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METHOD OF PRODUCING GASTROINTESTINAL SPASMOLYTIC ACTIVITY WITH ALKYLPHENOXYPOLY(ETHYLENEOXY)ETHANOLS

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ABSTRACT OF THE DISCLOSURE

Pharmaceutical compositions having gastrointestinal spasmolytic activity containing a polyoxyethylene polymer of an alkylphenol in which the polyoxyethylene groups are present from about 10% to about 80% of the molecule and a method of producing gastrointestinal spasmolytic activity.

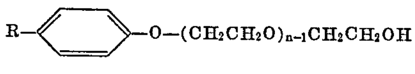
This invention relates to pharmaceutical compositions having spasmolytic activity and to a method of producing gastrointestinal spasmolytic activity using said compositions. More specifically, this invention relates to a method of producing spasmolytic activity without the concomitant limiting or anticholinergic side effects common to prior art spasmolytic compositions.

Prior to the present invention, there has been a great need for compounds and compositions which produce spasmolytic activity without the usual anticholinergic side effects, such as, for example, dry mouth and mydriasis which are common to known anticholinergic-antispasmodic compounds. The need of a safe and effective composition devoid of the above noted side effects and having spasmolytic activity has been great.

The novel pharmaceutical compositions and methods of this invention are unique in that they promptly and consistently depress or completely eliminate abnormal gastric motility. These compositions are not only useful in the treatment of spasticity or hypermotility of the gastrointestinal tract, but are also free of systemic side effects. Such biological activity has never been reported for compounds of the chemical class described hereinafter.

Most advantageously the compositions of this invention are in dosage unit form and comprise a nontoxic pharmaceutical carrier and a nonionic polyoxyethylene polymer of an alkylphenol. More specifically the compositions of this invention comprise polymers of alkylphenols having the following structural formula:

FORMULA I



wherein R is an alkyl group comprising from 4 to 16 carbon atoms and *n* is a positive integer such that the polyoxyethylene groups are present from about 10% to about 80% of the molecule.

Preferably, the above compounds of Formula I are those having an alkyl group containing from 8 to 12 carbon atoms and the polyoxyethylene units are present from about 20% to about 70% of the molecule.

Most advantageously, the compositions of this invention comprise an oral dosage unit containing the above compounds of Formula I wherein the alkyl group contains 12 carbon atoms and the polyoxyethylene content is from about 63% to about 66% of the molecule.

The amount of antimotility or musculotropic activity of the above noted novel spasmolytic compounds varies according to the length of the aliphatic substituent on the hydrophobic phenolic nucleus and the percent of the hydrophilic ethylene oxide units present in the molecule.

The polyoxyethylene ethers as illustrated in Formula I and present in these novel compositions are prepared by methods well known to the art. For example, an excess of ethylene oxide is reacted with an alkylphenol under moderate conditions of temperature and pressure in the presence of an alkaline catalyst. This method of preparation is set forth in the textbook Surface Active Agents, Their Chemistry and Technology, Schwartz-Perry, 1949.

The polyoxyethylene polymers of alkylphenols of this invention have been demonstrated as having gastrointestinal spasmolytic activity without the corresponding anticholinergic side effects in a standard animal pharmacological test procedure reported in The Physiologist, vol. 12, No. 3, August 1969. Briefly, the test comprises implanting a cannula in the stomach of an animal. The animals are fasted for eighteen hours prior to testing and the stomach lavaged with saline to remove traces of food. A miniature rubber ballon is placed in the stomach via the cannula and the balloon is connected to a pressure transducer by a polyethylene tube to record gastric contractions. The system is filled with water and 0.5 ml. of water is introduced into the balloon.

A one hour pre-drug control recording is obtained and the test compounds are administered via a cannula in aqueous solution in a dose volume of 1 ml./kg. The post drug motility is recorded for three hours after drug administration.

Spasmolytic activity is expressed as the duration in minutes of inhibition of propulsive gastric contractions.

The above test was conducted on rats to determine the gastric spasmolytic effect obtained by altering both the length of the alkyl chain and the polyoxyethylene content of the compounds as represented by Formula I and following are the results obtained:

TABLE I

Compound SK & F No.	Dose, mg./kg.	Side chain length (R)	Percent polyoxyethylene	Molecular weight	Duration of spasmolytic activity, min.
32,356	100	C_8	66	602	70
27,990	100	C_9	61	614	109
32,357	100	C_{12}	63	715	>145

TABLE II

Compound SK & F No.	Dose, mg./kg.	Side chain length (R)	Percent polyoxyethylene	Molecular weight	Duration of spasmolytic activity, min.
27,993	100	C_9	95	4,637	(1)
27,992	100	C_9	80	1,101	39
27,990	100	C_9	61	614	106
27,947	100	C_9	23	287	124

[1] No effect.

In summary, the above standard pharmacological animal test procedure demonstrates the gastrointestinal spasmolytic activity of the polyethoxylated ethers of alkylphenols present in the pharmaceutical compositions of this invention. The results further indicate that when the aliphatic chain substituent is increased and the polyoxyethylene content is held relatively constant, spasmolytic potency increased. There is also an increase in spasmolytic potency when the alkyl side chain remains the same with decreasing percentage of polyoxyethylene. However, particularly significant in these test results is that they demonstrated the compounds as represented by Formula I produced spasmolytic activity without the concomitant limiting or anticholinergic side effects.

