This similarity witnessed for the appearance of sodium ions indicates that the inherent disintegration–deaggregation–dissolution process for the tablet formulation itself is not affected by pH.

In conclusion, tablets containing binders, lubricants, and disintegrants as well as drug itself dissolve in much the same manner as tablets containing only drug. The inclusion of these additional ingredients into the formulation may show changes in the dissolution profiles, but the overall relativity of behavior seems to remain the same. By following the appearance of sodium in the dissolution of a tablet containing the salt of a drug as well as the drug, two processes may be defined: (*a*) the disintegration–deaggregation–dissolution procedure, which is dependent on the tablet formulation; and (*b*) the solubility–dissolution behavior of the drug itself. Consequently, the inherent dissolution characteristics of the tablet formulation may be seen and changes in dissolution caused by various formulation ingredients may be adjusted. Furthermore, availability of the drug itself can be analyzed.

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Suspension Polymerization for Preparation of Timed-Release Dosage Forms

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Abstract □ An investigation was undertaken to develop a process, utilizing suspension polymerization, for the production of timed-release medicated dosage forms. The effects of production variables upon dissolution of acetaminophen from these dosage forms were studied. Nonexpanded spherical polystyrene beads produced in the presence of acetaminophen exhibited no timed release of medication. However, timed release of medicament was observed when spherical polystyrene beads produced in the absence of acetaminophen were expanded with the aid of a blowing agent and subsequently allowed to absorb medicament. In general, 64% of the available drug was released from the free expanded polystyrene beads within the 1st hr of dissolution, with an additional 29% being released by the conclusion of dissolution testing.

Keyphrases □ Suspension polymerization—formation of timed-release dosage forms, polystyrene beads containing acetaminophen □ Polymerization, suspension—formation of timed-release dosage forms, polystyrene beads containing acetaminophen □ Acetaminophen timed-release dosage forms—prepared by suspension polymerization of polystyrene □ Polystyrene beads—prepared by suspension polymerization for timed release of drugs (acetaminophen) □ Timed-release dosage forms—preparation, suspension polymerization

Although the technique of suspension polymerization has been in use for more than 40 years, its application to the production of a pharmaceutical dosage form had not been studied until very recently. One of the first pharmaceutical investigations involving suspension polymerization was undertaken by Khanna *et al.* (1). In their work, methyl methacrylate, vinyl acetate, and divinylbenzene were polymerized in suspension to produce spherical beads containing medicament. The variables studied included type of medicament, speed of agitation, length of polymerization, and concentration of suspension stabilizers added to the aqueous phase.

An investigation into the release of medicament from spherical beads produced by suspension polymerization has been undertaken. Styrene monomer, alone or in the presence of medicament, was polymerized to produce spherical beads. A portion of these beads was then expanded with the aid of a blowing agent, and dissolution studies were conducted on both the nonexpanded and expanded polystyrene beads.

Suspension polymerization is synonymous with bead or pearl polymerization. In this process, the monomer is dispersed by vigorous mechanical agitation into small droplets. These droplets are suspended in a second liquid phase in which both the monomer and polymer are insoluble. The droplets of monomer are polymerized with the aid of a catalyst and heat while dispersion is maintained. Agents that hinder the coalescence of these droplets during polymerization are added to the suspending liquid.

Depending upon the particular monomer treated, hard or soft spheres, beads, or, less often, irregularly shaped granules are formed. The intense heat of polymerization, common to most monomers, is dissipated rapidly; easily filtered products, which may then be dried, can be obtained from many types of monomers.

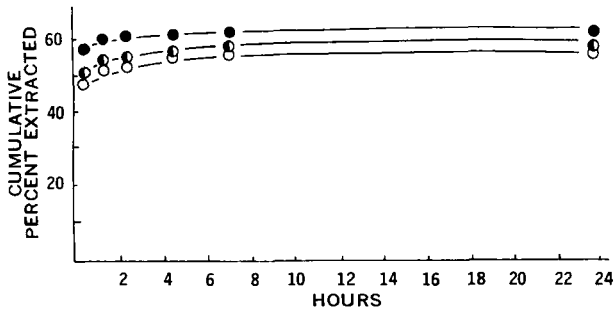

Figure 1—*Dissolution patterns of acetaminophen from non-expanded polystyrene beads. Key:* ●, $N_3S_2P_1$; ◐, $N_3S_2P_2$; *and* ○, $N_3S_2P_3$.

