(13) T. Higuchi, J. Perrin, J. Robinson, and A. Repta, *J. Pharm. Sci.*, **54**, 1273(1965).

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Epoxy Resin Beads as a Pharmaceutical Dosage Form I: Method of Preparation

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Abstract □ The preparation of various epoxy resins containing acidic and basic curing agents was investigated. These resins were prepared in bead and bulk forms. The effects of the types of curing agents and their concentrations on the solubility of the resins in artificial gastrointestinal juices have been studied. The addition of basic and acidic curing agents in the resins was observed to influence their solubility in acidic and alkaline buffer, respectively. The method of preparation of these resins into bead forms was developed in the presence of drugs.

Keyphrases □ Epoxy resin beads—dosage forms □ Acids, bases—epoxy resin curing agents □ Drug-epoxy resin beads—preparation □ UV spectrophotometry—analysis

Many synthetic and natural polymers have been developed and used in pharmacy for various purposes. However, little attention has been paid to the use of epoxy resins in dosage forms. Epoxy compounds cured with amine can be used to incorporate the drugs by coating (1), by embedding (2), and by extrusion molding (2, 3). Drugs can furthermore be incorporated in the bulk or beads of water-insoluble monomers during polymerization (4).

In the present work epoxy compound was condensed with either basic or acidic curing agent to prepare resins in bulk as well as in bead form and three drugs were embedded in the beads. Furthermore, the possibilities of these resins for enteric coating and sustained-release dosage forms have been shown.

EPOXY COMPOUNDS

The epoxy compounds are prepared by heating epichlorohydrin and 2,2′-bis-*p*-hydroxyphenyl propane at 99–119° for 3.5 hr. in

