Approaches for Improving the Stability of Ketorolac in Powder Blends

MICHAEL BRANDL[x], ADINA MAGILL, VARMA RUDRARAJU, AND MARC S. GORDON[‡]

Received May 3, 1995, from the *Pharmaceutical Research, Syntex Research, 3401 Hillview Avenue, Palo Alto, CA 94304.* Accepted for publication July 12, 1995[⊗]. [‡]Present address: Inhale Therapeutic Systems, 1001 East Meadow Circle, Palo Alto, CA 94303.

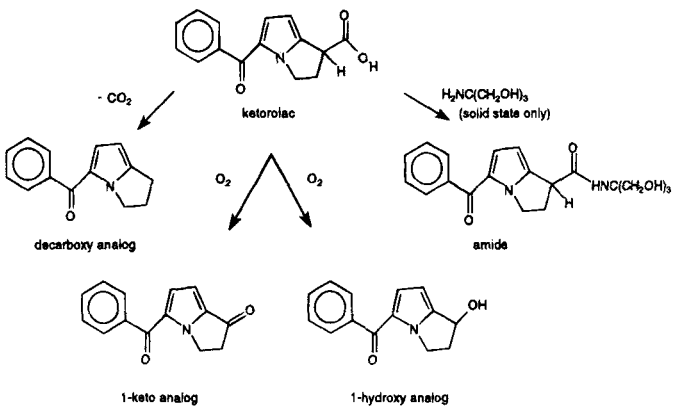
Abstract □ Methods for improving the stability of ketorolac powder blends under elevated humidity and temperature conditions were investigated. The approaches that were examined for potentially increasing the stability of ketorolac were varying the ketorolac salt form, altering the excipient ratios, and adding antioxidants or pH modifiers to the formulation. The ketorolac powder blends were stored for 3 months at 75% relative humidity (RH) and 40, 50, and 60 °C. The results showed that the salt form of ketorolac had a large impact on stability after 3 months of storage at 50 °C/75% RH. The calcium salt powder blend and the free acid powder blend exhibited only 0.2% and 0.5% drug loss, respectively, whereas the tromethamine salt powder blend showed a 10.2% drug loss. Varying the ratios of lactose, microcrystalline cellulose, and croscarmellose sodium in the powder blends of ketorolac tromethamine showed that croscarmellose sodium and microcrystalline cellulose destabilized ketorolac. Addition of propyl gallate (1% w:w) to ketorolac tromethamine powder blends increased the stability of the ketorolac significantly. Addition of pH modifiers caused a modest improvement in the stability of ketorolac.

Ketorolac tromethamine (Toradol) is a nonsteroidal anti-inflammatory drug[1] which exhibits potent analgesic, anti-inflammatory, and antipyretic effects. In clinical studies, ketorolac tromethamine is an effective analgesic when administered intramuscularly and orally.[2-4] The ketorolac tromethamine oral tablet core consists of 10 mg ketorolac tromethamine and 190 mg of a mixture of lactose, microcrystalline cellulose, and magnesium stearate.[5]

The degradation of ketorolac tromethamine in solution has been studied under thermal and photochemical stress conditions.[6,7] Scheme 1 illustrate the solution degradation products (decarboxy, 1-keto, and 1-hydroxy analog) that also form in the solid state. In the solid state, condensation of ketorolac with tromethamine to form an amide also occurs.[8] To explore methods of improving the stability of powder blends of ketorolac when exposed to stress conditions an investigation was conducted consisting of three studies: a study of the salt forms that have been used clinically (tromethamine, calcium, and free acid), a study of the effect of disintegrants and fillers (lactose, microcrystalline cellulose, and croscarmellose sodium) on the ketorolac tromethamine salt formulation, and a study of the effect of pH modifiers or antioxidants on the tromethamine salt formulation. This report provides the results obtained after 1 and 3 months of storage at 40 °C/75% RH, 50 °C/75% RH, and 60 °C/75% relative humidity (RH).

Methods

All salts of ketorolac and the free acid were crystalline and obtained from Syntex Chemicals. Other reagents were USP/NF grade. Powder blends (400 g) were prepared as follows: The pH-modifying agent or antioxidant, if present, was passed through a #80 mesh screen. Then using geometric dilution with 3 min blending time intervals, the pH-modifying agent or antioxidant, the drug substance, and 95% of the lactose (Foremost Whey Products) were blended together in a PK "V" blender. The lactose was the first material charged to the blender.



Scheme 1—Degradation pathways of ketorolac in solution and in the solid state.

