Preparation and Evaluation of Diclofenac Sodium Controlled Release Tablets using Spray-Drying Technology in Aqueous System

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Diclofenac sodium is one of the most widely used NSAIDS and its short half-life of 1-2 h necessitates preparation of a controlled release formulation. Spray drying, a one step process establishes intimate contact of the drug with the polymer and finds increasing applications in the area of controlled release formulations. Eudragit NE 30D is reported to be useful for preparation of controlled release formulations. An attempt has been made to prepare microparticles of diclofenac sodium with Eudragit NE 30D, using spray-drying technology in aqueous system. Aerosil was found to overcome the tackiness caused by Eudragit NE 30D and improved yield and flowability of the product, while talc did not overcome tackiness and did not prove to be suitable excipient. The microparticles were evaluated for percent yield, average particle size and flowability and were compressed into tablets. The tablets were studied for drug assay and dissolution profiles. The tablets containing drug polymer ratio of 1:1.212 were found to release the drug at the rate of 9.3 mg/h over the period of 10 h.

Diclofenac sodium with its low oral bioavailability, short plasma half life and low dose is an ideal candidate for formulation as a controlled release drug delivery system for chronic pain associated with musculoskeletal disorders like arthritis and gout[1]. Spray drying is a single step, cost effective technique that establishes intimate contact of the drug with the release retardant and is being used successfully to prepare controlled release products[2,3]. Eudragit NE 30D is an acrylic polymer, which has been reported to be useful in the preparation of controlled release products[4,5]. It is available as 30% aqueous dispersion and offers advantage of being used in aqueous system for spray drying. However it causes tackiness and therefore talc and Aerosil were evaluated as excipients to improve this property.

A table top mini spray dryer (S. M. Scientech, Kolkata) fitted with a borosilicate glass chamber, two fluid nozzle, peristaltic pump with variable speed arrangement, air blower with concurrent air flow, sheathed air heater with thermostatic control and a glass cyclone collector was used for the study. Diclofenac sodium was mixed with the polymer and the excipient. Water was added to the above mixture to get the feed concentration of around 30%. The slurry was stirred well and kept on magnetic stirrer through out the spray drying process. Instrument related variables like drying air temperature, drying air flow rate and feed rate were set to desired value and spray drying of the slurry was carried out and the spray dried product collected in glass cyclone collector.

Spray drying conditions were optimized at drying air temperature 275°, drying airflow rate 6 cfm, feed rate 9 ml/min and atomizing pressure 2 kgf/cm^2.

Spray dried microparticles were assessed for percent yield, particle size and flowability. Particle size was measured using a calibrated optical microscope. Flowability was measured in terms of angle of repose of the spray-dried product. Angle of repose was measured using fixed funnel and free standing cone method[6]. The spray-dried microparticles were compressed into tablets (9.5 mm diameter) on a single stroke-punching machine and were evaluated for drug assay at 285 nm. Dissolution was carried out using validated USP dissolution rate apparatus in pH 7.2 buffer maintaining the temperature at 37° and stirring speed of 100 rpm.

Compositions and evaluation results of spray-dried microparticles containing Eudragit NE30D and talc have been tabulated in Table 1. All the products showed particle size in the range of 10-15 μm. Products A1 to A5, except A2 contain Eudragit NE30D and talc in the ratio of 0.303:2. These products showed good flowability but had low yield of around 40%. As the polymer content in the formulations was increased, talc content had to be increased to maintain a minimal ratio of polymer: talc,

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0.303:2. Spray dried product A2 containing higher amount of talc (0.303:2.5) did not show any improvement in flowability or percent yield of the product. These spray-dried microparticles were further compressed into tablets and the tablets were evaluated for drug assay and dissolution characteristics (Table 1). As the amount of Eudragit NE30D was increased in the formulation, dissolution rate was found to decrease. Tablet A1, A3 and A5 containing increasing amount of Eudragit NE30D were found to show increase in $t_{90\%}$ from 4.3 h to 6.2 h with decrease in release rate from 13.7 to 12.3 mg/h. Tablets A5 containing drug polymer ratio of 1:0.757 showed controlled release till around 7h releasing the drug at the rate of 12.3 mg/h.

With increasing concentration of Eudragit NE30D, very high amount of talc had to be incorporated, therefore further increase in polymer concentration was not possible. Formulations B1 to B7 containing higher amounts of Eudragit NE30D were prepared. In these formulations aerosil was added as an excipient instead of talc. Compositions and evaluation results of spray dried microparticles containing Eudragit NE30D and Aerosil have been tabulated in Table 2. Spray dried products containing polymer aerosil ratio of 0.303:0.1 (formulation B5) showed good flowability and high percent yield. Aerosil was found to decrease the tackiness of the polymer and overcome the agglomeration thus increasing the flowability and percent yield of the product. Addition of Aerosil also decreased the size of microparticles, which can be attributed to the decreased agglomeration of the product. However, any further increase in the amount of Aerosil (formulation B6) was not found to improve the product characteristics any further.