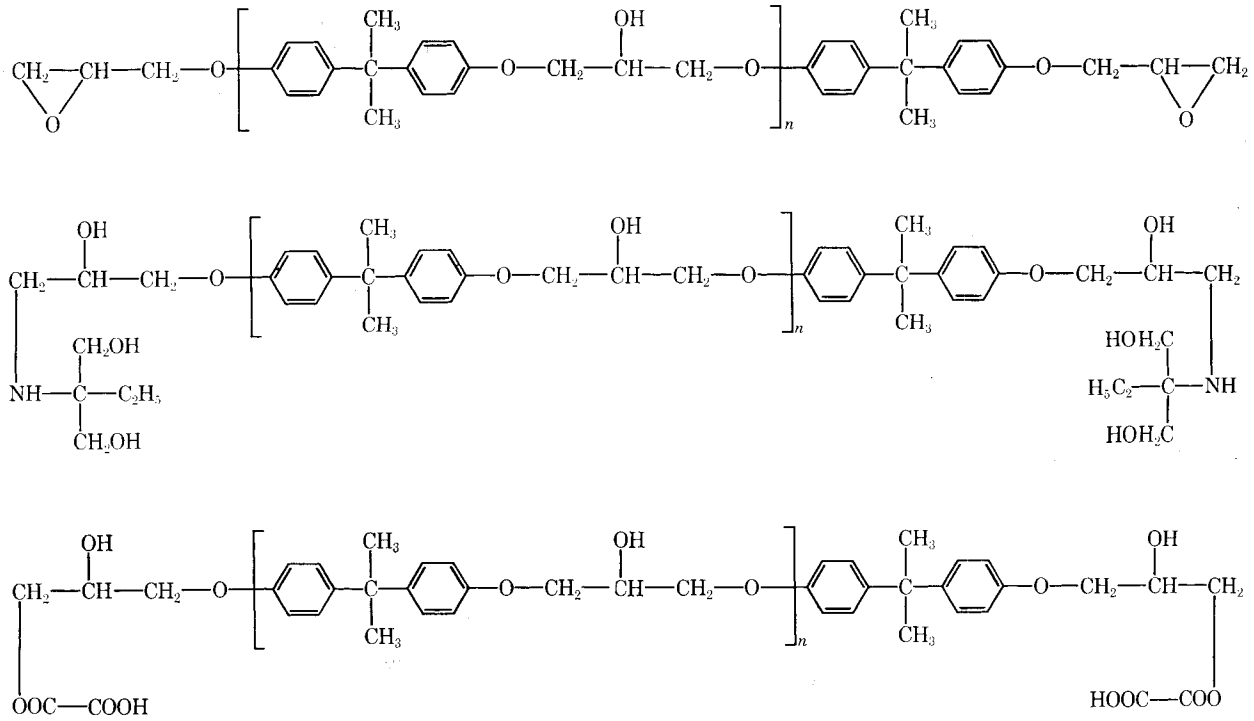

Table I—Technological Data of Epoxy Resin Bulk Polymerization

Ratio of Epoxy/Curing Agent, %	Curing Agent	Color of Polymer	Reaction Temp., °C	Exothermic Temp., °C	Softening Temp., °C	Buffer Solutions in which the Resins Dissolve
67.3:32.7	2-Amino-2-ethyl-1,3-propandiol	White to yellow	At 70° immediately	170–230°	85–90°	pH 1.2–4.0
72.0:28.0						pH 1.2–4.0
80.0:20.0	*o*-Phosphoric acid	White to violet	Room temp.	110–115°	40–50°	pH > 3.2
66.6:33.3						pH > 1.2
72.8:27.2	Adipic acid	White	140° for 2 hr.	175–180°	70–75°	Insoluble
57.1:42.9						pH > 7.2
81.3:18.7	Oxalic acid	White	70°	125–130°	75–80°	pH > 3.2
68.4:31.6						pH > 3.2
61.0:39.0	Citric acid	White	140° for 4 hr.	—	Above 200°	Insoluble
70.0:30.0	Tartaric acid	Whitish-violet	140° for 4 hr.	—	Above 200°	Insoluble

40% aqueous sodium hydroxide. The commercial products available are blends of various degrees of condensation. They vary from solid to liquid and have the general formula (I). Epoxy compounds may be converted into the thermoset solid state through the epoxy group reaction with different classes of chemical compounds (acids, alcohols, and amines, *etc.*), known as curing agents and the products obtained are known as epoxy resins. The general formulas for the resins with basic and acidic curing agents are (II) for epoxy resin with 2-amino-2-ethyl-1,3-propandiol and (III) for epoxy resin with oxalic acid.

Epoxy compounds cured with primary amines dissolve in strong acidic buffers and hence may liberate the drug in the stomach. However, the compounds cured with acids dissolve in weak acidic to neutral buffers and thus may release the drug in the intestine only.

Epoxy compounds have been reported to be nontoxic on ingestion and LD_{50} for rats is 8 g./kg. weight. However, when taken orally by man in very high doses some acute gastrointestinal disorder has been observed (5). The disorder was of a few hours duration and had no lasting effect.

EXPERIMENTAL

Chemical Used—Epoxy compound[1]; curing agents—basic: 2-amino-2-ethyl-1,3-propandiol[2]; acidic: adipic acid, *o*-phosphoric acid, oxalic acid, citric acid, and tartaric acid[3] (all of pure quality); and drug models—chloramphenicol USP, barium sulfate, and dehydroemetine dihydrochloride.[4]

Procedure for Preparation of Epoxy Resins in Bulk and Examination of Some Technological Data (Table I)—The epoxy compound was mixed with an appropriate amount of curing agents in a beaker and heated to reaction temperature. An exothermic reaction took place and converted the mixture to a solid mass which could easily be broken or milled to the required particle size, and could also be worked up to dosage forms by compression, extrusion, injection molding, *etc.*

A certain amount of the resin obtained was placed in each of the tubes of the modified USP tablet disintegration apparatus (4) containing 50 ml. of different buffers varying from pH 1.2 to 8.2 at 37 ± 0.5°. The buffer solutions in which the resins dissolved were determined.

Preparation of Epoxy Resin-Drug Beads—During bead polymerization the mixture of epoxy compound, curing agent and drug was stirred in insoluble continuous phase to form droplets which are then polymerized (6).

