SHORT COMMUNICATIONS

Comparative Evaluation of Hydrotropically and Thermally Gelled Starch Pastes as Granulating Agents for Diclofenac Sodium

H.N. SHIVAKUMAR*, B.S. NATH AND B.G. DESAI
Department of Pharmaceutics, K.L.E. Society's College of Pharmacy
Rajajinagar, Bangalore-560 010

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Hydrotropically gelled maize starch (HTGS) was investigated as granulating agent for preparing tablets of diclofenac sodium. Granular and tablet properties were determined and compared with those obtained using conventionally prepared starch paste (THSP). Both types of granules could be compressed into satisfactory tablets with a mean disintegration times of 13 min 5 s and 7 min 42 s, respectively, for HTGS and THSP. However, tablets prepared with HTGS gave faster dissolution (88% in 70 min), whereas the other type gave 77% in the same time in phosphate buffer of pH 7.2. Hydrotropically gelled starch exhibited good stability even after storing for one month where as conventionally prepared starch paste was spoilt within 24 h.

The term hydrotropy was originally put forward by Neuberg[1] to describe the increase in the solubility of a solute by the addition of a fairly large concentration of additives (alkali metal salts of various organic acids). Miyahara and Takahasi[2] studied the solubility of benzoquinone with sodium benzoate and other phenol derivatives. Hamaza and Paruta[3], Badman *et al.*,[4] Jain and Patel[5] have reported the hydrotropic solubalisation of paracetamol, diazepam and nifedipine using sodium benzoate or sodium salicylate. Further, these agents were reported to inhibit the gelling of gelatin[6], denaturing of haemoglobin[7] and bring about gelling of starch[8] without heating. The present investigation reports the use of hydrotropically gelled maize starch as granulating agent for preparing diclofenac sodium tablets.

Diclofenac sodium was a gift sample from BPRL, Bangalore. Maize starch was purchased from BDH, England, potassium dihydrogen phosphate, sodium benzoate, talc IP, magnesium stearate IP, lactose IP were purchased from Loba Chemie Pvt. Ltd., Mumbai.

A quantity of 10 g of maize starch was added to 30 ml of water and stirred to give a uniform slurry. Twenty grams of sodium benzoate was dissolved in 40 ml of water and added slowly with constant stirring. A good gel was formed within one hour without any heating. Thermally gelled Starch paste was prepared by taking 10 g of maize starch and made into a uniform slurry using 30 ml of water. The slurry so prepared was added into 70 ml of boiling water with constant stirring to get a translucent gel. Two batches of granules were prepared making use of the two different granulating agents (HTGS and THSP). A quantity of 40 g of the drug was weighed and mixed with 25 g of lactose, 4 g of starch and granulated the respective granulating agents (HTGS and THSP) into a dough mass and passed through sieve No. 16. The granules obtained were dried at 56° in a thermostatic hot air oven (Serwell Instruments Inc) for 3 h. The dried granules were re-sieved by passing through the same sieve to break any lumps. The granules retained on sieve No 44 were characterized before compressing into tablets.

The granules were evaluated for various properties. Particle size was determined by sieve analysis using standard sieves No. 22, 30, 44, 60 and 85 with a standard sieving time of 30 min using an automatic sieve shaker. Granular density was determined by liquid dis-

*For correspondence

placement method by using 50 cc specific gravity bottle with toluene as immersion fluid in three replicate determinations. Bulk density was determined graphically by successive addition of 2 g of the granules and noticing the volume by tapping three times in a bulk density apparatus (Cambell Electronics, India) and further adding 2 g and noticing the volume after tapping until a total of 20 g of granules were added. The bulk volume versus weight was then plotted, from the linear graph, the slope value was calculated and is taken as the bulk density. Tap density was determined by tapping a quantity of 25 g of the granules in a 50 ml measuring cylinder until no further reduction in the volume was observed. The tapped density was calculated by dividing the weight of the sample by the final consolidated volume. of the sample in three replicates.

Compressibility is a dimensionless entity, which proved to be useful to the same extent as angle of repose values for predicting the flow characteristics and is calculated by using the expression. compressibility = 1-bulk density/tap density. Void porosity values were computed by following the relationship, void porosity = 1-bulk density/granular density.

The angle of repose was determined using Pilpel's method[9]. A glass tube open at both ends having 140 cm length and 2.3 cm diameter was used, a fixed volume of loosely packed granules were poured into the tube which was held vertically at right angles to the base. The tube was raised mechanically at constant and uniform speed allowing the granules to descend down and form a heap on the surface of a glazed tile wrapped with a graph paper, which served as a base. The height and the diameter of the heap was measured (by calculating the area) and the angle of repose (θ) was determined by using the expression $\theta = \tan^{-1} 2H/D$. The moisture content of the granules was determined by heating the granules to a constant weight in a hot air oven maintained at 110°. The granules retained on sieve No. 44 were mixed thoroughly with 15% of the fines, 5% starch as disintegrant, 1% talc and 1% magnesium stearate as lubricants and compressed into tablets weighing 200 mg to a hardness of 5 kg/cm² using 9 mm flat punches with bevel edges in a rotary tablet press (Rimek minipress model RSB-4, Karnavathi Engineering, India).

