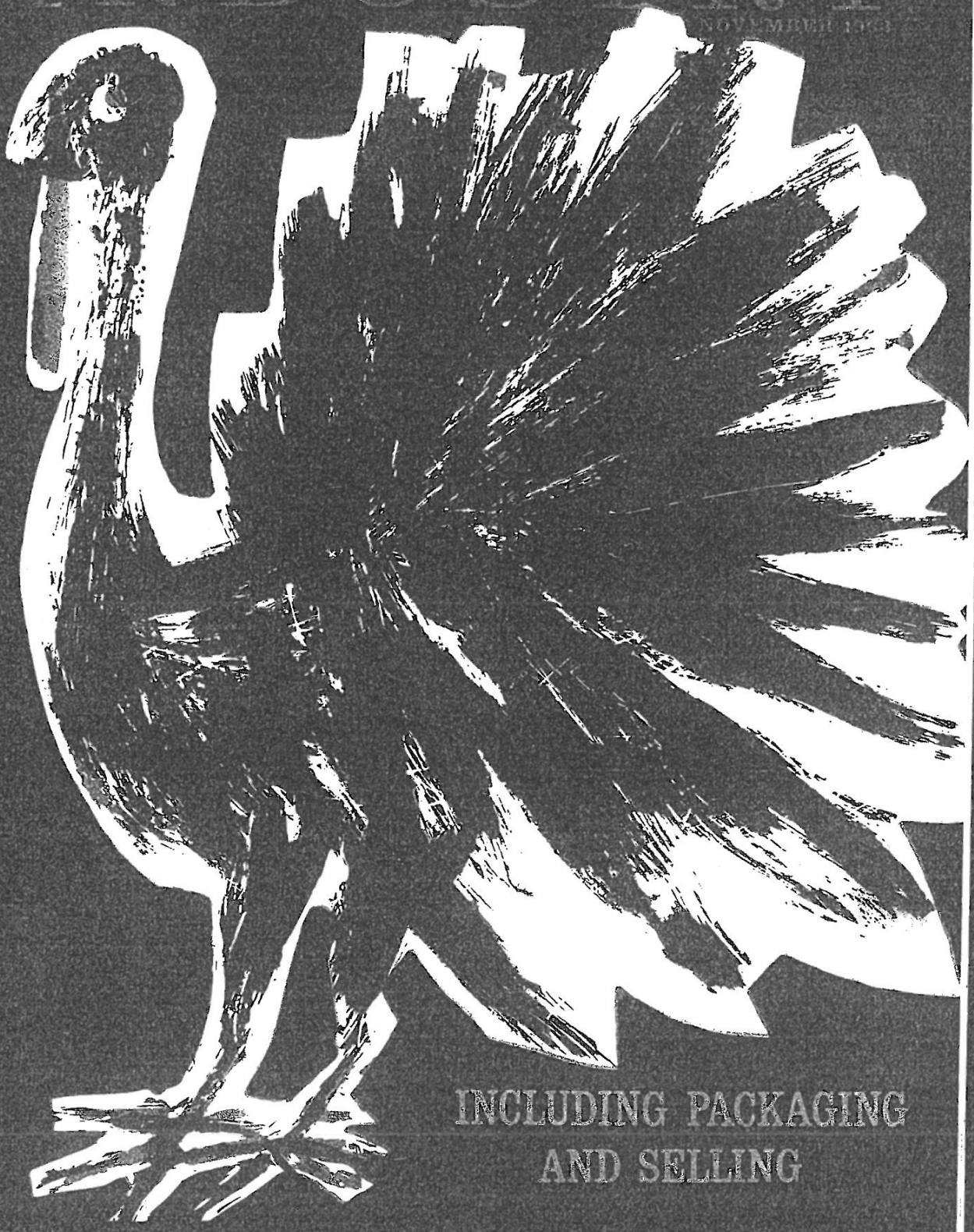
DRUG & COSMETIC INDUSTRY



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PHARMACEUTICAL ASPECTS OF DEXTROMETHORPHAN HYDROBROMIDE, N. F. XI

A SAFE NON - NARCOTIC, EFFECTIVE ANTITUSSIVE

by LOUIS MAGID, Ph. D. HOFFMANN - LA ROCHE, INC.