For this purpose the continuous phase was heated in a round-bottom flask to a temperature of approximately 40° above the epoxy resin softening temperature. The drug was dissolved or suspended in a melted mixture of epoxy compound and curing agent. The melted mixture was then poured over the continuous phase which had already been stirred at the optimum speed to form the desired size of beads. After complete polymerization, the suspension was cooled slowly to room temperature. The solid beads were separated from the solution by filtration. The remaining oil was absorbed by adding traces of talc powder. The formulations of the beads are given in Tables II and III.

Choice of the Continuous Outer Phase for Bead Polymerization—As most of the curing agents and drugs are hydrophilic, the epoxy resins could not be prepared in bead form in an aqueous outer phase. Furthermore, due to the lack of any protective properties, fatty oils or organic solvents were less capable of protecting the droplets from agglomeration.

It was found that silicone oil hindered their agglomeration during polymerization due to the formation of a polymethylsiloxane layer on the beads.

General Conditions Used for Bead Preparation (See Also Tables II and III)—Outer phase: silicone oil (1 l.), inner phase: epoxy compound + curing agent (100 g.), temperature: 120°, speed of stirring: 200 r.p.m., and time of polymerization: 2 hr.

Table II—Bead Preparations of Epoxy Resins with Basic Curing Agent

Prep. No.	Inner Phase	Any Variation from General Conditions
1.	Epoxy compound, 67.3% 2-Amino-2-ethyl-1,3-propandiol, 32.7%	—
1.1	Preparation No. 1, 80% + chloramphenicol, 20%	—
1.2	Preparation No. 1, 65% + chloramphenicol, 35%	—
1.3	Preparation No. 1, 50% + chloramphenicol, 50%	Temp., 140°; speed of stirring, 260 r.p.m.
1.4	Preparation No. 1, 80% + barium sulfate, 20%	—
1.5	Preparation No. 1, 60% + barium sulfate, 40%	—
1.6	Preparation No. 1, 90% + dehydroemetine dihydrochloride, 10%	—
2.	Epoxy compound, 72% 2-Amino-2-ethyl-1,3-propandiol, 28%	—
2.1	Preparation No. 2, 80% + chloramphenicol, 20%	—
2.2	Preparation No. 2, 65% + chloramphenicol, 35%	—
2.3	Preparation No. 2, 50% + chloramphenicol, 50%	Temp., 140°; speed of stirring, 260 r.p.m.
2.4	Preparation No. 2, 80% + barium sulfate, 20%	—

[1] Araldit (Cy F 205), Ciba A. G., Basel, Switzerland.
[2] Ciba A. G., Basel.
[3] All of reagent grade.
[4] Hoffmann-La Roche A. G., Basel, Switzerland.

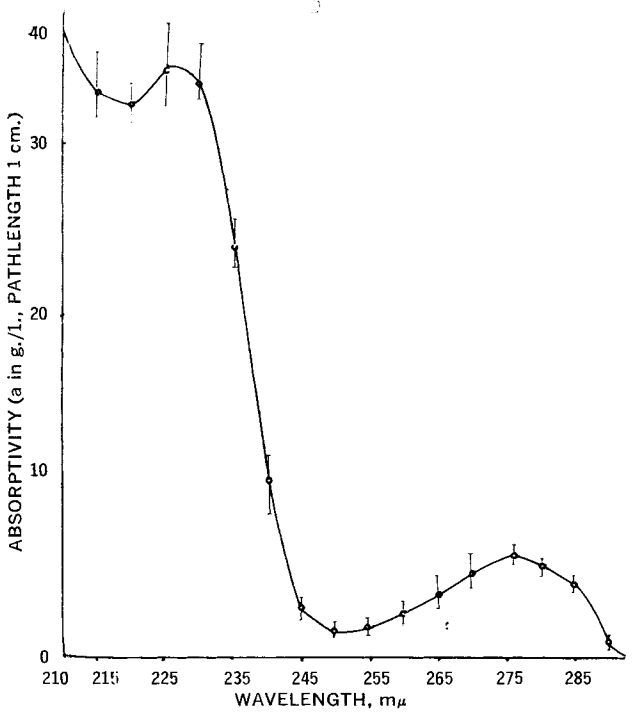

Figure 1—*Mean UV absorption curve of epoxy-amine Resin I prepared under different conditions (Table IV).*

RESULTS AND DISCUSSION

The beads obtained were soluble in buffers of pH's ranging from 1.2 to 7.5 (gastrointestinal juices) and were softened to liquid or semisolid state at a temperature slightly higher than the reaction temperature except for the resins cured with citric and tartaric acids (Table I). This difference is due to the dense crosslinking and net formation in these latter resins.