Hardness of the tablets was evaluated using a Stokes-Monsanto hardness tester (Cambell Electronics, India). Uniformity of weight was determined by following the official method given in IP[10]. Disintegration time was determined by following the IP method[11] using a USP XXIII disintegration tester (model ED-2, Electrolab, India). The friability of the tablets from each batch was carried out by using a Roche friabilator by following USP method[12].

In vitro drug release from the tablets was carried out in phosphate buffer of pH 7.2±0.1 using a USP XXIII dissolution apparatus (model TDT-06T, Electrolab, India) for a period of 70 min. Dissolution fluid of 900 ml maintained at 37±1° was used with stirrer (paddle) speed of 100 rpm. An aliquot sample of 2 ml of the dissolution fluid was withdrawn at 10 min intervals by using a filter tipped pipette and immediately replaced by same quantity of fresh dissolution fluid equilibrated to the same temperature. The aliquots were analyzed spectrophotometrically at an absorption maxima of 276 nm against phosphate buffer as a reagent blank using a double beam UV-visible spectrophotometer. (model V-530 PC Jasco, Japan).

TABLE 1: PROPERTIES OF GRANULES AND TABLETS

Properties	HTGS	THSP
Starch paste used	33.61% w/w	30.99% w/w
Average particle size	523.5 μ	523.6 μ
Bulk density	0.586 g/cc	0.613 g/cc
Tap density	0.654 g/cc	0.674 g/cc
Granular density	1.339 g/cc	1.357 g/cc
Porosity	56.24 %	54.82 %
Compressibility	10.40 %	9.05 %
Angle of repose	31°51'	31°58'
Weight uniformity	passes	passes
Friability	0.368 %	0.426 %
Disintegration time	13 min 5 s.	7 min 42 s.

The obtained values for various granular and tablet properties are shown in Table 1. The average particle size of the granules was found to be 523.5 μ and 523.6 μ for granules prepared by using HTGS and THSP respectively with little difference. Similarly the values of granular, bulk and tap densities were found to be 1.339, 0.586 and 0.654 g/cc, respectively, for the granules prepared

with HTGS and 1.357, 0.613 and 0.674 g/cc, respectively, for the granules prepared with THSP. These values were found not to differ significantly. Porosity and compressibility values were found to be almost the same for both the batches. The granules were found to be free flowing and gave values of angle of repose 31°51' and 31°58', respectively, for HTGS and THSP. The results conclusively proved that the properties of the granules prepared with hydrotropically gelled starch were comparable with those obtained by using starch paste.

Satisfactory tablets could be compressed without any capping with negligible weight variation. Both types of tablets were found to comply with the prescribed standards of friability test, which is less than 0.8%. Tablets prepared with hydrotropically gelled starch gave a DT of 13 min 5 s with a standard deviation of 3.64 and co-efficient of variance of 26.36%. where as the other batch gave the mean value of 7 min 42 s with a standard deviation of 1.718 and co-efficient of variance of 22.3%. Both the batches of tablets were found to disintegrate within the official time.

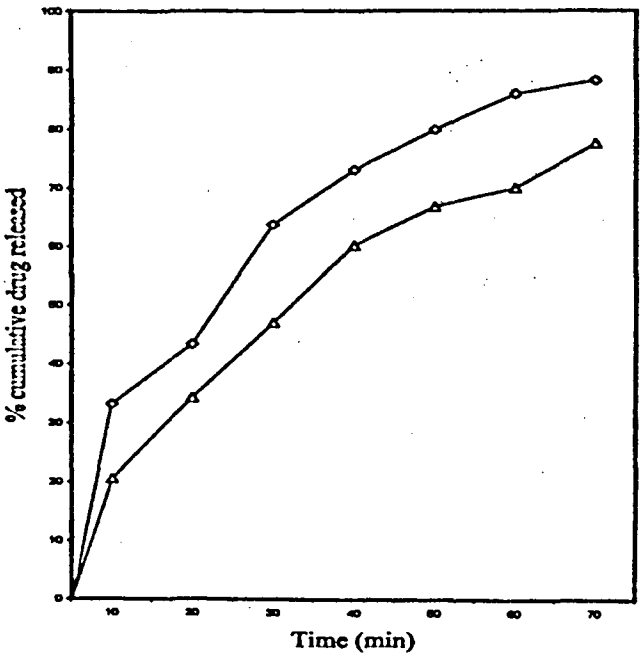

Fig. 1: *In vitro* release of diclofenac sodium from tablets. *In vitro* release of diclofenac sodium was determined using a USP XIII dissolution apparatus for 70 min in phosphate buffer of pH 7.2 from tablets prepared with hydrotropically-gelled starch (HTGS, -◇-) and thermally-gelled starch paste (THSP, -Δ-)