Dextromethorphan hydrobromide, N.F. XI, is a safe, effective, non-narcotic antitussive, approximately equal in activity to codeine. The effectiveness of dextromethorphan has been demonstrated in clinical appraisals by Cass and Frederik[1,2,3] in patients suffering from disease entities associated with chronic cough and by Bickerman et al.[4,5] in citric acid aerosol stimulated cough response in normal human subjects. Clinical evaluation by Ralph[9] in human pathologic cough showed that dextromethorphan is an effective and safe cough suppressing agent having the antitussive activity of codeine without sharing its addictive properties and without producing the side effects typical of codeine. In a series of double-blind investigations, Cass et al.[1,2,3] found that dextromethorphan has a specific effect on cough which is equal, if not superior, to that of codeine. Bickerman et al.[5] observed no statistical difference in the antitussive activity of 10 mg. of dextromethorphan hydrobromide and 15 mg. of codeine. According to Ralph[9], dextromethorphan takes effect in about twenty minutes and has a good duration of action. Thus, administration of the drug from one to three times daily generally provides effective relief—even when the cough is chronic.

Dextromethorphan has been widely used in prescription-type products and is now approved for OTC use. The Food and Drug Administration removed the prescription legend requirements on dextromethorphan hydrobromide in July 1956. Since that time the use of this non-narcotic antitussive has grown steadily.

Dextromethorphan has become a leader[6] in the antitussive field and is rapidly replacing codeine in cough preparations. Of the top fifty proprietary cough syrups, about 15 per cent are made with dextromethorphan and this percentage represents more than 50 per cent of the dollar sales of the leading proprietary syrups. A review of the composition and sales of the leading dextromethorphan cough preparations was presented recently by Kalish[6].

Cough and cold sales have increased over 40 per cent during the past few years. Narcotic preparations with and without antihistamines have held their dollar sales, but have not increased their dollar volume with the growing market. Several years ago narcotic cough preparations with and without antihistamines accounted for more than two-thirds of the market. A few years later their share declined approximately one-third. If proprietary products are included in this evaluation, the share of the market enjoyed by this group is further lowered by more than 20 per cent. The trend and comparison of sales of the important cough product groups are shown in the following graph.

The above trends are not surprising in view of the side effects common to the opiate derivatives. These toxic effects include anorexia, nausea, vomiting, constipation, drowsiness, headache and vertigo, together with addiction liability, which presents a hazard, particularly in the chronic cougher.

The numerous disadvantages of the opiates prompted the search for a clinically effective, non-narcotic antitussive which was equiactive to codeine. Dextromethorphan was one of the first synthetic non-narcotic antitussive agents. The studies by Isbell and

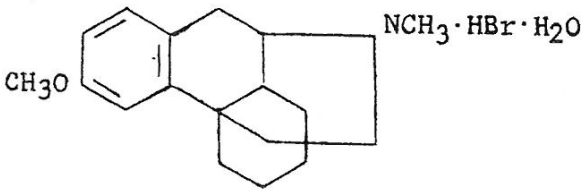
Fraser[11] in 1953 demonstrated that dextromethorphan showed no addiction liability. Long-term clinical trials have disclosed no evidence of toxicity[9]. According to Bickerman[5], Ralph[9] and Cass and Frederik[1], the incidence of adverse side effects was remarkably low and consisted of occational drowsiness or gastrointestinal intolerance which appeared to be of the same order of magnitude as that of placebo.

Dextromethorphan has become the antitussive of choice in cough preparations for the following reasons:

1—It is non-narcotic
2—It is safe and effective
3—Excellent stability
4—It is approved for OTC sale
5—Rapid onset of action
6—Adequate duration of action
7—Pharmaceutically acceptable for incorporation into various dosage forms.