The beads obtained were spherical in form approximately from 0.5 to 10 mm. in diameter. The size of the beads can be governed by the stirring conditions and the protective properties of the continuous phase. The color and appearance of the beads depended on the curing agents and the drugs used. If the drug was dissolved in the resin, the beads were transparent; if the drug was incorporated in suspended form they were opaque. Polymerization of epoxy amine resin at higher temperature and for a longer time gave beads more uniform in size without inclusion of air bubbles (Table IV). The intensity of color of these resin beads changed due to these varying conditions; however, no change in UV spectrophotometric absorbance was observed (Fig. 1) showing that the resin remained unchanged.

The solubility of the resins in buffer solutions depended on the type and amount of curing agents. Resins prepared by curing with 2-amino-2-ethyl-1,3-propandiol dissolved easily in artificial gastric juice and in acidic buffers having a pH below 4.0. They may serve as a protective coating material or as a soluble matrix for the initial dose in sustained-release dosage forms. Resins obtained with acidic curing agents dissolved in weakly acidic to alkaline buffers and hence may be used as a matrix for the sustained-release portion in a depot dosage form. Furthermore, as the epoxy resins are soluble in organic solvents and flexible in nature (2, 3), the resins with acidic curing agents may be applied as an enteric coating material. The solubility in buffers was enhanced with the increase of the amount of curing agents in resin. Thus the onset of the dissolution of the beads could be controlled by varying the amount of curing agents (Table I).

The beads were prepared with three drugs in various concentrations to observe the applicability of the preparation method. The loss of the amount of drugs during preparation was practically negligible since most of the drugs were insoluble in the outer phase selected. Silicone oil was the outer phase of choice, having good protective and lubricant properties.

Table III—Bead Preparations of Epoxy Resins with Acidic Curing Agents

Prep. No.	Inner Phase	Any Variation from General Mentioned Conditions
3.	Epoxy compound, 72.8% Adipic acid, 27.2%	Temp. 140°
4.	Epoxy compound, 57.1% Adipic acid, 42.9%	Temp. 140°
4.1	Preparation No. 4, 80% + chloramphenicol, 20%	Temp. 140°
4.2	Preparation No. 4, 80% + barium sulfate, 20%	Temp. 140°
5.	Epoxy compound, 80% *o*-Phosphoric acid, 20%	Temp. 150°
5.1	Preparation No. 5, 80% + chloramphenicol, 20%	Temp. 150°
5.2	Preparation No. 5, 80% + barium sulfate, 20%	Temp. 150°
6.	Epoxy compound, 66.6% *o*-Phosphoric acid, 33.3%	Temp. 150°
6.1	Preparation No. 6, 80% + barium sulfate, 20%	Temp. 150°
7.	Epoxy compound, 81.3% Oxalic acid, 18.7%	Temp. 110°
8.	Epoxy compound, 68.4% Oxalic acid, 31.6%	Temp. 110°
8.1	Preparation No. 8, 80% + chloramphenicol, 20%	Temp. 110°

SUMMARY

A new group of epoxy resins has been prepared and studied as an auxiliary material for solid oral-dosage forms. Acidic and basic curing agents were used during the polymerization of the epoxy

Table IV—Effect of Temperature and Time during Bead Polymerization of Epoxy-Amine Preparations

Properties	Polymerization Temperature, °C	1 hr.	4 hr.	7 hr.
(1) Bead diameter	90°	0.5–10 mm.	1–4 mm.	2–4 mm.
(2) Color		White	White	Yellowish-white
(3) Air inclusion		Many bubbles	Few bubbles	None
(1) Bead diameter	120°	1–4 mm.	2–4 mm.	2–4 mm.
(2) Color		Yellowish-white	Yellowish	Yellowish
(3) Air inclusion		Few bubbles	Very few bubbles	None
(1) Bead diameter	150°	1–4 mm.	2–4 mm.	2–4 mm.
(2) Color		Yellowish	Yellow	Orange
(3) Air inclusion		Few bubbles	None	None

compound to get specific dissolution profiles in artificial gastrointestinal fluids.