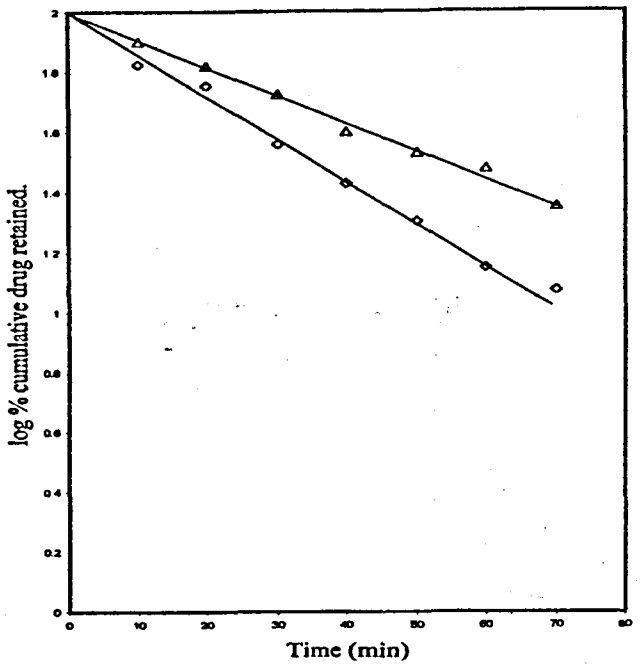

Fig. 2: Release kinetics of diclofenac sodium. Release kinetics of diclofenac sodium from tablets prepared with hydrotropically-gelled starch (HTGS, -◇-) and thermally-gelled starch paste (THSP, -Δ-) at pH, 7.2

The *in vitro* data was plotted as amount of drug dissolved against time (fig.1) and as sigma minus plots (fig. 2). The results showed that an amount of 33.27% and 20.6% of the drug was found to be dissolved with in 10 min from the tablets prepared using HTGS and THSP as granulating agent and at the end of 70 min the percent drug dissolved were found to be 88.3 and 77.6 respectively. Further, from the plots time taken for the 50% drug release (T_{50}) was found to be 23 min in case of tablets prepared using HTGS and 33 min in case of tablets prepared using THSP as granulating agents. So the results of *in vitro* drug release clearly indicated that there is an enhancement in dissolution rate of the drug when HTGS was used as a granulating agent. The unreacted sodium benzoate present in each tablet was negligible. The sigma minus plots (fig. 2) were found to be linear with a linear regression co-efficient values of 0.999 and 0.981 indicating that the release of the drug obeyed first order rate kinetics. The dissolution rate was calculated from the slope of sigma minus plots ad found to be 0.03 mg/min and 0.02 mg/min respectively for HTGS and THSP systems.

Hydrotropically gelled maize starch was investigated as granulating agent using diclofenac sodium as drug.

Both granular and tablet properties were evaluated and compared with the results obtained by using thermally heated starch paste. The dissolution rate has been enhanced from the tablets prepared by using HTGS as binder. Due to its stability, HTGS may be preferred over conventional starch paste.

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Role of Skin Cholesterol in Permeation of Indomethacin

ANAND, O., GUPTA, S. AND TIWARY, A.K.*

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala-147 002

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The possible role of skin cholesterol in modifying the percutaneous permeation of indomethacin was studied by employing lovastatin, an inhibitor of cholesterol synthesis. The decreased cholesterol content of solvent perturbed skin was maintained till 24 h by topical application of lovastatin (1.125 mg/cm^2). Solvent perturbed-lovastatin treated viable skin excised after 24 h produced enhanced *in vitro* permeation of indomethacin. The time for 75% reduction in edema was significantly less in rats with perturbed-lovastatin treated skin as compared to that with normal skin.

The permeability barrier properties of skin are mediated by a series of extra cellular lipid multi-layers enriched in fatty acids, ceramide and cholesterol. When the barrier is perturbed by removal of these lipids, a sequence of biological response is initiated that accelerates epidermal synthesis of these lipids[1-3] in a bid to restore the barrier status of skin. Cholesterol synthesis is reported to be mainly responsible for the early phase of epidermal barrier repair[4]. Hence, the role of lovastatin (LVN), a competitive inhibitor of HMG-CoA reductase in enhancing the percutaneous permeation of indomethacin (IDN), a highly lipophilic drug with low transcutaneous permeation[5,6] was investigated.

Lovastatin (Ranbaxy, New Delhi) and indomethacin (Jagsonpal, New Delhi) were gift samples. Cholesterol estimation kit was purchased from SPAN Diagnostics (Surat, India). Dorsal hairs of Wistar rats were removed by an electric razor and the skin excised after 24 h. Freshly excised skin was used for all experiments. Cholesterol (CHL) leaching ability of methanol-chloroform or acetone-

* For Correspondence