CHEMICAL PROPERTIES

Dextromethorphan hydrobromide (d-3-Methoxy-N-methylmorphinan hydrobromide) is isolated as the crystalline monohydrate with the empirical formula $C_{18}H_{25}NO\text{-}HBr\text{-}H_20$ and a molecular weight of 370.35. The structural formula is a follows:



Dextromethorphan hydrobromide is unaffected by mild oxidizing or reducing agents. It is stable in the cold in 1N HC1 or 1N HaOH and is stable in the pH range of 4 to 5.6 under ordinary storage conditions and up to 3 months storage at 45°C. It reacts with alkalies to form the free base which is insoluble in water. It forms a nitrate of low solubility and is precipitated from aqueous solutions by tannic acid, salicylates and concentrated solutions of iodides. In aqueous solutions it is slowly decomposed on exposure to sunlight. It is incompatible with some of the certified dyes (see section on compatibility).

Physical Properties

Appearance	Crystalline powder
Color	White
Odor	None
Color of solution	Colorless
pH of 1% solution	5.2 - 6.5
Residue on ignition	Max. 0.1%

Solubility

Water at 25°C	About 1.5%
at 50°C	5%
at 70°C	10%
at 85°C	25%
Alcohol, U.S.P.	25%
Glycerin, U.S.P.	10%
Propylene Glycol, U.S.P.	Soluble
Chloroform, U.S.P.	Soluble
NaCl equivalent of 1% solution	0.158%

$[\alpha]_D^{20} = +26$ to $+28°$ (2% solution in water)

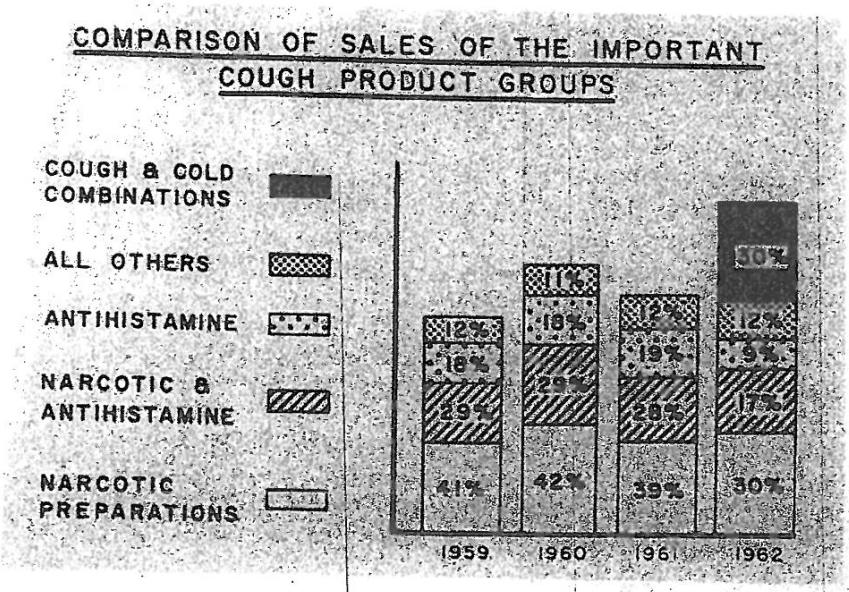
Stability

Crystals

Light	Stable to normal indoor illumination
Air	Stable
Moisture	Non-hygroscopic

Aqueous Solutions

pH	Stable in pH range of 4 to 5.6
Air	Stable
Light	Stable on exposure to normal indoor illumination. Slowly decomposed on exposure to sunlight.



Tablets and Capsules
Stable under all normal conditions of storage.

COMPATIBILITY

There are relatively few incompatibilities encountered with dextromethorphan hydrobromide in the formulation of various types of liquid products. Among these are the formation of compounds having a reduced solubility in water, such as the nitrate, salicylate, tannate and the reaction products with concentrated solutions of iodides, and some of the certified dyes. However, all of these incompatibilities can be easily overcome by the judicious use of alcohol, sorbo and glycols. A list of various substances, compatible and incompatible with syrup formulations of dextromethorphan hydrobromide, is presented below. Additional compatibility information has been published by Husa[7].

