

[54] **DICLOFENAC AND TOBRAMYCIN FORMULATIONS FOR OPHTHALMIC AND OTIC TOPICAL USE**[75] Inventors: **Michael V. W. Bergamini**, Alella; **José A. Vallet Mas**, Barcelona; **Gemma T. Cabello**, El Masnou; **Antonio L. Cabrera**, Barcelona, all of Spain[73] Assignee: **Laboratorios Cusi, S.A.**, Spain[21] Appl. No.: **419,387**[22] Filed: **Apr. 10, 1995**[30] **Foreign Application Priority Data**

May 17, 1994 [ES] Spain 9401078

[51] Int. Cl.⁶ **A61K 31/74**[52] U.S. Cl. **424/78.04**; 424/78.05;
514/912; 514/914[58] Field of Search 424/78.04, 78.05;
514/912, 914[56] **References Cited****U.S. PATENT DOCUMENTS**

4,087,538	5/1978	Portnoff	514/420
4,407,792	10/1983	Schoenwald et al.	514/397
4,478,822	10/1984	Hasam et al.	424/94.6
4,668,506	5/1987	Bawa	424/429
4,829,088	5/1989	Doulakas	514/567

FOREIGN PATENT DOCUMENTS

2013188	9/1990	Canada	.
0038698A2	10/1981	European Pat. Off.	.
0306984A1	3/1989	European Pat. Off.	.
WO89/09057	10/1989	WIPO	.

OTHER PUBLICATIONS

Human Conjunctivitis, Howard M. Leibowitz, MD, et al., Arch Ophthalmol, vol. 94, Oct. 1976, pp. 1752-1756.

Association diclofenac-dexamethasone dans le traitement de l'inflammation postopératoire: étude prospective en double-insu, Dr. Philippe Othenin-Girard, et al., Klin. Mbl. Augenheilk, 200, 1992, pp. 362-366.

The Effect of 0.1% Indomethacin Eyedrops on Cataract Surgery, Journal of Ocular Pharmacology, vol. 7, No. 1, 1991, pp. 77-81.

The Effect of Ketorolac Tromethamine in Reducing Postoperative Inflammation: Double-Mask Parallel Comparison with Dexamethasone, Allan J. Flach, MD, et al., Ann Ophthalmol 1989; 21:407-411.

Infections of the Eye—35. Endophthalmitis, David W. Parke II, et al., pp. 563-583.

Incompatibility of indometacin and benzalkonium in eye drops due to ion-pair formation, S. M. Dreijer-Van Der Glas, et al., vol. 9, 1987, Pharmaceutisch Weekblad Scientific Edition, pp. 29-32.

Effects of Pretreatment with Mydriatics on Intraocular Penetration of 0.1% Pranoprofen, Takahiro Ogawa, et al., Jpn J Ophthalmol, vol. 37: 47-55, 1993.

Prediction of Skin Permeability of Drugs: Comparison of Human and Hairless Rat Skin, Yasunori Morimoto, et al., J. Pharm. Pharmacol. 1992, 44: 634-639.

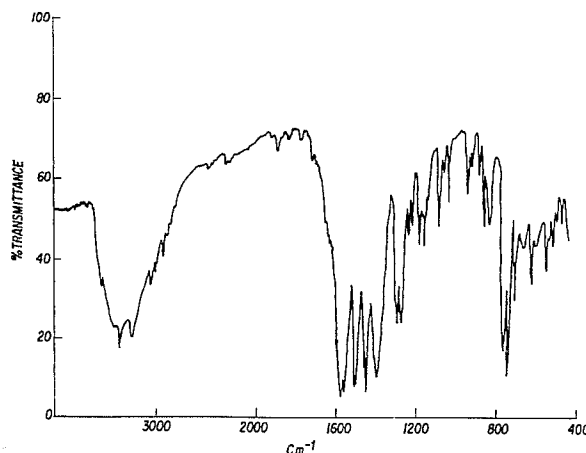
Binary Diclogenac Diethylamine-Water Systems: Micelles, Vesicles and Lyotropic Liquid Crystals, Katrin Kriwet, et al., Eur. J. Pharm. Biopharm, 39 (6) 234-238, 1993.

Degradation of Tobramycin in Aqueous Solution, Michael Brandl and Leo Gu, Drug Development and Industrial Pharmacy, 18(13), 1423-1436, 1992.

(List continued on next page.)