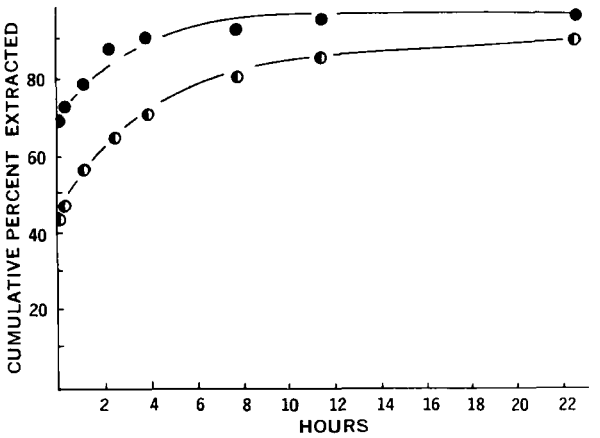

Figure 2—*Dissolution patterns of acetaminophen from expanded polystryrene bead formulations. Key:* ●, *Formulation 1; and* ◐, *Formulation II.*

EXPERIMENTAL

Materials—The following were used:

Monomers—Styrene[1], divinylbenzene[1], ethylvinylbenzene[2], and methyl methacrylate[1].

Catalysts—Benzoyl peroxide[1] and 2,2′-azobisisobutyronitrile[1].

Suspension Stabilizers—Reagent grade sodium sulfate, sodium polyacrylate[3], polyvinyl alcohol[1], and reagent grade dibasic calcium phosphate.

Drugs—Acetaminophen and sulfaethidole, drug grade.

Suspension Polymerization Apparatus—*Principle of Operation*—An apparatus similar to that used by Khanna *et al.* (1) was employed. Bead size was controlled by carefully regulating the rate of agitation and by varying the concentration of suspension stabilizers added to the aqueous phase. For this investigation, a bead size of approximately 30 mesh was desired.

Production Procedures—Polymerization with styrene as the only monomer was conducted in the presence of 0.4 g of calcium phosphate and 0.1 g of polyvinyl alcohol. Polymerization of styrene–divinylbenzene–ethylvinylbenzene terpolymer was conducted in the presence of 2.4 g of sodium carboxymethylcellulose. Three speeds of agitation, 400, 450, and 500 rpm, were used to obtain dispersion of the monomer; two dispersion stabilizers, sodium polyacrylate (in concentrations of 0.05, 0.10, and 0.15%) and sodium sulfate (in concentrations of 0.50, 1.00, and 1.50%), were incorporated in the formulations. To designate individual samples, the following system of nomenclature was used for the non-expanded polystyrene beads:

Speed of Agitation	Sodium Polyacrylate Concentration	Sodium Sulfate Concentration
N_3 = 400 rpm	P_1 = 0.05%	S_1 = 0.50%
N_4 = 450 rpm	P_2 = 0.10%	S_2 = 1.00%
N_5 = 500 rpm	P_3 = 0.15%	S_3 = 1.50%

All formulations of nonexpanded beads were prepared in 600 ml of water using 100 g of monomer and 1 g of benzoyl peroxide as catalyst. To produce beads, the water was added to a 1000-ml, three-necked, round-bottom flask and then placed in an 84° water bath. While stirring, the dispersion stabilizers were added to the flask through the center neck and the flask was flushed with nitrogen. When the contents of the flask were well dispersed, with continuous stirring, the monomer, catalyst, and medicament, previously mixed, were added through the center neck. The reaction was allowed to continue for 24 hr at the specified temperature and rate of agitation. Following polymerization, the beads were filtered, washed with several portions of water, and allowed to dry at 70°.