Compatible:

p-Acetaminophenol	Desoxyephredrine HCl
Ammonium chloride	Emetine HCl
Antimony potassium tartrate	Ephedrine sulfate
Antipyrine	Glyceryl guaiacolate
Ascorbic acid	Papavetine HCl
Benzoic acid	Phenindamine tartrate
Chloral hydrate	Phenylephrine HCl
Chlorphemiramine maleate	Phenylpropanolamine HCl
Citric acid	Potassium citrate
Codeine phosphate	Potassium guaiacol sulfonate
Codeine sulfate	Sodium bromide
Demerol HCl	Sodium citrate

Incompatible:

Chloroform*	Sodium iodide*[a]
Some certified dyes*	Tannic acid*
Menthol*	Sodium Salicylate*
Potassium iodide*[a]	

*These incompatibilities can be overcome by judicious use of alcohol and/or Sorbo and glycols.
[a]Incompatible in concentrated solutions.

TYPE OF PRODUCTS

Dextromethorphan hydrobromide is a very stable compound and lends itself readily to incorporation in various pharmaceutical dosage forms. Among the various dextromethorphan dosage forms that have appeared are the following:

Product Type	Usual Active Ingredients
Simple syrups	Dextromethorphan
Expectorant cough syrups	Dextromethorphan, ammonium chloride, glyceryl guaiacolate, potassium guaiacol sulfonate
Cough-cold preparations	Dextromethorphan, antihistamine, expectorant, decongestant
Analgesic cough-cold preparations	Same as above with N-acetyl-p-aminophenol (APAP) or sodium salicylate
Chewable tablet	Dextromethorphan, ascorbic acid
Lozenges	Dextromethorphan, benzocaine, antiseptic, ascorbic acid, antihistamine
Candies	Same as above
Capsules—hard shell	Dextromethorphan, antihistamine, analgesic, decongestant
Capsules—soft shell	Dextromethorphan
Tablets	Dextromethorphan

DEXTROMETHORPHAN HYDROBROMIDE ABSORBATE POWDER

The formulation of chewable tablets and lozenges, ect., is now possible with a new form of dextromethorphan which is known as Dextromethorphan Hydrobromide Adsorbate Powder[8]. It is composed of dextromethorphan, along with a small amount of soluble saccharin, adsorbed on magnesium trisilicate. The product is compounded so that it contains 5 per cent of the active ingredient. Dextromethorphan Hydrobromide Adsorbate Powder was specifically developed for use in the manufacture of chewable tablets, lozenges, cough drops and similar dosage forms. The advantage of the product over the uncompounded substance is that the slightly bitter taste of the dextromethorphan hydrobromide is practically eliminated and it is, therefore, the preferred form of the antitussive for preparing these forms that are persistent in the mouth. With the adsorbate powder it is possible to prepare pleasant-tasting chewable tablets and lozenges containing the equivalent of as much as 15 mg. equivalent of dextromethorphan hydrobromide. The adsorbate powder is stable and based on animal studies has an onset of activity and a duration of antitussive action similar to that of dextromethorphan hydrobromide per se.

An important feature of the dextromethorphan adsorbate, in connection with its use in the preparation of oral dosage forms, such as lozenges and chewable tablets, is its ability to be combined with citric acid and possibly other organic acids without losing its tasteless qualities. The combination of dextromethorphan adsorbate and citric acid in a formulation, followed by subsequent granulation, gives a product having an acidic reaction, thus widening the scope of flavors which may be used for the product. In addition, other medicinal substances, not suitable for incorporation in alkaline media, can be combined with the dextromethorphan adsorbate-citric acid mixture.

PHARMACEUTICAL FORMULATION

Dextromethorphan hydrobromide, by virtue of its excellent stability and relatively few incompatibilities, which can be overcome by use of alcohol, Sorbo or glycols, is easily incorporated in standard tablet, capsule and syrup formulations. In syrup formulations, dextromethorphan hydrobromide exhibits a slight bitter taste which is easily masked with suit-

(*Continued on page 757*)

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