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RESEARCH PAPER

Formulation and Stability Evaluation of Ketoprofen Sustained-Release Tablets Prepared by Fluid Bed Granulation with Carbopol® 971P Solution

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ABSTRACT

The objectives of the present study were: (1) to investigate the possibility of using a Carbopol polymeric solution as granulating agent by the fluid bed granulating process; (2) to select a suitable method of tabletting for sustaining the release of ketoprofen for 12 hr; (3) to perform stability studies according to International Committee on Harmonization (ICH) guidelines and photostability on ketoprofen SR tablets; (4) to study the influence of the storage conditions on release kinetics and melting endotherm of ketoprofen; and (5) to predict the shelf-life of the ketoprofen SR tablets. Tabletting ingredients were ketoprofen, anhydrous dicalcium phosphate, Carbopol® 971P, talc, and magnesium stearate. Carbopol® 971P solution (0.8% w/v) was used as a granulating solution in the fluid bed granulator. For comparative evaluation, tablets were also prepared by direct compression and wet granulation, and subjected to dissolution. Tablets prepared by fluid bed granulation technique were stored in incubators maintained at 37, 40, 50, and 60°C, 40°C/75% RH, 30°C/60% RH, and 25°C/60% RH, and in a light chamber with light intensity of 600 ft candle at 25°C. Melting endotherms were

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obtained for the drug as well as the tablets during stability studies by differential scanning calorimetry. Tablets prepared by fluid bed granulation technique prolonged the release of ketoprofen better than tablets obtained by direct compression and wet granulation. Further, it complied with the requirements of ICH guidelines for stability testing. Higher temperature and humidity (40 ± 2°C/75% RH, 40°C, 50°C, and 60°C) adversely affected the rate and extent of the dissolution. Ketoprofen SR tablets stored in amber-colored bottles demonstrated a good photostability for 6 months at 600 ft candle. The shelf-life of the formulation was predicted as 32 months.

Key Words: *Stability; Carbopol 971P; Fluid-bed granulation; Sustained release*

INTRODUCTION

Polymers are used to control the release of drugs from different dosage forms administered orally. Carbopol® 934P, 974P, and 971P resins are generally known as carbomers. These polymers readily hydrate, absorb water, and swell quickly. Since these polymers are crosslinked and differ to a certain extent in crosslinking, they are good candidates for use in controlled-release drug delivery systems. A matrix-type dyphylline tablet containing Carbopol® 971 as controlled-release agent showed a zero-order release.[1] Several other investigators[2,3] studied the release kinetics of therapeutic agents from carbomer matrix tablets and found that these matrices exhibited a zero-order drug release at several different concentrations of polymers. Carbopol polymers have also been reported for use in oral formulations such as tablets and capsules for modifying the release pattern, topical products such as lotions, creams, and gels to modify rheology of water-based systems, and in suspensions and emulsions to stabilize, suspend, and modify flow characteristics.[4] Due to their bioadhesive properties, Carbopol polymers have also been used in mucous membrane-targeted formulations such as buccal, nasal, intestinal, vaginal, and rectal applications.[4] However, the use of Carbopol polymeric solutions as granulating agent by the fluid bed process has not been reported so far.

Ketoprofen, 2-(2-benzoylphenyl) propionic acid, is a non-steroidal anti-inflammatory drug poorly soluble in water in its unionized form. It exists as a crystalline solid, melting at 96°C and rapidly absorbed when administered orally. Ketoprofen was found to be relatively stable in aqueous injections and the shelf-life (90% of initial drug) was determined as 228 days.[5] Ketoprofen has been successfully formulated as solid dispersions, matrix tablets, microspheres, and suppositories.[6–9] Solid dispersions of ketoprofen prepared with polyethylene glycol 6000 and poloxamer 188 were evaluated,[6] and not only was the dissolution improved, but also the formulation stored under ambient conditions was stable and no change in dissolution behavior was observed even after 12 months. Batzdorf et al.[10] reported a ketoprofen instability in cyclodextrin ketoprofen physical mixture, though the drug was stable in inclusion complexes.