The compositions of this invention are in dosage unit form and comprise a nontoxic pharmaceutical carrier and the polyoxyethylene polymers of alkylphenols of Formula I in an amount sufficient to produce gastrointestinal spasmolytic activity. Preferably, the composition will contain the polymer ingredient in an amount of from about 50 mg. to about 1000 mg. per dosage unit. Advantageously, the compositions will contain the polyoxyethylene polymer ingredient in an amount of from about 250 mg. to about 500 mg. per unit dose.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, sugar seeds, acacia, magnesium stearate, stearic acid, and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly the carrier or diluent may include any time delay material well known to the art, such as, for example, glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used the preparation can be tableted, placed in a hard gelatin capsule in powder or sustained release pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 gm. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or an aqueous or nonaqueous liquid suspension.

The method in accordance with this invention comprises administering internally to animals, preferably humans, in an amount sufficient to produce gastrointestinal spasmolytic activity a compound as represented by Formula I combined with a pharmaceutical carrier. The polyoxyethylated alkylphenol active ingredient will be present in dosage unit form in an amount of from about 50 mg. to about 1,000 mg. Preferably the above active ingredient will be present from about 250 mg. to about 500 mg. per unit dose. The administration may be parenterally or orally. The administration of the unit doses is preferably orally to animals suffering from gastric hypermotility or other similar gastrointestinal abnormalities. Advantageously equal doses will be administered one to four times daily. Preferably the daily dosage will be from 50 mg. to about 4.0 gm. and most advantageously from 250 mg. to about 1.0 gm. of active ingredient.

When the method of administration described above is carried out, spasmolytic activity is achieved without the concomitant mydriatic and antisalivary side effects common to known antispasmodic medicaments.

The following examples are not limiting but are illustrative of compounds of this invention and the procedures for their preparation. Other variations of this invention will be obvious to those skilled in the art.

EXAMPLE 1

Ingredients:	Mg./capsule
Octylphenoxypoly(ethyleneoxy)ethanol (68% polyoxyethylene)	1000
Peanut oil	100

Disperse the peanut oil in the polymer and place in a soft gelatin capsule.

One capsule is administered orally twice a day.

EXAMPLE 2

Ingredients:	Mg./tablet
Dodecylphenoxypoly(ethyleneoxy)ethanol (63% polyoxyethylene)	50
Calcium sulfate dihydrate	150
Sucrose	25
Starch	15
Talc	5
Stearic acid	3

The sucrose, calcium sulfate and the dodecylphenoxypoly(ethyleneoxy)ethanol are thoroughly mixed and granulated with hot 10% gelatin solution. The wetted mass is passed through a #16 U.S. Standard mesh screen directly onto drying trays. The granules are dried at 120° F. and passed through a #20 U.S. Standard Mesh screen. These granules are then mixed with starch, talc and stearic acid, passed through a #60 U.S. Standard mesh screen and compressed into tablets.

One tablet is administered four times a day.

EXAMPLE 3

Ingredients:	Mg./capsule
Nonylphenoxypoly(ethyleneoxy)ethanol (23% polyoxyethylene)	500
Peanut oil	200

The ingredients are thoroughly mixed and filled into a soft gelatin capsule.

One capsule is administered three times a day.

EXAMPLE 4

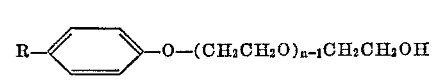
Ingredients:		
Heptylphenoxypoly(ethyleneoxy)ethanol (80% polyoxyethylene)	gm.	2.00
Soluble saccharin	gm.	0.10
Sodium benzoate	gm.	0.05
Citric acid	gm.	0.02
Oil of orange	ml.	0.01
Oil of custard flavor	ml.	0.05
Sugar syrup	ml.	90.00
Distilled water q.s. to	ml.	100.00

The saccharin, sodium benzoate, citric acid and heptylphenoxypoly(ethyleneoxy)ethanol are dissolved in the distilled water and the syrup added. The mixture is filtered. The oil of orange and oil of custard flavor are then added and the mixture thoroughly stirred.

One teaspoonful is administered four times a day.

What is claimed is:

1. A method of producing gastrointestinal spasmolytic activity which comprises administering orally to animals suffering from gastric hypermotility an amout sufficient to produce said activity of a polyoxyethylene polymer of an alkylphenol having the formula:



wherein:

R is an alkyl group comprising from 8 to 12 carbon atoms and n is a positive integer such that the polyoxyethylene groups are present from about 20% to about 70% of the molecule.

2. The method of claim 1 wherein said polymer is administered in a daily regimen of from about 50 mg. to about 4.0 gm.

3. The method of claim 1 wherein the alkyl group contains 12 carbon atoms and the polyoxyethylene units are present from about 61% to about 63% and said polymer is administered in a daily dosage regimen of from about 250 mg. to about 1.0 gm.

4. The method of claim 1 wherein a tablet or capsule containing from about 50 mg. to about 1000 mg. of the polymer is administered from one to four times daily.

5. The method of claim 1 wherein a tablet or capsule containing from about 250 mg. to about 500 mg. of the polymer is administered from one to four times daily.

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