studies. The dissolution studies (n=3) were performed using USP XXII basket apparatus at a rotational speed of 50 RPM. at 37° in 900 ml phosphate buffer (pH 7.2). Samples (10 ml) were withdrawn at regular time intervals and filtered through 0.45 μ membrane filter. The drug content was determined in the filtrate.

The amount of water used for the preparation of lipospheres was found to influence the characteristics of the product. Large and aggregated lipospheres were obtained when the level of water was used in the range of 10 to 30 ml. Superior quality of lispospheres i.e. small in size and discrete in nature were obtained when 60 ml of water was used. Sphericity of the product was lost when 100 ml of water was used. The drug loading was found to be inversely related with the amount of water used in the preparation. It is therefore concluded that morphological characters and the drug content in the lipospheres may be optimized by using appropriate quantity of aqueous phase.

The presence of Tween 80 (2%) was found to be essential to obtain a discrete product. Butyl alcohol, a co-surfactant, was also found to influence the characteristics of the product. Aggregated lipospheres with non-spherical shape were obtained in batches B1 to B4 probably due to faster evaporation of butyl alcohol. Hence, it may be concluded that over and above the amount of butyl alcohol, other processing conditions such as stirring speed and temperature also play a critical role in the preparation of lipospheres. It was difficult to remove the excess amount of butyl alcohol from batches B6 and B7. Hence, 1.5 ml of butyl alcohol is suggested as the correct amount. Washing with water (3 x 50 ml) was found to be essential to avoid lumping of lipospheres.

The results depicted in Table 1 demonstrates that the drug content in the lipospheres was found to be dependent on the lipid:drug ratio. The most probable reason for lower percentage of drug loading is the higher aqueous solubility of diclofenac sodium (10 mg/ml). A higher drug to lipid ratio yielded a faster drug release. The surface characteristic of diclofenac sodium particles was modified by treating the drug particles with wax solution in an effort to increase the percentage drug loading in the lipospheres. It may be expected that if wax treated drug particles are used for the preparation of lipospheres, less leakage of the water soluble drug would occur in the outer aqueous phase[11].

The method used by Kawashima and co-workers[12] was modified and used for coating the drug particles. The drug particles were suspended in a 3% w/v solution of caranuba wax (M.P. 81- 86°). Chloroform (batch 4) and ethyl alcohol (batches 5,6,7) were tried as a solvent for coating the drug particles. The drug particles coated using alcoholic caranuba wax solution yielded lipospheres containing higher percentage of drug loading (12.7%, 4:1 lipid to drug ratio) whereas only 5.5% of the drug was loaded when chloroformic solution of caranuba wax was used at the same lipid to drug ratio.

The results of sieve analysis of batch I (uncoated diclofenac sodium particles, lipid to drug ratio 4:1) showed that about 70% of the lipospheres were of particle size range 180 to 250 μ. The results of batch 6 (wax coated diclofenac sodium particles, lipid to drug ratio 4:2) showed that about 70% of the lipospheres were found to be in the range of 250 to 500 μ. The main factors influencing the size distribution were the surface characteristics of the drug particles, stirring rate, cooling rate and congealing process. The *in vitro* drug release profile of pure diclofenac sodium powder and that of lipospheres of batch 3 (lipid to drug ratio of 4:2) and that of batch 6 (lipid to drug ratio of 4:2 containing wax coated drug particles) is depicted in Fig. 1. From the figure, one can conclude that sustained release of diclofenac sodium was obtained from the lipospheres. Batch 7 was prepared using 5% polaxomer as the surfactant instead of Tween 20. Satisfactory lipospheres were obtained, confirming that the wax coated drug particles helps in obtaining higher percentage of drug loading (Table 1). The drug release was greatly retarded when wax coated drug particles were used (Fig. 1).

The goodness of fit test proposed by Bamba and co-workers[13] was used to determine the mechanisms of drug release. The data of Batch 6, a potential candidate for 12 h *in vitro* release, was fitted to the different models. The release profile fitted best to Korsmeyer and Peppas equation (log time vs. log fraction of drug released, F = 2.43) showing the least residual sum of square as compared with Higuchi equation (sq. rt. of time vs percentage drug released, F = 4.96) or Weibull equation (log log plot of time vs -ln (1-m), where m=fraction dissolved at time t, F= 10.23). This superiority is, however statistically insignificant as shown by F-ratio test. The values of correlation coefficient were found to be 0.9979, 0.9965, and 0.9868 for Korsmeyer and Peppas, Higuchi and Weibull models respectively. The values of slope and intercept were found to be 0.5547 and - 1.6020 for Korsmeyer model respectively. From the value of the slope, it may be concluded that the drug is released by diffusion of anomalous type (non-Fickian).

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