Dicalcium phosphate has been widely used as an excipient in pharmaceutical dosage form due to its low hygroscopicity, excellent flowability and compressibility, low cost, and physical and chemical stability.[11–13] The compatability of dicalcium phosphate with several drugs and excipients has been studied extensively.[14,15] Landin et al.[16] investigated the long-term chemical stability of acetyl salicylic acid in tablets prepared with different particle size fractions of a commercial brand of dicalcium phosphate dihydrate and found that degradation of aspirin to salicylic acid was linearly correlated with mean particle size of the excipient. Follonier and Doelker[17] investigated the accelerated aging test for predicting short-term change of mechanical strength of compressed tablets and concluded that an accelerated aging test can be helpful for adjusting the tabletting machine setting to reach the target crushing strength in production. Differential scanning calorimetry was used to investigate the physicochemical compatibility between labetalol hydrochloride and dicalcium phosphate, and they were found to be compatible.[18]

Fluid bed granulation has been reported to offer distinct advantages over conventional tray drying

for tablet granulations.[19] The only requirements are that the granules are not so wet that they stick together on drying, and that the dried product is not very friable to produce excessive amounts of fine particles through attrition. Nellore et al.[20] investigated the development of model extended-release matrix formulations for metoprolol tartarate sensitive to manufacturing variables to serve as the scientific basis for regulatory policy development on scale-up and post-approval changes for modified-release dosage form. They concluded that fluid bed granulation is the process of choice for critical and non-critical formulation and processing variables. The objectives of the present study were: (1) to investigate the possibility of using a Carbopol polymeric solution as granulating agent by the fluid bed granulating process; (2) to select a suitable method of tabletting for sustaining the release of ketoprofen for 12 hr; (3) to perform stability studies according to International Committee on Harmonization (ICH) guidelines and photostability on ketoprofen SR tablets; (4) to study the influence of the storage conditions on release kinetics and melting endotherm of ketoprofen; and (5) to predict the shelf-life of the ketoprofen SR tablets.

MATERIALS AND METHODS

Ketoprofen was purchased from Sigma Chemicals, St. Louis, MO. Anhydrous dicalcium phosphate was purchased from Penwest, Patterson, NY. Carbopol® 971P was obtained as a gift sample from BFGoodrich Performance Materials, Cleveland, OH. Cab-O-Sil® was obtained as a gift sample from Cabot Corp., Tuscola, IL. Monobasic potassium phosphate, sodium hydroxide, and magnesium stearate were purchased from Spectrum Chemicals, Gardena, CA. Glycerin, ammonium nitrate, sodium chloride, and 0.45-μm syringe filters were purchased from Fisher Scientific. Ethyl alcohol was purchased from VWR Scientific. Deionized water was used in the preparation of phosphate buffer.

Preparation of Ketoprofen Sustained-Release Tablets

Ingredients for the preparation of tablets by direct compression are given in Table 1. Ketoprofen, Carbopol® 971P, and anhydrous dicalcium phosphate were passed through sieve #25, except Cab-O-Sil® and magnesium stearate that passed through sieve #30.

Table 1

Composition of Ketoprofen SR Tablets

Ingredients	% w/w
Ketoprofen	20.0
Carbopol® 971P	9.75
Dicalcium phosphate	69.0
Cab-O-Sil®	0.5
Magnesium stearate	0.5

Direct compression: ketoprofen, Carbopol® 971P, and dicalcium phosphate were mixed uniformly in a V-blender and mixed with Cab-O-Sil® and magnesium stearate.

Wet granulation: ketoprofen, Carbopol® 971P, and dicalcium phosphate were mixed uniformly in a V-blender and water equivalent to 0.8% of the total weight was sprinkled over the powder mixture. The moist mass was passed through sieve #8 and dried at 40°C for 1 hr. The dried granules were passed through sieve #12 and mixed with magnesium stearate and Cab-O-Sil®.