Primary Examiner—Carlos Azpuru*Attorney, Agent, or Firm*—Wigman, Cohen, Leitner & Myers, P.C.[57] **ABSTRACT**

This invention includes a pharmaceutically acceptable formulation of Diclofenac, Tobramycin, a solubility agent and, optionally, excipients, tonicifiers, buffers, viscosity modifying agents, preservatives, and chelating agents, at a pH from greater than 7.0 to about 9. The invention also discloses the use of this pharmaceutically acceptable formulation of an antibiotic and NSAIDs to treat eye and ear conditions accompanied by infection and inflammation.

96 Claims, 4 Drawing Sheets

OTHER PUBLICATIONS

- Spectrophotometric Method for Determination of Tobramycin, Apramycin and Kanamycin in Formulations*, P. R. Bontchev, et al., *Mikrochimica Acta (wien)* 1984 III, 459–465.
- The Top Ten NSAIDs – A molecular modelling study*, S. Winiwarter, et al., *Pharmaceutica Acta Helvetiae* 68 (1994) 181–189.
- Conjunctival Disorders*, *Current Veterinary Therapy X Small Animal Practice*, Cecil P. Moore, D.V.M., 1989, pp. 673–678.
- A New Corticosteroid–Antibiotic Preparation in Eye and Ear Infections*, *General Practitioner Clinical Trials*, Alexander, J. et al., Jul., 1966, vol. 197: 94–96.
- Canine Conjunctiva and Nictitating Membrane*, *Veterinary Ophthalmology*, Dennis E. Brooke, pp. 290–304, 1991.
- Diseases of the Ear*, *Textbook of Veterinary Internal Medicine — Diseases of the Dog and Cat*, vol. I, Dennis W. Macy, pp. 246–257.
- American Academy of Ophthalmology, Final Program, Scientific Posters, p. 101.
- XXVIIth International Congress of Ophthalmology '94, Final Program, Scientific Papers.