Furthermore, a new method for the preparation of these epoxy resins in bead form in a lipophilic outer phase has been developed. Three drugs in various concentrations were embedded in these beads to prove the applicability of the method. Epoxy resins with basic curing agent are soluble in strong acidic buffers and may serve as a matrix for the initial oral dose while resins with the right amounts of acidic curing agents are soluble in weak acidic to neutral buffers and may serve as matrices for the sustained portion in long-acting oral dosage forms.

REFERENCES

(1) R. Hiltpolt, W. Fisch, and P. Speiser, Swiss pat. 364117 (1957).

(2) G. Bechmann, ETH diss. 3531, 1964, Cl. Vogt, Frankfurt am Main, W. Germany.

(3) A. Elegakey, ETH diss. 4080, 1968, Juris Verlag, Zurich, Switzerland.

(4) T. Jecklin, ETH diss. 3704, 1965, Juris Verlag, Zurich, Switzerland.

(5) H. Lee and K. Neville, in "Encyclopedia of Polymer Science and Technology," vol. 6, Interscience, New York, N. Y., 1967, p. 267.

(6) P. Speiser, APV Informationsdienst 1, 1969, in press; *Farm. Aikakauslethi*, **7**, 8(1968).

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DRUG STANDARDS

Polarographic Assay of Niacinamide in Pharmaceutical Preparations

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Abstract □ A rapid polarographic determination of niacinamide in pharmaceutical preparations had been developed and is compared with the König colorimetric assay using barbituric acid. The niacinamide is extracted from the sample using a combination of column and liquid-liquid partition chromatography. The extracted niacinamide is determined in a supporting electrolyte of 0.1 *N* sodium hydroxide using a conventional d.c. polarograph equipped with an H-cell. A wide variety of samples was analyzed repetitively by this procedure and the standard deviation was calculated. The method is rapid, specific, and accurate.

Keyphrases □ Niacinamide dosage forms—analysis □ Column, liquid-liquid partition chromatography—extraction □ Polarography—analysis

The most widely accepted analytical method for niacinamide is based on the König reaction (1). This method utilizes the reaction of pyridine or its derivatives with a cyanogen salt and an aromatic amine. A significant variation of the König reaction is the use of various amines in the reaction. Both the USP (2) and the AOAC (3) employ this assay with sulfanilic acid as the aromatic amine; the product shows an absorption maximum at 450 mμ. In both methods for multivitamin preparations, niacinamide is first hydrolyzed to nicotinic acid and then the color is formed. Other amines which have been used include barbituric acid (4, 5) and procaine hydrochloride (6). With procaine hydrochloride as the amine coupling reagent, niacinamide is hydrolyzed to nicotinic acid before the color development; with barbituric acid as the reagent, niacinamide is treated directly and a red color develops with a maximum absorbance at 550 mμ.

UV spectrophotometry has been used in the determination of niacinamide. However, the niacinamide must first be separated from complex preparations by such techniques as ion-exchange chromatography before the UV determination (7). Niacinamide has been separated from interfering substances by thin-layer and paper chromatography (8) and then determined by photometry and polarography. Microbiological (9–11) and titrimetric methods (12) have also been used.

The polarographic behavior of niacinamide is well documented (13–17) and a number of workers have reported the polarographic assay of niacinamide in simple vitamin preparations. Zuman (18) and Knobloch (19) determined niacinamide in a tablet and in an injection, respectively, by simply diluting the preparation with a 0.1 *N* sodium hydroxide supporting electrolyte and recording the polarogram. Sodium carbonate has also been used as the supporting electrolyte in the analysis of a simple tablet preparation (20). Most complex preparations, however, cannot be determined di-