Fluid bed granulation: ketoprofen, Carbopol® 971P, and dicalcium phosphate were mixed uniformly in a V-blender and the granulating solution (0.8% Carbopol® 971P solution) was sprayed at 40°C. The granules were dried at 60°C. Dried granules were mixed with Cab-O-Sil® and magnesium stearate. The powder mixture prepared from direct compression, granules from wet granulation and dry granulation were compressed by a Korsch rotary tablet press (Korsch America Inc., Peapack, NJ) using 3/8-inch toolings. The average weight of tablets was 300 mg, in which the ketoprofen content was 60 mg.

Stability Studies

Ketoprofen SR tablets were packed in amber-colored 100-mL glass containers with polypropylene closures. Containers simulated actual packaging and the closures were secured tightly on the containers. Each container consisted of 30 ketoprofen SR tablets. They were stored in incubators maintained at 37, 40, 50, and 60°C (accelerated stability studies), 40°C/75% RH, 30°C/60% RH, and

25°C/60% RH (ICH guidelines), and in a light chamber with light intensity of 600 ft candle at 25°C (Hotpack Corporation, Philadelphia, PA). Appropriate salts were used to provide humidity in desiccators. At each time point, one container was taken out from the respective storage condition and subjected to content, dissolution, and thermal analysis. Ketoprofen SR tablets were analyzed periodically for 12 months in the case of ICH guidelines and for 6 months in the case of accelerated stability studies.

Extraction and Analysis of Ketoprofen

Histological grade ethyl alcohol was used for extraction of ketoprofen. At least three tablets were used for estimating the ketoprofen content. Initially ketoprofen tablets were triturated with 1 mL of glycerin until a smooth paste was formed. About 20 mL of ethyl alcohol was added, triturated well, and transferred to a 500-mL standard flask. The mortar and pestle were rinsed with ethyl alcohol, which was transferred to a 500-mL flask, and the volume made up to 500 mL with ethyl alcohol. It was sonicated for 6 hr for complete extraction of ketoprofen. Water in the sonicator was changed often to avoid heat building up. Five milliliters of alcohol extract was filtered with a 0.45-μm syringe filter and the first few milliliters were discarded. The filtrate was diluted further and the absorbance was measured at 252 nm in a UV spectrophotometer (HP 8451A Diode Array Spectrophotometer, Hewlett Packard, Wilmington, DE).

Dissolution Studies

Dissolution studies were performed using the USP 23 paddle method (50 rpm, 37 ± 0.5°C) in phosphate buffer medium (900 mL, pH 7.4) in a Vandercamp® six-spindle dissolution tester (VanKel Technology Group, Cary, NC). Samples were collected periodically for 24 hr, diluted suitably, and analyzed for ketoprofen at 252 nm by UV spectrophotometer.

Thermal Analysis

Differential scanning calorimetry (DSC) scans were performed using a DSC 4 (Perkin Elmer, Norwalk, CT) to obtain melting endotherms of ketoprofen per se and SR tablets. A ketoprofen tablet was ground and powder equivalent to 2 mg of ketoprofen was subjected to thermal analysis. Samples were heated from 50 to 150°C at a rate of 10°C/min in nitrogen atmosphere. Thermograms were normalized and autoscaled.

