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COMMUNICATION

Product Development Studies on the Tablet Formulation of Ibuprofen to Improve Bioavailability

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ABSTRACT

To improve the bioavailability of ibuprofen, a thorough preformulation trial was undertaken. As a part of these studies, particle size of the drug, solubility–pH profile, and pH–partition coefficient profile were studied. The probability of improving solubility by solid dispersion technique was also investigated. The effects of different binding agents and incorporation of various proportions of sodium lauryl sulfate on the release rate of ibuprofen were also studied. The in vitro release profiles of the developed tablets showed superiority over the popular marketed tablets.

INTRODUCTION

Ibuprofen is one of the safest and most potent nonsteroidal anti-inflammatory agents available in the market. However, it suffers from potential bioinequivalence problem (1), compounded by the limited aqueous solubility, gastrointestinal (GI) side effects (2), and hardening of the tablets on aging. Therefore, thorough preformulation studies were undertaken to minimize these problems.

EXPERIMENTAL

Materials

Ibuprofen IP was generously supplied by Cipla Laboratories, Bombay, India. All other chemicals were of analytical grade obtained commercially and were used as such without further purification.

Methods

Step 1: Particle Size Analysis

It is recognized that poorly water-soluble drugs such as ibuprofen, which show a dissolution rate-limiting step in the absorption process, will be more readily bioavailable when administered in a finely subdivided state rather than as a coarse material. Particle size also plays a role in the homogeneity of the final tablet; fine materials are expected to be distributed more uniformly. Size and shape influence the flow and the mixing efficiency of powder and granules. Size can also be a factor in stability.

Because of these significant roles played by particle size, it is important to decide on a desired size range, and then to maintain and control it. For the analysis of particle size, the optical microscopic method was adopted.

Step 2: Solubility–pH Profile

Aqueous solubility is a useful biopharmaceutical parameter. Ibuprofen is practically insoluble in water (3). The bioavailability or absorption problems are often present when the aqueous solubility of a drug is less than 1 g/100 ml over the pH range 1–8 (4). Conversely, the solubility of acidic or basic drugs is pH dependent. Therefore, to get an accurate value, the solubilities of ibuprofen at 37°C in distilled water, in acid buffers of pH 1.2 and 2.0, and in phosphate buffers of pH 4.0, 5.5, 6.0, and 7.0 were measured.

Step 3: pH–Partition Profile

The measurement of the partition coefficient is an important preformulation activity because passive diffusion, a common mechanism of drug absorption, is very much dependent on the partition coefficient. Partition coefficients were determined according to the Hansch method (5) between *n*-octanol saturated with buffer and buffer saturated with *n*-octanol. Commercial *n*-octanol for purification was thoroughly washed with 10% (w/v) sodium hydroxide solution followed by 5 N sulfuric acid, and finally with 10% (w/v) sodium bicarbonate solution. The washed sample was dried over anhydrous sodium sulfate overnight and distilled under reduced pressure. The mid-fraction of the distillate was collected and used.

The equilibrium concentrations of ibuprofen were measured spectrophotometrically and the partition coefficients (P) were calculated using the formula: P = conc. of drug in *n*-octanol/(1-μ). conc. of drug in water, where μ is the degree of ionization. The calculated values for pH and P, respectively, are as follows: 1.2, 52.00; 2.0, 92.08; 4.0, 75.70; 4.5, 90.00; 5.5, 84.40; 6.0, 60.70; and 7.0, 20.83.

Step 4: Feasibility Studies for Exploiting Solid Dispersion Technique to Improve the Dissolution

For drugs whose GI absorption is rate limited by the dissolution process, reduction of the particle size generally increases the rate of absorption and total bioavailability, and for this purpose ibuprofen was formulated as solid dispersion. Both melting method (6) and solvent method (7,8) were employed. The prepared formulations with polyethylene glycol (PEG) 4000 and polyvinyl pyrrolidone (PVP) were passed through a no. 80 sieve. The *in vitro* dissolution studies were done by USP XXII rotating basket method using 500 ml 0.1 N HCl solution as dissolution media, i.e., under nonsink condition. The dissolution rate data were compared with the physical mixture of drug and carrier in the same ratio and with control containing the same amount of ibuprofen (200 mg) only.