This mixture was passed through an Erweka oscillator equipped with a #20 mesh screen. The microcrystalline cellulose (Avicel PH 102 from FMC Corp.) and, if required, the croscarmellose sodium (Ac-Di-Sol from FMC Corp.) were passed through an Erweka oscillator equipped with a #20 mesh screen. These components and the drug substance mixture were blended in the PK "V" blender for 15 min. The remaining 5% of the lactose was passed through a #20 mesh screen, blended with the magnesium stearate (Mallinckrodt Specialty Chemicals) in a miniature "V" blender for 1 min, and then combined with the drug mixture and mixed for 3 min in a PK "V" blender. The final blend was stored in two layers of tightly closed polyethylene bags and protected from light.

Approximately 200 mg of a powder blend was accurately weighed into a 20 mL vial. The vials were covered with aluminum foil that had several small holes punched in it and then enclosed in humidity chambers containing saturated sodium chloride to give a 75% RH environment.[9] The chambers were placed in 40, 50, and 60 °C ovens. After 1 and 3 months of storage, two vials of each powder blend were analyzed as follows.

Water (5 mL) was added to each vial and the mixture was sonicated for 5 min. Then 15 mL of methanol was added and the mixture was sonicated for an additional 10 min. This procedure solubilized all salts of ketorolac, leaving some residual excipients. A 2 mL portion was centrifuged (2500 rpm) for 10 min. The supernatant was diluted with mobile phase and assayed by HPLC. The percent ketorolac remaining was determined using the ratio of peak areas and the relative molar response factors for the known degradation products (Figure 1).

The HPLC system consisted of a SP 8700 ternary solvent delivery system from Spectra Physics and a Micromeritics model 725 autoinjector equipped with a 25 μL loop and a Kratos 757 variable wavelength detector. The detector was interfaced to a Macintosh SE computer and the data analyzed with Dynamax software from Rainin. The method used an Alltech Spherisorb ODS 1 column (250 × 4.6 mm i.d.) with an isocratic mobile phase consisting of water:methanol:acetic acid (40:59:1). A flow rate of 1.2 mL/min and detection at 254 nm were used. The method was validated for linearity and accuracy for ketorolac and its degradation products. A representative chromatogram of ketorolac and its degradation products is shown in Figure 1.

Results and Discussion

The effect of the various salt forms on the stability of ketorolac in a powder blend is summarized in Table 1. After

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1995.

© 1995, American Chemical Society and American Pharmaceutical Association

0022-3549/95/3184-1151$09.00/0

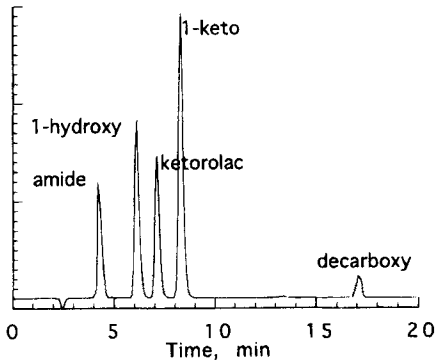


Figure 1—HPLC chromatogram of a mixture of the degradation products of ketorolac. The relative molar response factors for the amide, 1-hydroxy, 1-keto, decarboxy analog, and ketorolac are 1.0, 1.1, 1.6, 1.2, and 1.0, respectively.

Table 1—Effect of Salt Forms on Powder Blends of the Ketorolac Control Formulation Stored at 50 °C/75% RH for 1 and 3 months[a]

Salt	% Ketorolac[b]	
	1 month	3 months
Ketorolac tromethamine	95.2	89.8
Ketorolac calcium salt	100.0	99.8
Ketorolac free acid	99.7	99.5

[a] Formulation consists of the molar equivalent of 10 mg of ketorolac tromethamine, plus 34.5% lactose, 60% microcrystalline cellulose, and 0.5% magnesium stearate. [b] Runs are based on the average of two vials stored in two separate containers and two injections per vial.

Table 2—Stability of Ketorolac Powder Blends Stored at Elevated Temperatures and 75% RH for 3 months[a]

Ratio			% Ketorolac[b]		
Lactose	Microcrystalline Cellulose	Croscarmellose Sodium	40 °C	50 °C	60 °C
19.5	70.0	5.0	90.7	85.7	78.0
36.3	53.2	5.0		87.3	
53.2	36.3	5.0		87.6	
70.0	19.5	5.0	90.8	87.9	83.2
28.8	63.8	1.9		88.3	
45.7	45.7	3.1		87.5	
62.0	30.1	2.4		90.2	
24.5	70.0	0	93.4	89.8	80.4
34.5	60.0	0	94.5	89.4	83.9
54.8	39.7	0		91.6	
70.0	24.5	0	95.7	93.9	87.3

[a] Containing 5% w:w ketorolac and 0.5% w:w magnesium stearate. [b] Runs are based on the average of two vials stored in two separate containers and two injections per vial.