RESULTS AND DISCUSSION

Preparation of Ketoprofen Sustained-Release Tablets

The objectives of the study were to compare wet granulation, fluid bed granulation, and direct compression techniques in the preparation of ketoprofen SR tablets as well as to focus on one particular technique for the development of ketoprofen SR tablets. On that basis, tablets prepared from all three techniques were subjected to dissolution and the tablets prepared by fluid bed granulation were selected for stability studies. Ketoprofen SR tablets prepared by wet granulation and direct compression exhibited 7- and 8-hr release (Fig. 1) and disintegrated within 2 hr. However, tablets prepared with Carbopol® 971P as granulating agent exhibited 12-hr release and did not completely disintegrate even after 12 hr. A typical usage level for Carbopol resins in tablets is 10–30% as a controlled-release agent.[21] However, various factors such as duration of sustained release, solubility of the drug, excipient other than Carbopol resins, and granulation technique play an important role. Presence of Carbopol® 971P in granulating solution facilitated bridging during granulation and compression. Carbopol® 971P has primarily been used as a sustained-release agent. In this study it was incorporated not only as sustained-release agent, but also as granulating agent. Fluid bed granulation is far superior to wet granulation due to two basic differences. Firstly, the granulating fluid is finely atomized by the compressed air before it comes into contact with the powder, thus facilitating a more uniform and extensive distribution of granulating fluid in the powder. Secondly, the fluid bed process comprises all unit operations: spraying of granulating fluid, mixing, drying until optimum moisture content is reached.

Ketoprofen Content

Several investigators identified the effect of dicalcium phosphate dihydrate on the stability of therapeutic agents. Dulin[22] reported that acid labile drugs such as bisoprolol degraded due to the acidic

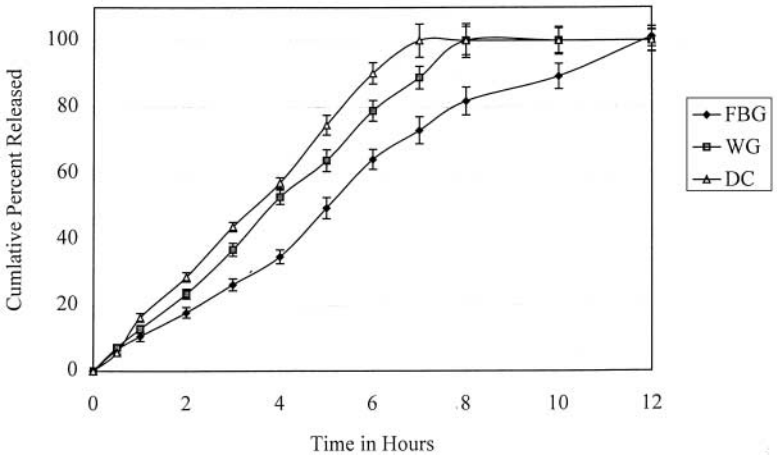

Figure 1. Dissolution profile of ketoprofen tablets prepared by direct compression (DC), wet granulation (WG), and fluid bed granulation (FBG). Average and standard deviation of three readings.

Table 2

Amount of Ketoprofen (%) Remaining in SR Tablets Stored Under Conditions Recommended by ICH

Time	40°C/75% RH	30°C/60% RH	25°C/60% RH
Initial	100.00	100.00	100.00
15 days	99.88	99.50	99.88
1 month	99.55	99.10	99.82
3 months	97.39	97.57	97.90
6 months	96.08	96.94	97.46
9 months	96.64	97.36	97.72
12 months	95.35	97.38	98.45

environment created by the dicalcium phosphate dihydrate. However, in the present study anhydrous dicalcium phosphate was incorporated and ketoprofen is stable in acidic conditions. The amounts of ketoprofen (%) in the tablets stored under conditions according to ICH guidelines and at elevated temperature are given in Tables 2 and 3, respectively. Less than 5% of the ketoprofen was lost during 12 months in the tablets stored at $40 \pm 2^{\circ}C/75\%$ RH, $30 \pm 2^{\circ}C/60\%$ RH, and $25 \pm 2^{\circ}C/60\%$ RH. The predicted shelf-life according to an Arrhenius plot for 90% ketoprofen content was 67 months, and for 95% ketoprofen 32 months. Ketoprofen appeared to be stable in the storage conditions tested.

