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A unique application and characterization of Eudragit E 30 D film coatings in sustained release formulations

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Summary

Eudragit is an aqueous dispersion of an acrylic resin that is based on poly(ethylacrylate-methylmethacrylate) esters. The polymer is neutral in character and hence is not sensitive to differences in pH. Incorporation of insoluble pharmaceutical additives in Eudragit E 30 D coating formulations instead of the commonly used hydrophilic polymers generated not only programmable sustained release reservoir systems but also protective coatings that are relatively resistant to water vapor permeation. The additives, such as kaolin and talc which are used as received without any pretreatment, exist as discrete particles within the polymeric matrix. Although they are not dispersed at the molecular level as are hydrophilic polymers, the insoluble solids are mixed uniformly within the polymeric dispersion to provide a homogeneous coat. The homogeneity of the coating material was confirmed both by dissolution studies and a microanalytical technique that utilizes an energy dispersive X-ray spectrometer. In addition, scanning electron microscopic examination of the surface morphology of coated pellets that released their contents during dissolution and those which were not subjected to dissolution indicated that the physical adsorption of the insoluble additive in the polymeric matrix is permanent. These properties ensure both short- and long-term stability of the coating material and reproducible in vitro and in vivo release profiles.

Introduction

In the last few years, universities and the pharmaceutical industry have been conducting extensive research aimed at developing water-based polymeric coatings that could be employed in drug delivery systems in order to circumvent the severe restrictions imposed on the use of organic solvents. Water-insoluble polymers such as ethylcellulose and the acrylic polymers, while used extensively in solvent coatings, have had little application in water-based systems until recently when separate groups in the U.S. and the F.R.G. developed aqueous dispersions that could have a tremendous impact on oral drug delivery research. Initially, aqueous film-coating was perceived to have some inherent problems that would render the technique impractical. Some of the drawbacks that were cited were: (a) water would erode the tablet surface during the coating operation; (b) the system would not be applicable to moisture-sensitive active ingredients; and (c) aqueous systems would require longer drying times than organic

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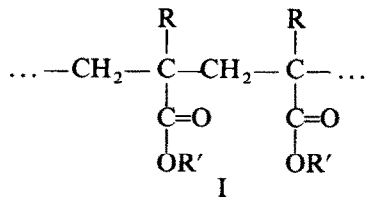
solutions (Hogan, 1982). However, subsequent application of aqueous film-coating to various dosage forms generally proved otherwise. Consequently, a major effort is being made to develop new water-based coating systems and maximize the utility of already existing polymeric dispersions. One of these polymeric colloidal dispersions, which is composed of 30% total solids and commercially available under the trade name of Eudragit E 30 D, has applications in immediate and prolonged release oral dosage forms.

Eudragit E 30 D is an aqueous dispersion of an acrylic resin formed from a copolymer based on poly(ethylacrylate-methylmethacrylate) esters. The polymer, which is prepared by emulsion polymerization (Lehmann and Dreher, 1973) and has a mean molecular weight of about 800,000, does not possess ionizable groups on its backbone (I) and hence is not affected by the pH gradient that prevails in the gastrointestinal tract (Lehmann, 1982).



I

where R = H, CH_3; R′ = CH_3, CH_2CH_3

Consequently, the dispersion has been recommended as a delayed release coating formulation when coupled with various water-soluble hydrophilic film-forming polymers such as polyethylene glycol, polyvinylpyrrolidone and polyvinylalcohol. In contrast, water-insoluble substances are used in conjunction with Eudragit E 30 D mainly as disintegrants in immediate release products or as part of pigment suspensions for providing colored layers of delayed release dosage forms (Lehmann and Dreher, 1981).

In this report, the use of Eudragit E 30 D in combination with a number of water-insoluble pharmaceutical additives as sustained-release formulations for oral dosage forms is described. Kaolin is employed as a model additive. (Additives and pigments are used interchangeably in the text.)

Experimental

Materials. Eudragit E 30 D [1], kaolin [2], non-pareil seeds [3], and hydroxypropylcellulose [4] were used as received. Diphenhydramine hydrochloride [5] was screened through 60 mesh screen [6] prior to preparing the pellets.

Preparation of free films. Different amounts of kaolin and PEG 8000 were respectively dispersed and dissolved in water using a magnetic stirrer and then thoroughly mixed with Eudragit E 30 D to provide dispersions containing 15% w/w total solids. The mixture was continuously stirred while being sprayed automatically and intermittently on a teflon-coated rotating plate. Warm air (60–70°C) was simultaneously directed at the plate to evaporate the water. The plates were temporarily stored at 4°C before the films were removed and stored in a desiccator at room temperature.

Water vapor transmission studies. The water vapor permeability of the films was measured using the Gardner-Park Permeability cup [7]. The cup has a test area of 25 cm^2 and was filled with 8 ml of distilled water. Once the free film was secured in place, the loaded cup was weighed on an analytical balance and placed in a standard glass desiccator using phosphorus pentoxide as the desiccant. The desiccator was kept at a controlled temperature of 37°C and the cup reweighed at specific time intervals for a period of seven days.