3 months of storage at 50 °C/75% RH the calcium salt, free acid, and tromethamine salt of ketorolac showed 0.2%, 0.5%, and 10.2% drug loss, respectively. The results with the different salt forms suggest that the oxidation reaction may be occurring in a dissolved water layer,[10] since the solubility in unbufferred water of the calcium salt (<1 mg/mL) and free acid (0.05 mg/mL), which exhibit significantly less degradation, are considerably lower than that of the tromethamine salt (>700 mg/mL).

The effect of varying the percentages of lactose (filler), microcrystalline cellulose (filler and disintegrant), and croscarmellose sodium (disintegrant) in powder blends of ketorolac tromethamine stored at 75% RH and 40, 50, and 60 °C, is summarized in Table 2. Croscarmellose sodium and microcrystalline cellulose both destabilized the powder blends at all temperatures studied.

Table 3—Effect of Antioxidants or pH Modifiers on Ketorolac Tromethamine Powder Blends Stored at 50 °C/75% RH for 1 and 3 months

Modifier	% Ketorolac[a]	
	1 month	3 months
Control formulation[b]	95.2	89.8
Propyl gallate (1% w:w)[c]	98.6	96.7
Propyl gallate (0.1% w:w)[c]	96.2	91.1
BHT (1% w:w)[c]	95.1	89.3
EDTA (1% w:w)[c]	94.8	88.2
Sodium carbonate (1% w:w)[c]	96.6	94.7
Sodium bicarbonate (1% w:w)[c]	96.5	94.4
Citric acid (1% w:w)[c]	96.3	93.3

[a] Runs are based on the average of two vials stored in two separate containers and two injections per vial. [b] Formulation consists of 5% ketorolac tromethamine, 34.5% lactose, 60% microcrystalline cellulose, and 0.5% magnesium stearate. [c] Added to control formulation.

The effect of 0.1% and 1% w:w propyl gallate, 1% w:w butylated hydroxytoluene (BHT), and 1% w:w disodium ethylenediaminetetraacetic acid (EDTA) on the stability of ketorolac tromethamine in the formulation is summarized in Table 3. The order for the stability of powder blends containing antioxidants after 3 months of storage at 50 °C/75% RH was propyl gallate (1%) ≫ propyl gallate (0.1%) > no antioxidant ≈ BHT (1%) ≈ EDTA (1%). The fact that propyl gallate stabilizes the powder blends, whereas BHT does not, gives further evidence that the decomposition reaction is occurring in a dissolved water layer since propyl gallate is more water soluble than BHT. The difference in propyl gallate 1% w:w and 0.1% w:w may partially reflect the microscopic nonhomogeneity of the propyl gallate in the powder blend when only 0.1% is used arising from excessive dilution.

Three pH-modifying agents were added to the control ketorolac tromethamine formulation at a 1% (w:w) concentration:sodium carbonate, sodium bicarbonate, and citric acid. Table 3 shows that each of the pH modifiers improved the ketorolac tromethamine stability. This may result in the case of the acidic agents by forming a more acidic microenvironment that reduces the solubility of ketorolac. Since sodium carbonate would increase pH, the source of its stabilizing effect cannot be explained in this manner (see ref 6 for the pH–rate profile for the degradation of ketorolac).

Table 4 shows the percentages of degradation products for samples stressed at 50 °C/75% RH for 3 months. The values were calculated using the response factors in Figure 1. The 1-keto analog was the only degradation product observed in powder blends formulated with the calcium salt or the free acid. Ketorolac tromethamine powder blends gave all four of the products shown in Scheme 1. The 1-keto analog was always the major product, as shown in Table 4. When oxidation was decreased by the addition of antioxidants and pH modifiers, the amide generally became a more significant product. Citric acid was the only excipient effective in decreasing the amount of amide formation in the ketorolac tromethamine powder blends. This may be due to a reaction of the citric acid with the tromethamine salt to form the tromethamine amide of citric acid. Calculations show that based on the molar ratios of ketorolac tromethamine and citric acid present in the citric acid formulation, about half as much of the ketorolac amide should form if the amide of citric acid also forms, which is in agreement with the observed results (Table 4).