Dissolution Studies

The fit factors f_1 and f_2 are two indices that compare the dissolution profiles of a reference formulation to that of a test formulation. These fit factors allow the systematic comparison of dissolution profiles at different time points. As discussed earlier, based on the release kinetics, long-term stability studies and short-term accelerated stability studies were conducted only for tablets prepared by fluid bed granulation. The dissolution profile of fresh tablets was considered as a reference profile, wherein the dissolution profile of sample tablets collected periodically during the stability studies was considered as the test profile. The f_1 and f_2 values were computed by the equations given below:[23]

$$f_1 = \frac{\sum_{t=1}^{n} R_t - T_t}{\sum_{t=1} R_t} \times 100$$

$$f_2 = 50 \log \left\{ \left[1 + 1/n \sum_{t=1}^{n} W_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t is the reference drug content at time point t and T_t is the test drug content at time point t, n is the number of sampling points, and W_t is an optional weight factor. Since all the dissolution time points were treated equally, W_t was taken as 1. The average

Table 3

Amount of Ketoprofen (%) Remaining in SR Tablets Stored Under Different Storage Conditions

Time	60°C	50°C	40°C	37°C	Room Conditions	Light Chamber
Initial	100.00	100.00	100.00	100.00	100.00	100
15 days	99.50	98.74	99.12	99.69	99.90	100
1 month	98.43	98.38	98.89	98.99	99.86	98.46
2 months	94.76	98.22	97.94	98.85	99.31	98.04
3 months	92.34	97.12	97.86	97.76	99.24	97.60
6 months	88.01	93.31	96.15	97.90	99.13	98.04

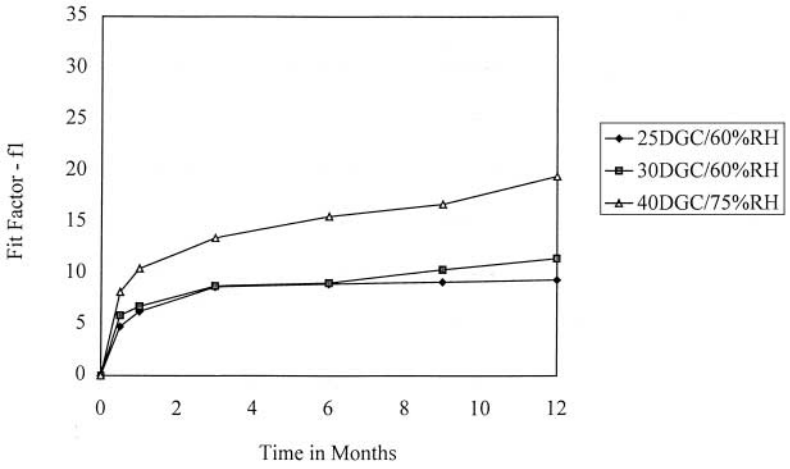

Figure 2. Comparison of fit factor f_1 for ketoprofen SR tablets stored under conditions recommended by ICH.

difference between the reference and test profiles is represented linearly by the test fit factor, f_1 and exponentially by the fit factor, f_2. Fit factor f_1 is 0 when the test and reference profiles are identical and increases proportionally with dissimilarity between the two profiles. Fit factor f_2 is 100 when the test and reference profiles are identical and decreases proportionally with dissimilarity between the two profiles.[23] The dissolution data points were taken at 0.5, 1, 2, 4, 6, 8, and 12 hr. In the calculation of f_2 values, the difference between the amount of drug released by reference and test formula at a given time point is $(R_t - T_t)$. The sum of squared difference is given as $\sum W_t(R_t - T_t)^2$. The f_1 and f_2 values were calculated using Microsoft Excel. The rate and extent of dissolution of ketoprofen from tablets stored at different conditions decreased with time. Therefore, an increase in f_1 or decrease in f_2 reflects a decrease in rate and extent of dissolution.