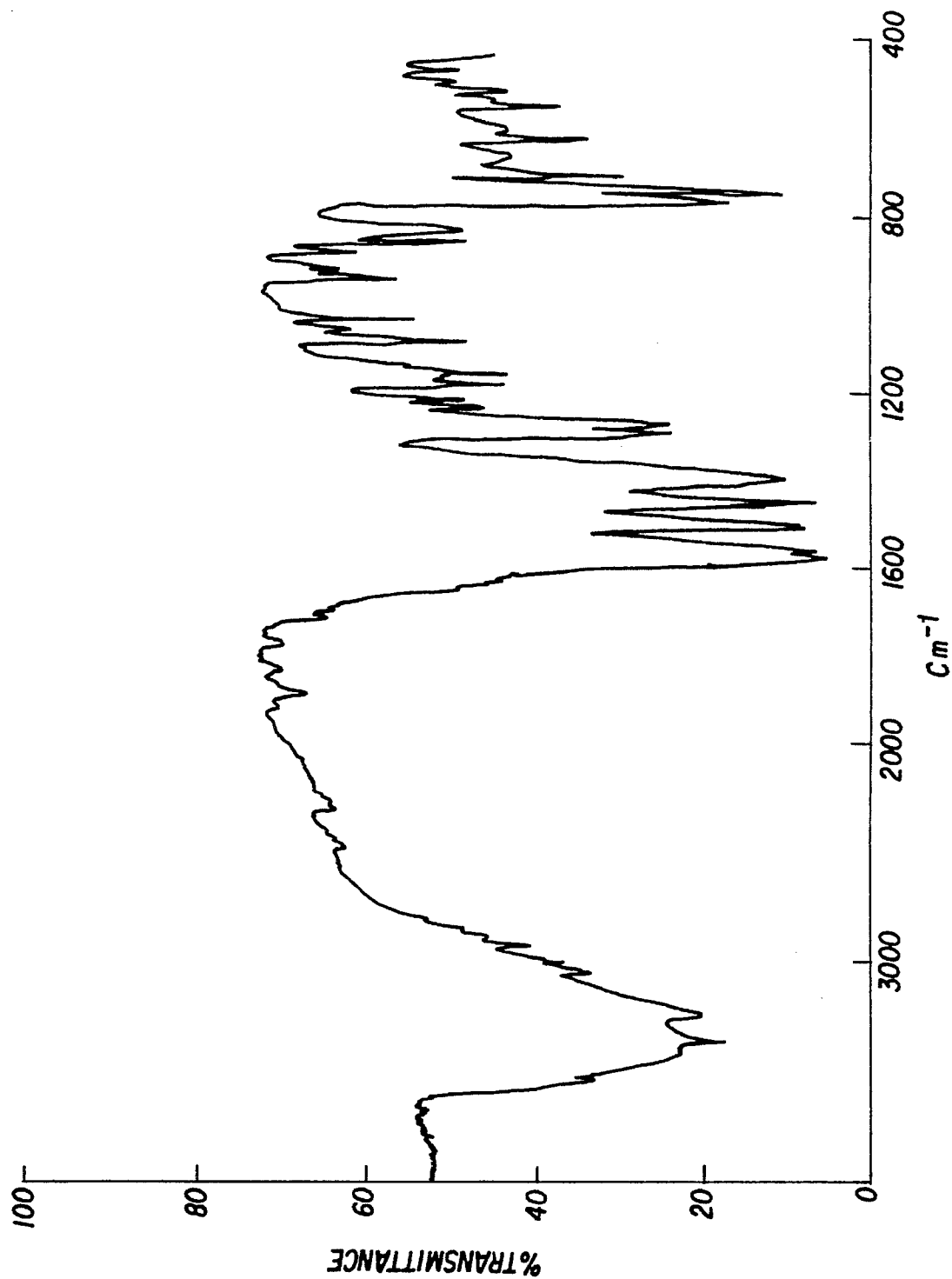


FIG. 1(a)

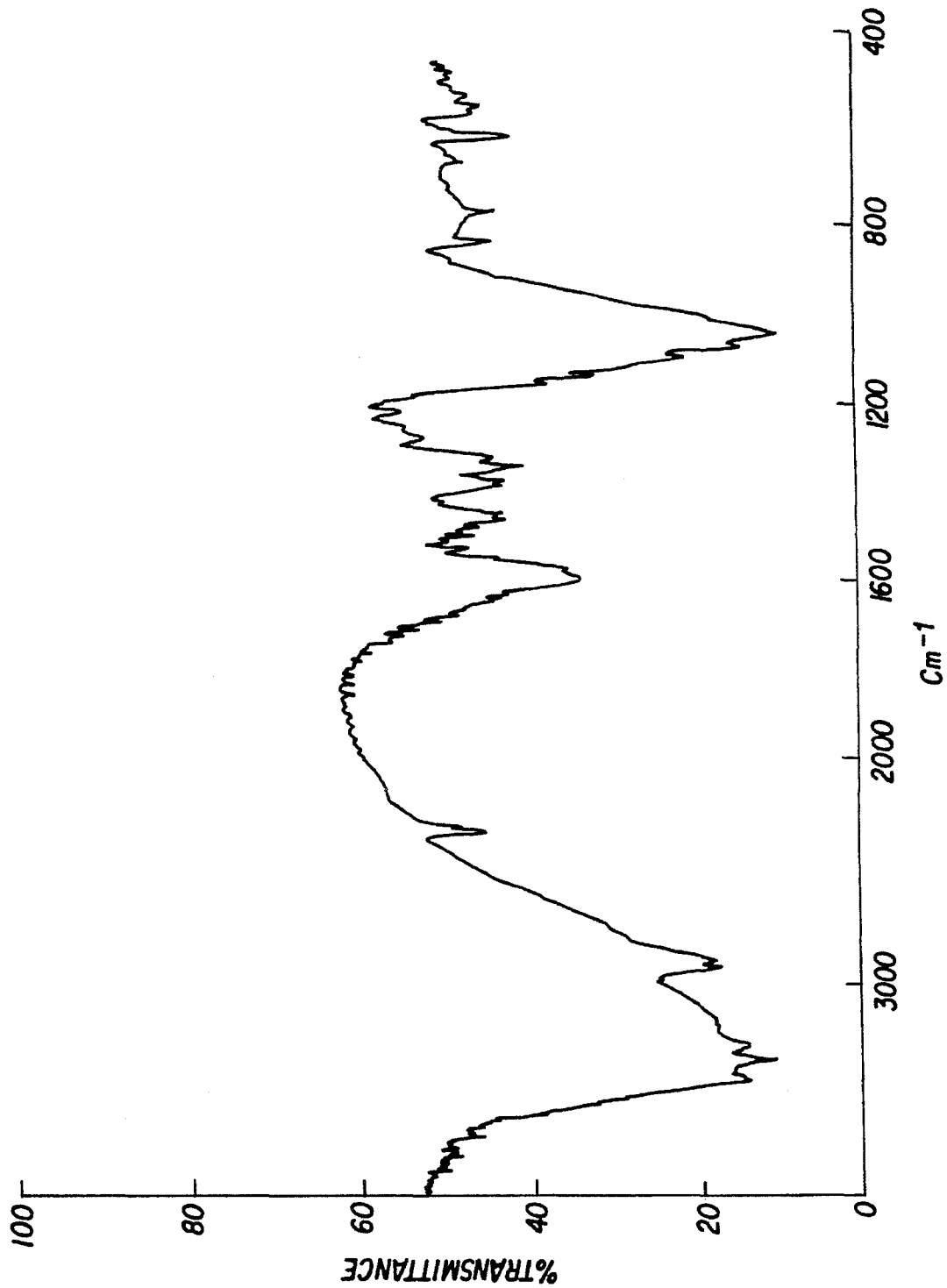


FIG. 1(b)