Preparation of Expanded Beads—To manufacture expanded beads, nonexpanded beads were first produced in the absence of drug according to the previous procedure using 450 rpm, 3 g of sodium sulfate, and 0.9 g of sodium polyacrylate. The beads were then sieved and those beads retained on a 30-mesh screen were placed in *n*-pentane and vigorously agitated for various times. When agitation was discontinued, the beads were filtered and added slowly to boiling water. Four formulations of expanded beads were prepared. All formulations were identical except for the length of time they were exposed to *n*-pentane. Formulations I, II, and III were exposed to *n*-pentane for 24 hr while Formulation IV was exposed to *n*-pentane for only 12 hr. After expansion, the beads were placed in a concentrated alcoholic solution of acetaminophen (1 g of acetaminophen/10 ml of 95% ethanol) and agitated for 24 hr.

Preparation of Tablets from Expanded Beads—Several samples of the dried expanded polystyrene beads containing acetaminophen were accurately weighed. Accurately weighed portions of potassium chloride were then added in specific proportions so that a mixture weighing exactly 0.5000 g would be obtained. Potassium chloride was added to demonstrate the effect of a channeling agent upon dissolution of acetaminophen from the compressed tablets. These mixtures were then compressed at each of two different pressures (3000 and 6000 psi) using a press[4] and a 1.27-cm (0.5-in.) test cylinder. The finished tablets weighed 0.5000 ± 0.005 g. Tablets were made to contain 0, 20, and 40% potassium chloride. No binders or lubricants were added.

Test Methods—*Assay Procedure*—A modified spectrophotometric assay based upon the NF assay for acetaminophen (2), using a grating spectrophotometer[5], was used to determine the acetaminophen content of the various formulations. A standard curve was constructed using five different concentrations of acetaminophen in absolute methanol, and absorbances were determined at 250 nm. Using the method of least squares, a plot of concentration *versus* absorbance was made to establish the existence of a linear relationship which agreed with Beer's law.

To assay for drug content, the polymer beads were pulverized using a wedgewood mortar and pestle to a fine (approximately 50-mesh) powder and accurately weighed portions were placed into 100-ml volumetric flasks containing 1.0 ml of 0.1 *N* hydrochloric acid and made to volume with absolute methanol. The flasks were allowed to stand for 1 hr with occasional shaking. At the end of this time, the contents of the flasks were filtered and the insoluble polymer removed. Specified quantities of the filtrate were added to each of two 50-ml volumetric flasks containing 0.5 ml of 0.1 *N* hydrochloric acid and made to volume with absolute methanol. Absorbances of the samples were then determined against a reference standard consisting of 1.0 ml of 0.1 *N* hydrochloric acid in enough methanol to make 100 ml. Samples of polystyrene beads containing no acetaminophen were treated in a similar manner to determine if any impurities had been extracted that might interfere with the assay. No interference was noticed.

Density—Bulk density of the various formulations was determined by placing a known quantity of the polymerized beads into a 100-ml cylindrical graduate. The graduate was then dropped,

[1] Matheson, Coleman and Bell, Norwood, Ohio. Monomers were washed with 1 *N* sodium hydroxide before use to remove stabilizer.
[2] Evisol, Foster Grant, Leominster, Mass.
[3] Acrysol, Rohm and Haas, Philadelphia, Pa.
[4] Carver laboratory press model C.
[5] Beckman model DB-GT.

from a height of 5.08 cm (2 in.), five times onto a desk top. The bulk density was then calculated by dividing the weight of beads added to the graduate by the volume occupied by the beads after tamping.

True density was determined using a pycnometer and filling it with 95% ethanol. Subsequent calculations provided the true density.

Dissolution—Dissolution studies were conducted using the apparatus described by Souder and Ellenbogen (3).

Approximately 2-g samples of beads, accurately weighed and containing drug, were placed into eight 90-ml, glass, screw-cap vials. To each vial was added 60 ml of prewarmed simulated gastric fluid USP. The glass vials were then rotated, end-over-end, at 40 rpm in a water bath maintained at 37°. One vial was removed at each of the following time periods: 0.25, 0.50, and 1.50 hr. The five vials remaining after 1.50 hr were also removed and filtered to allow replacement of gastric fluids by prewarmed simulated intestinal fluid USP. The five vials were returned to the dissolution apparatus, and one vial was then removed at 2.33, 4.50, 7.00, and 24 hr from the start of dissolution testing.