The f_1 and f_2 values of ketoprofen SR tablets for all stability conditions are shown in Fig. 2 through 5. The rate and extent of dissolution decreased in the tablets stored at 40 ± 2°C/75% RH, 40°C, 50°C and 60°C. The FDA recommends the use of f_2 values to compare the dissolution of two different products. If the value falls below 50, the dissolution profiles of the two products are considered to be significantly different from each other. The same principle was used to check at what time point the dissolution profile was significantly different from the initial dissolution profile. The dissolution profiles of the tablets stored at 50°C and 60°C differed from the fresh tablets in the first month itself. The dissolution profiles of the tablets stored at room temperature and in a light chamber remained similar to that of fresh tablets. There are several reports on the use of f_2 values in stability studies.[1,24] Tablets stored under these conditions did not disintegrate during dissolution after a month of storage. During

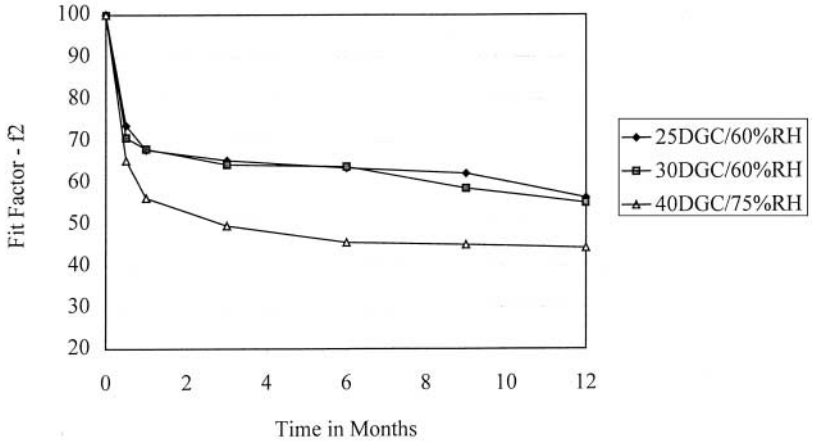

Figure 3. Comparison of fit factor f_2 for ketoprofen SR tablets stored under conditions recommended by ICH.

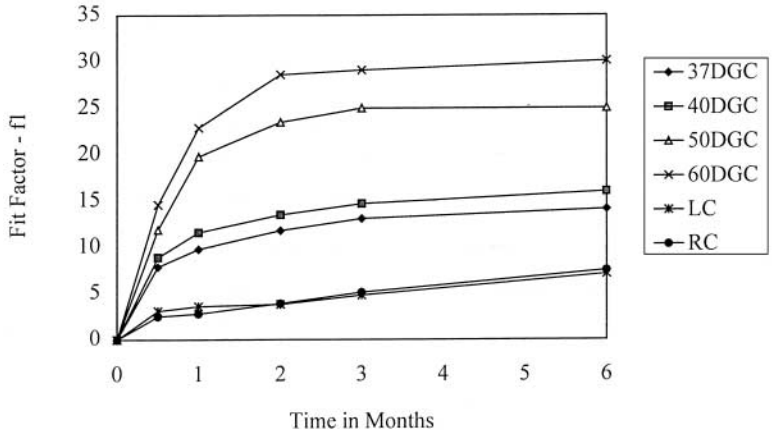

Figure 4. Comparison of fit factor f_1 for ketoprofen SR tablets stored under different storage conditions.

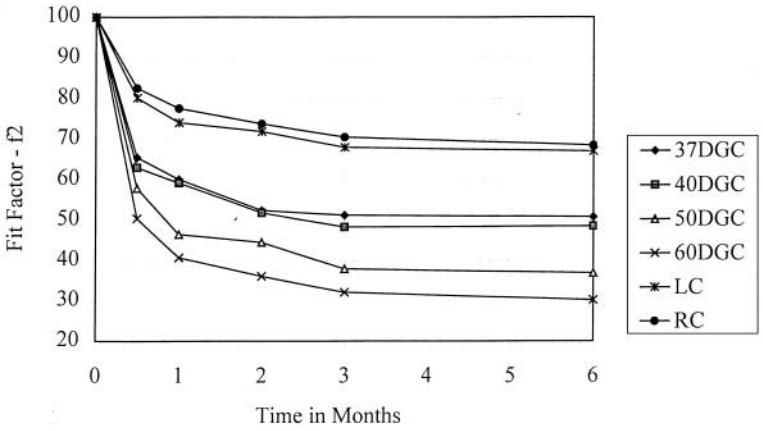

Figure 5. Comparison of fit factor f_2 for ketoprofen SR tablets stored under different storage conditions.