Step 5: Tablet Formulation and In Vitro Evaluation

Thorough preformulation trials were undertaken to study the effects of various binding agents, diluents, or buffering agents (9), and presence of surfactants in the dissolution medium (10), on the release rate of ibuprofen from the formulated granules. Thirteen formulations were developed as shown in Table 1 and the granules were prepared by the wet granulation method using the components after they were passed through 60 mesh. Four hundred milligrams of 12 mesh granules of each batch containing 200 mg of ibuprofen was taken for the dissolution study done by the same method.

Based on the experimental data of the preformulation trials, two tablet formulations (numbers 12 and 13) were developed and the release profiles of ibuprofen from these developed formulations were compared with the three popular brands of marketed tablets.

Table 1

Composition of Formulations

	Formulation Numbers												
Ingredients (mg)	1	2	3	4	5	6	7	8	9	10	11	12	13
Ibuprofen	200	200	200	200	200	200	200	200	200	200	200	200	200
Magnesium trisilicate	150	–	–	–	–	–	150	150	150	100	–	100	–
Starch	50	50	50	50	50	50	50	50	50	40	40	40 + 20	40 + 20
PVP sol (10% w/v in 90% ethanol)	q.s	q.s	q.s	q.s	q.s	q.s	–	–	–	q.s	q.s	q.s	q.s
Lactose	–	150	–	–	–	–	–	–	–	–	–	–	–
Calcium carbonate	–	–	150	–	–	–	–	–	–	–	–	–	–
Sodium bicarbonate	–	–	–	150	–	–	–	–	–	40	40	40	40
Dicalcium phosphate	–	–	–	–	150	–	–	–	–	20	20	20	20
Dried $Al(OH)_3$	–	–	–	–	–	150	–	–	–	–	100	–	100
MC sol 10% (w/v)	–	–	–	–	–	–	–	–	q.s	–	–	–	
Sodium carboxy-methylcellulose sol 10% (w/v)	–	–	–	–	–	–	–	q.s	–	–	–	–	–
Sodium lauryl sulfate	–	–	–	–	–	–	–	–	–	–	–	2.5	2.5
Talc	–	–	–	–	–	–	–	–	–	–	–	5	5
Magnesium stearate	–	–	–	–	–	–	–	–	–	–	–	2.5	2.5
Starch paste 10% (w/v)	–	–	–	–	–	–	q.s	–	–	–	–	–	–

q.s: Quantity sufficient for manufacture.

RESULTS AND DISCUSSION

In step 1, it was observed that no specific shape of the particles predominated and the arithmatic mean diameter of the particles was 5.16 μm.

In step 2, it was observed that the aqueous solubility of ibuprofen at 37°C was only 0.13 g/liter, whereas at acidic pH of 1.2 it was 0.3 g/liter. Thereafter, the solubility gradually decreased and reached a minimum value of 0.075 g/liter at pH 2.0, and then there was a gradual increase in solubility up to pH 4.0 where this value was 0.35 g/liter. Then up to pH 5.5 there was no significant rise in the solubility (0.375 g/liter). There was then a sharp rise in solubility; at pH 6.0 and 7.0 it was 2.325 g/liter and 5.6 g/liter, respectively. Above pH 7 it was freely soluble in water. As is expected, the solubility studies indicate that the solubility of ibuprofen is pH dependent.

In step 3, the *n*-octanol–water partition coefficient was very much in favor of the organic phase. From the experimental data it was observed that the lipophilic character of the drug gradually decreases with the increase in pH. Lipid solubility was maximum at pH 2–4.5, indicating greater passive transport. However, aqueous solubility in that range is too low, which is an important factor for the absorption of the drug, because before absorption the drug must go into solution. Hence, if the aqueous solubility of the drug is increased, it will result in greater absorption, because although it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate must not be neglected.