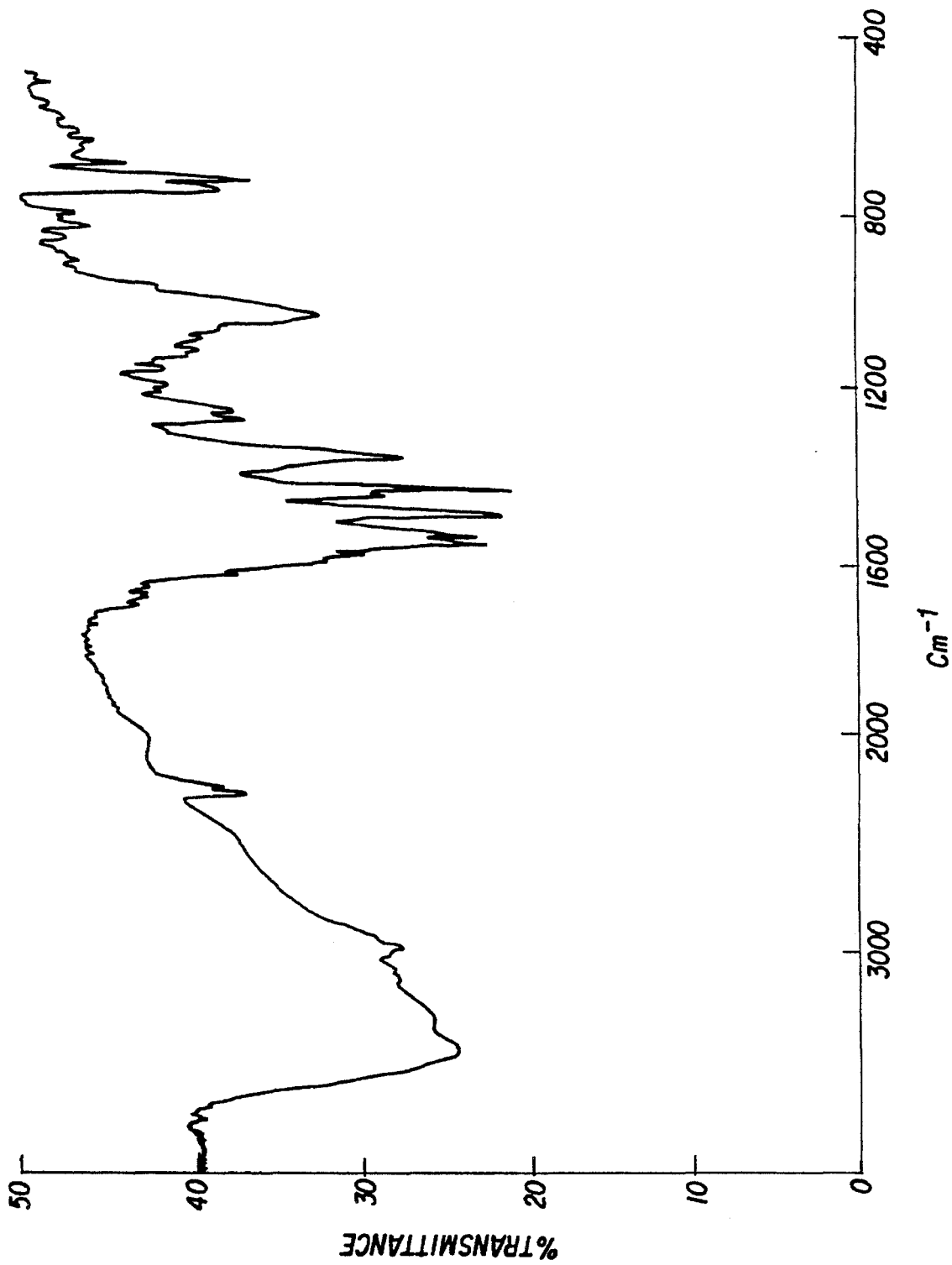


FIG. 1(c)

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.