storage in these conditions, the tablets might have lost the moisture content (retained during granulation) and hardened. Therefore, during dissolution the tablets took more time for hydration, and ionic repulsion of the polymer (since the dissolution medium was phosphate buffer at pH 7.2) to manifest on a macro level as swelling. Since the tablet remained intact without any disintegration or deaggregation, the surface area did not increase to augment the dissolution as happened with the fresh tablets. Intact tablets offered a lengthy pathway for the drug to diffuse across the swollen gel. All these effects contributed to the decrease in rate and extent of dissolution. However, the dissolution profile of tablets stored under other conditions remained very close to the dissolution profile of fresh tablets.

Thermal Analysis

Interaction between drug and excipient may be observed by interpreting the thermal events displayed on a DSC scan, such as the appearance or elimination of an endothermic or exothermic peak. Changes in peak shape, peak onset, or peak maximum temperature and relative peak height might also be considered.[25] The melting point of ketoprofen obtained from the thermograms of DSC for the tablets stored under different conditions are given in Tables 4 and 5. Except at room conditions and in a light chamber, a decrease in melting point was observed in the tablets stored in all other conditions. The melting endotherm of ketoprofen tablets at the initial time point was 92.77°C. The shift in the endotherm was observed with time, and after 3 months, the direction of the shift was reversed. This pattern of melting point endotherm suggests that the interactions between the drug and excipients with time are reversible.

Table 4

Melting Point (°C) of Ketoprofen and SR Tablets Stored Under Conditions Recommended by ICH

Time	40°C/75% RH	30°C/60% RH	25°C/60% RH
Initial	92.77	92.77	92.77
1 month	88.69	89.59	91.39
3 months	90.5	89.97	89.5
6 months	93.18	90.8	93.58
12 months	92.5	92	93.4

Photostability

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals. A drug can be affected chemically by radiation of a particular wavelength only if it absorbs radiation at that wavelength and the energy exceeds a threshold. In the present study, radiation in the photostability chamber mimicked room light. No significant decrease in ketoprofen was observed in the tablets stored in the light chamber (Table 3). Ketoprofen is photolytic and must be protected from light. The amber-colored bottles protected the tablets for the duration of this study.

CONCLUSIONS

Among wet granulation, direct compression, and fluid bed granulation techniques employed for tabletting the ketoprofen SR tablets, fluid bed granulation provided 12-hr ketoprofen sustained-release tablets. Tablets provided by fluid bed granulation (0.8% Carbopol® 971P solution used as granulating

Table 5

Melting Point (°C) of Ketoprofen and SR Tablets Stored Under Different Storage Conditions

Time	60°C	50°C	40°C	37°C	Room Conditions	Light Chamber
Initial	92.77	92.77	92.77	92.77	92.77	92.77
1 month	86.86	86.11	91.17	88.54	89.93	91.7
2 months	88.81	88.54	89.9	90.91	90.69	91.8
3 months	91.69	89.19	89.99	93.1	91.4	91.6
6 months	92.8	93.16	90.21	92.8	90.85	92

solution) complied with the requirements of ICH guidelines for stability testing. Higher temperature and humidity ($40 \pm 2^{\circ}C/75\%$ RH, $40^{\circ}C$, $50^{\circ}C$, and $60^{\circ}C$) adversely affected the rate and extent of dissolution of drugs. Ketoprofen SR tablets stored in amber-colored bottles demonstrated good photostability for 6 months at 600 ft candle. The shelf-life of the formulation was predicted as 32 months. Therefore Carbopol® 971P has been successfully used as a granulating agent to prepare ketoprofen sustained-release tablets.

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