In step 4, because of the high dose of ibuprofen (200–400 mg thrice daily) it was not possible to formulate a dispersion with low drug content generally used in solid dispersion formulation (5–10%). A 20% ibuprofen–PEG 4000 dispersion prepared by coprecipitation as well as fusion methods gave marginally better results as compared to the control and physical mixture (Fig. 1). An interesting observation was seen for ibuprofen–PEG 4000 physical mixture, in which after an initial improvement of the dissolution rate over the first 10 min, dissolution was found to be lower than the control. Perhaps some sort of eutexia took place; the matter requires further investigation. Ibuprofen–PVP solid dispersion prepared by solvent method (drug:PVP 1:2) as well as the physical mixture showed a marked improvement in the dissolution rate which was found to be considerably higher than the control (Fig. 1) at the end of

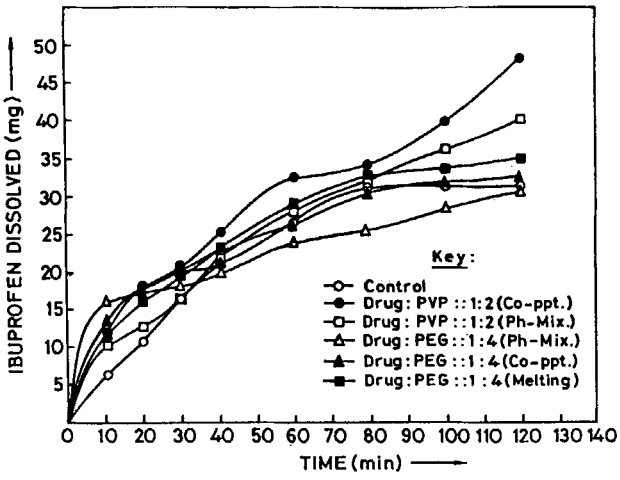

Figure 1. The dissolution profiles of ibuprofen solid dispersions with PEG 4000 and PVP in 0.1 N HCl.

2 hr during which the experiment was conducted. It may be safely recommended that a routine inclusion of PVP in ibuprofen formulation as excipient would lead to a superior formulation with faster release rate and better overall bioavailability.

In step 5, the effects of binding agents, buffering agents, and presence of sodium lauryl sulfate in dissolution media on the dissolution rate of ibuprofen were studied. PVP as binder gave excellent result (Fig. 2) as was expected from the earlier studies in step 4. Out of the four binders used in the formulations, starch paste could be used as an effective substitute for PVP. Ibuprofen granules prepared with different buffering agents

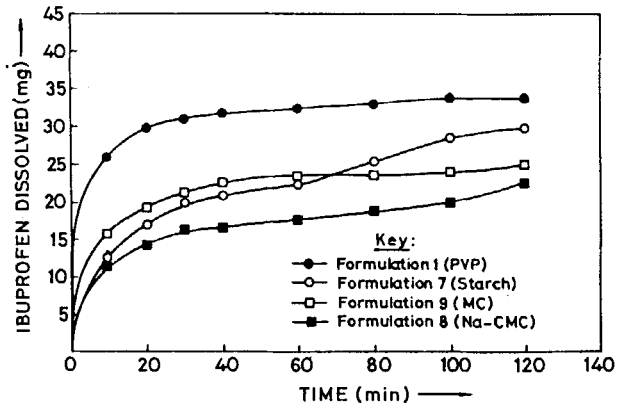

Figure 2. The dissolution profiles of ibuprofen granules prepared with various binding agents.