These spray-dried particles were tabletted and evaluated as earlier. As the polymer concentration was increased drug release rate was found to decrease. Tablets B6 containing drug: polymer ratio of 1:1.212 released the drug at the rate of 9.55 mg/h over the period of 10 h. Lower concentration of Eudragit NE30D (formulation B1 and B2) gave a $t_{90\%}$ of 6.30 and 7.05 h respectively but the drug release did not follow zero order kinetics. As the polymer concentration was increased to drug:polymer ratio of 1:1.06 (formulations B3 and B4) and 1:1.212 (formulations B5 and B6), the $t_{90\%}$ increased to 7.9 and 9.1 h, respectively. Tablets B5 with optimized drug, polymer and Aerosil ratio released the drug at the rate of 9.31 mg/h over the period of 10 h. These formulations were found to follow zero order drug release kinetics as is evident from the coefficient of correlation value of drug release vs. time profiles. Overlapping dissolution profiles of tablets B3 and B4 containing same amount of polymer but different amount of Aerosil indicates that Aerosil did not have any effect on dissolution profiles (fig. 1).

TABLE 1: COMPOSITION AND COMPARATIVE EVALUATION OF FORMULATIONS CONTAINING EUDRAGIT NE30D AND TALC

	Formulation code	A1	A2	A3	A4	A5
Composition	Diclofenac sodium (mg)	100	100	100	100	100
	Eudragit NE30D (mg)	30.3	30.3	45.4	60.6	75.7
	Talc (mg)	200	250	300	400	500
Evaluation of spray dried micro particles	% yield	43.6	43.9	40.8	39.9	40.8
	Average particle size (μm)	10.71	10.73	10.90	10.96	11.40
	Angle of repose (θ)	32.6	32.4	32.6	33.6	33.7
Evaluation of tablets	Drug assay (%)	100.2	100.2	99.6	98.2	100.1
	Release rate (mg/h)	13.72	13.8	12.41	12.38	12.30
	Regression coefficient	0.912	0.946	0.952	0.952	0.963
	$t_{90\%}$ (h)	4.33	4.41	5.92	6.11	6.23

TABLE 2: COMPOSITION AND EVALUATION OF FORMULATIONS CONTAINING EUDRAGIT NE 30D AND AEROSIL.

	Formulation code	B1	B2	B3	B4	B5	B6
Composition	Diclofenac sodium (mg)	100	100	100	100	100	100
	Eudragit NE30D (mg)	75.70	90.90	106.5	106.5	121.2	121.2
	Talc (mg)	25	30	20	35	40	60
Evaluation of spray dried micro particles	%Yield	78	75.6	70.60	72.60	76.20	77.80
	Average particle size (mm)	10.50	10.60	12.90	11.90	12.20	12.40
	Angle of repose (θ)	27	28.30	32.10	26.90	28.20	26.40
Evaluation of tablets	Drug assay (%)	100.2	100.5	99.90	99.80	99.50	99.50
	Release rate (mg/h)	12.04	11.94	10.78	10.79	9.31	9.55
	Regression coefficient	0.954	0.972	0.992	0.996	0.997	0.997
	$t_{90\%}$ (h)	6.30	7.05	7.91	7.96	9.11	9.11

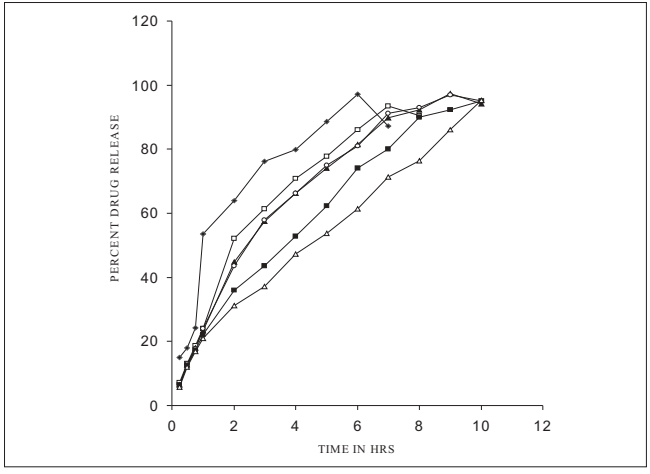

Fig. 1: Dissolution profiles of formulations containing Eudragit NE30D and aerosil
♦ Formulation B1, □ Formulation B2, ▲ Formulation B3, ○ Formulation B4, ■ Formulation B5, Δ Formulation B6

Thus spraying drying was found to be a suitable method for preparing controlled release tablets of diclofenac sodium with precise zero order release while Eudragit NE30D has proved to be a useful polymer for formulating a controlled release product using spray drying technology in an aqueous system.

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