A similar procedure was followed for samples of tablets compressed from the expanded beads.

Typical release patterns from nonexpanded and exanded bead formulations are presented in Figs. 1 and 2. The effect that slight changes in porosity has upon dissolution is very evident in Fig. 2. Although Formulations I, II, and III were exposed to *n*-pentane for the same time, they each exhibited slightly different values for porosity, thus leading to different rates of dissolution.

RESULTS AND DISCUSSION

All beads produced by the suspension polymerization procedure employed in this investigation were of a white opaque nature and were free flowing. The nonexpanded polystyrene beads of all formulations were almost perfect spheres containing several areas of entrapped gas. Closer examination indicated that these areas of entrapped gas were not interconnecting. Expansion of the polystyrene beads produced particles which were distorted; however, they still possessed spheroidal characteristics. These beads possessed many internal interconnecting channels and considerable external pore openings. Examination of tablets compressed from the expanded beads revealed that most individual beads retained their original shape, but some were deformed to various degrees. Channels between the individual beads in the tablet were also in abundance.

A major preliminary problem encountered in this investigation was the instability of the medicament in the reaction medium during the polymerization period. Initially, sulfaethidole was the test drug chosen for incorporation. However, it underwent considerable chain transfer and was, therefore, unsuitable for use in the polymerization process. Acetaminophen was selected on the basis of its compatibility with the reactants.

Polymerizations involving the terpolymer, styrene–divinylbenzene–ethylvinylbenzene, did not yield beads suitable for this investigation. Considerable agglomeration of the polymer and degradation of the medicament were observed. It was, therefore, decided to limit this study to styrene.

Initially, styrene was polymerized in the presence of acetaminophen. The average percent acetaminophen in the 27 different formulations of the nonexpanded beads was found to be 1.30%. Dissolution studies revealed that the nonexpanded polystyrene beads released an average of 64% of the available medicament within the first 30 min of dissolution. No further increase in the amount of drug released was noticed throughout 24 hr of dissolution testing. This appears to indicate that 64% of the dissoluted drug was drug located on or near the surface of the bead; the 36% not available for use was bound internally by the plastic matrix.

To overcome this problem, several samples of spherical polystyrene beads were produced in the absence of drug. These beads were then expanded with the aid of a blowing agent. After expansion they were exposed to a concentrated alcoholic solution of acetaminophen (1 g of acetaminophen/10 ml of 95% ethanol) for 24 hr. Drug content of these formulations was dependent on the porosity of each formulation. Those beads exposed to *n*-pentane for 24 hr (Formulations I, II, and III) exhibited an average porosity of 92.4% and contained an average of 20.4% acetaminophen. Formulation IV, exposed to *n*-pentane for only 12 hr, showed considerably less porosity, 40.5%, and a greatly diminished drug content, 5.78%. Dissolution studies indicated that the expanded polystyrene beads released 64% of the available medicament within the first 30 min of dissolution. However, they also provided for an exponential release of an additional 29% throughout the 24 hr of dissolution testing.

Tablets compressed from the expanded beads, containing a channeling agent, released 86% of the drug during the first 30 min and released an additional 12% of available acetaminophen over 12 hr. The expanded polystyrene beads employed were found to exhibit two distinct phases of drug release. The first phase occurs very rapidly and is believed to be due to dissolution of the drug from the surface of the bead. The second phase occurs at a much slower rate and is attributed to leaching of the drug through the channels present in the plastic matrix of the expanded beads.

The investigation was limited to the study of suspension polymerization using initiators which decompose when heated to form free radicals. Most of these initiators are strong oxidizers and, therefore, limit the types of medicaments that may be added to the polymerization reaction. The process of expanding the polystyrene beads and incorporating the medicament after bead expansion allows for an unlimited choice of medicaments.

SUMMARY

The technique of suspension polymerization for incorporation of drugs into a polymer was studied. Nonexpanded polystyrene beads exhibited no timed release of medicament. Expansion of the beads produced a large number of interconnecting channels and allowed the medicament to be released from the bead in a timed-release manner. Drug incorporation into the nonexpanded beads was limited to 1.30% while that of the expanded, more porous beads was about 20.4%.

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