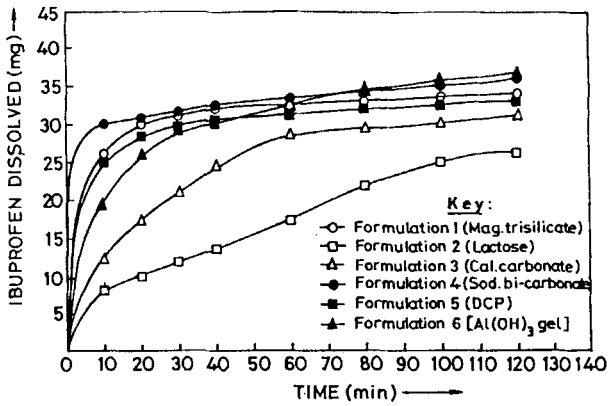

Figure 3. The dissolution profiles of ibuprofen granules prepared with various diluents.

showed a gross difference in release pattern (Fig. 3). A moderate-to-good release of ibuprofen was obtained with aluminum hydroxide, sodium bicarbonate, and magnesium trisilicate. It was observed that the formulation containing sodium bicarbonate liquified during granulation stage, perhaps because of some acid–base reaction. A combination of excipients (formulation numbers 10 and 11) with PVP binder showed a marked improvement in the dissolution rate which was found to be considerably better with the presence of SLS in the dissolution fluid (Fig. 4). A wide variation in the dissolution

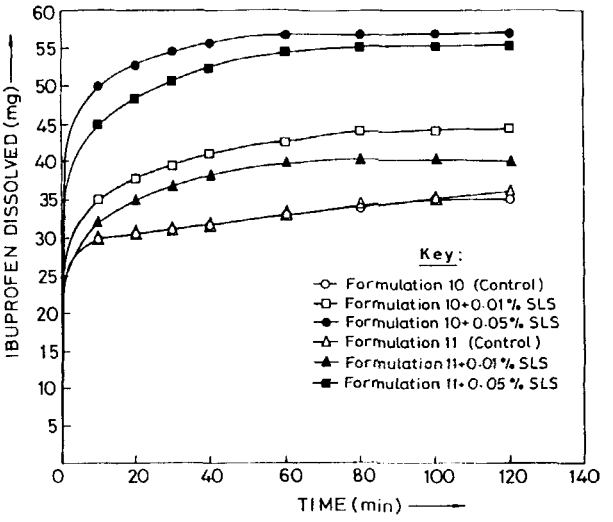

Figure 4. Effect of sodium lauryl sulfate on dissolution profiles of ibuprofen granules.

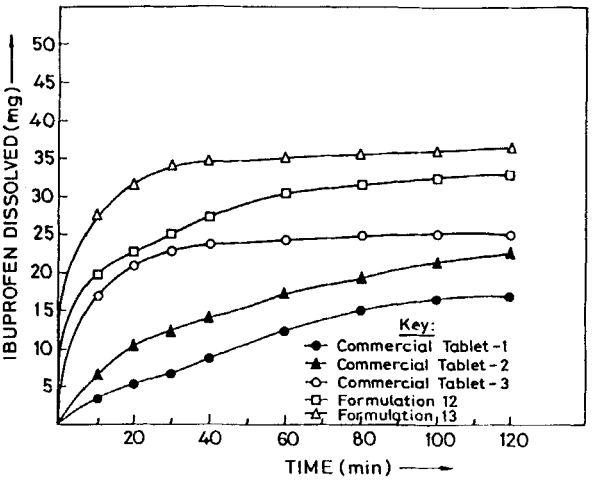

Figure 5. Comparison of dissolution profiles among commercial tablets and developed tablets.

rates of commercial tablets was observed (Fig. 5). Considering all of the dissolution studies of prepared granules, tablet formulation numbers 12 and 13 were developed and compared with the marketed tablets available for study (Fig. 5). It was observed that the developed formulations showed better result than the leading brands of marketed tablets.

From these investigations, it may be safely concluded that the developed tablet products (formulation numbers 12 and 13) are superior to the available market products.

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