Decarboxylation of ketorolac to the decarboxy analog was a relatively minor reaction. The formation of this product was most significant as a proportion of the total amount of degradation in formulations containing sodium bicarbonate

Table 4—Degradation Product Distribution of Ketorolac Powder Blends Stored at 50 °C/75% RH for 3 months

Formulation Modifier	Percent[a]				
	Ketorolac	1-Keto	Amide	Decarboxy	1-Hydroxy
Ketorolac tromethamine salt[b]	89.8	8.9	0.7	0.4	0.2
Ketorolac calcium salt[c]	99.8	0.2	0.0	0.0	0.0
Ketorolac free acid[c]	99.5	0.5	0.0	0.0	0.0
Propyl gallate (1%)[d]	96.7	2.6	0.6	0.0	0.0
Propyl gallate (0.1%)[d]	91.1	7.7	0.5	0.6	0.1
BHT (1%)[d]	89.3	8.8	1.0	0.8	0.1
EDTA (1%)[d]	88.3	9.8	0.9	0.8	0.1
Citric acid (1%)[d]	93.3	6.0	0.3	0.3	0.1
Sodium carbonate (1%)[d]	94.7	3.9	0.7	0.5	0.2
Sodium bicarbonate (1%)[d]	94.4	4.0	0.7	0.7	0.2
Lactose:microcrystalline cellulose 70:24.5[e]	93.9	5.2	0.6	0.2	0.1
Lactose:microcrystalline cellulose 24.5:70[e]	89.4	9.4	0.8	0.3	0.1
Croscarmellose sodium[f]	87.3	11.7	0.6	0.2	0.1

[a] Ratios are corrected for differences in response factors. [b] Formulation consists of 5% ketorolac tromethamine, 34.5% lactose, 60% microcrystalline cellulose, and 0.5% magnesium stearate. [c] Substituted for original ketorolac tromethamine drug substance. [d] Added to the formulation consisting of 5% ketorolac tromethamine, 34.5% lactose, 60% microcrystalline cellulose, and 0.5% magnesium stearate. [e] Percent of the ketorolac tromethamine powder blend. [f] The ratio of lactose: microcrystalline cellulose:croscarmellose sodium is 36.3:53.2:5.

(1% w:w), where it accounted for approximately 0.7% of the total mass balance.

Several approaches to improving the stability of ketorolac powder blends have been identified. The most stable powder blends are achieved by substituting either the calcium salt or the free acid of ketorolac for the tromethamine salt. This modification will produce an extremely stable formulation due to the low solubility of either form in water. A second approach is the addition of the antioxidant propyl gallate. This work showed that dry-blended propyl gallate (1% w:w) stabilized the drug while propyl gallate (0.1% w:w) was considerably less effective. pH modifiers such as sodium carbonate, sodium bicarbonate, and citric acid also increase the stability of ketorolac powder blends. Additionally, increasing the lactose:microcrystalline cellulose ratio, and avoiding croscarmellose sodium, also improves the stability of the powder blend. These approaches could also be combined to provide a more stable formulation.

References and Notes

1. Muchowski, J. M.; Unger, S. H.; Ackrell J.; Cheung, P.; Cooper, G. F.; Cook, J.; Callegra, P.; Halpern, O.; Koehler, R.; Kluge, A. F.; Van Horn, A. R.; Antonio, Y.; Carpio, H.; Franco, F.; Galeazzi, E.; Garcia, I.; Greenhouse, R.; Guzman, A.; Iriate, J.; Leon, A.; Pena, A.; Perez V.; Valdez, D.; Ackerman, N.; Ballaron, S. A., Murthy, D. V. K.; Rovito, J. R.; Tomolonis, A. J.; Young, J. M.; Rooks, W. H., II *J. Med. Chem.* **1985**, *28*, 1037–1049.
2. Bloomfield, S. S.; Mitchell, J.; Cissell, G.; Barden, T. P. *Clin. Pharmacol. Ther.* **1984**, *35*, 228.
3. Yee, J.; Brown, C. R.; Allison, C.; Wildman, K. *Clin. Pharmacol. Ther.* **1985**, *37*, 239.
4. Yee, J.; Brown, C. R.; Sevelius, H.; Wild, V. *Clin. Pharmacol. Ther.* **1984**, *35*, 285.
5. *Physicians' Desk Reference*; Medical Economics Data; Montvale, NJ, 1993; pp 2411.
6. Gu, L.; Chiang, H.-S.; Becker, A. *Int. J. Pharm.* **1988**, *41*, 95–104.
7. Gu, L.; Chiang, H.-S.; Johnson, D. *Int. J. Pharm.* **1988**, *41*, 105–113.
8. Malefyt, T.; Liu, C. unpublished results.
9. Nyqvist, H. *Int. J. Pharm. Tech. Prod. Manuf.* **1983**, *4*, 47–48.
10. Ahlneck, C.; Zographi, G. *Int. J. Pharm.* **1990**, *62*, 87–95.

Acknowledgments

The authors thank Tom Calderwood, Mike Hale, Dave Lokensgard, John Jee, Susan Speciale, and George Watson for their contributions.

JS950181G