Pellet preparation. Non-pareil seeds composed of sugar and starch were placed in a prewarmed chamber of a centrifugal granulator [8]. A binder solution of hydroxypropylcellulose was sprayed onto the seeds while diphenhydramine hydrochloride powder was simultaneously fed at a rate of 50 g/min. Once the pellets were made, they were transferred to a tray and allowed to dry in an oven at 45°C for 24 h. The 12–18 mesh fraction was

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[1] Rohm Pharma GmbH Darmstadt, F.R.G.
[2] Georgia Kaolin, Elizabeth, NJ, U.S.A.
[3] Beaver Food Products, Pennsauken, NJ, U.S.A.
[4] Hercules, Wilmington, DE, U.S.A.
[5] Warner-Lambert, Holland, MI, U.S.A.
[6] U.S. Standard Sieves, E.H. Sargent and Co., Chicago, IL, U.S.A.
[7] Gardner Laboratory Division, Bethesda, MD, U.S.A.
[8] CF-360, Freund Industrial Col., Ltd., Tokyo, Japan.

screened and stored at room temperature prior to coating.

Coating procedure. The coating formulation was prepared by intimately mixing a suspension of kaolin in water and the desired quantity of Eudragit E 30 D dispersion. The polymeric dispersion was filtered through a fine sieve (120 mesh) prior to use in order to remove solid or film particles. Kaolin was used as received, although it can be ball-milled, if necessary. A known weight of pellets was transferred to a fluidized bed coating machine [9] and coated to a 20% weight increase. The coated pellets were then transferred to a paper-lined tray and dried at room temperature. The formulation was stirred throughout the coating process.

Dissolution. In vitro dissolution studies were carried out using the USP dissolution apparatus II (Paddle) at 37°C and 75 rpm [10]. The dissolution medium was water. Samples were withdrawn and dissolution medium replaced automatically at preselected time intervals. The quantity of diphenhydramine hydrochloride was assayed spectrophotometrically [11] at 258 nm.

Scanning electron microscopy. In one experiment, coated pellets were embedded in a mixture of purified paraffin and a synthetic polymer and sliced to provide cross-sectional views of the particles. The embedded and sliced samples were then mounted on a metal stub, coated with gold and examined using a scanning electron microscope [12] at a magnification of 500× and 5000×. In another experiment, coated drug pellets were sectioned, mounted on carbon paint and coated with a conductive carbon coat. The samples were then subjected to an electron beam of sufficient energy (30 kV) and the emitted X-rays were detected by an energy dispersive X-ray spectrometer [13]. X-Rays characteristic of the elements within the sample were collected and displayed as a function of the cross-sectional area of the pellet. While the entire spectrum was collected, only the relative intensities of silicon and aluminum in the coating material and chlorine in the drug layer were monitored and compared. Furthermore, free films were mounted on a metal stub, coated with gold and examined.

[9] Strea I, Aeromatic, Towaco, NJ, U.S.A.
[10] Hanson Research, Northridge, CA, U.S.A.
[11] DU-7 Spectrophotometer, Beckman Instruments, Inc., Somerset, NJ, U.S.A.
[12] Amray, Bedford, MA, U.S.A.
[13] Econ 9100/60, Edax International, Prairieview, IL, U.S.A.

Results and Discussion

Eudragit E 30 D aqueous dispersion has a great potential as an oral controlled-release agent. It has high resistance to environmental effects such as light, air and water, and is inert towards digestive secretions and pH as well as towards microbial attack (Lehmann and Dreher, 1973). Consequently, predictable and reproducible drug release characteristics may be consistently achieved. However, the resin is extremely tacky and almost impossible to be used alone as a coating formulation. Polyethylene glycol and other water-soluble hydrophilic polymers, when employed in sufficient quantities, not only reduce the inherent tackiness associated with Eudragit E 30 D but also modify the permeability characteristics of the polymeric network and provide sustained release formulations (Lehmann and Dreher, 1981). These substances, however, by virtue of their hydrophilicity may increase the uptake of moisture from the surroundings and reduce the shelf-lives of products. It was hypothesized, therefore, that a formulation composed of Eudragit E 30 D and a number of water-insoluble pharmaceutical additives could circumvent the problem of reduced shelf-life while maintaining the advantages of the water-soluble hydrophilic polymers cited above. One such additive that is commonly used as disintegrant in the pharmaceutical industry and was chosen as a model is kaolin. Therefore, coating formulations composed of different ratios of Eudragit E 30 D and kaolin were prepared and characterized.

Mechanism of film formation

Unlike other methods of film deposition, film-formation from polymeric emulsions, including Eudragit E 30 D, is a complex process that involves loss of water, either into the atmosphere or

into a porous substrate with a concomitant fusion of individual and discrete polymer particles into a homogeneous mass (Waldie, 1983). The driving force for the coalescence of the polymer particles arises from surface tension and capillary forces. Water has a high tensile strength and generates enough pressure to deform the small polymeric spheres during evaporation and film-drying. Whether the specific requirements for film-formation are met with or not depends upon the deformability and hence the chemical composition of the polymer. The polymeric spheres must deform sufficiently under the existing stresses to achieve a continuous and permanent film. In addition, the rate of water withdrawal should not outpace the rate of deformation of the polymer particles. Otherwise, film integrity will be greatly impaired. Other factors which accelerate, retard or even inhibit film-forming are relative humidity and, particularly, temperature. Water evaporates slowly at lower temperatures and would theoretically provide better film-forming conditions. However, as the temperature drops, the polymeric particles start to harden and their resistance to deformation increases.

Although favorable conditions are essential to obtaining desirable film characteristics, the key to film formation is the glass transition temperature (T_g) of the polymer. Above the T_g, the polymer chains have appreciable mobility and are conducive to film formation, while below T_g, the chains are immobile, except for movements around the equilibrium position, making it very difficult for the polymer particles to coalesce. A closely associated property of polymers is the minimum film formation temperature (MFFT), which is several degrees above T_g. A well-integrated film is obtained only if the processing temperature is above MFFT. Since the film-forming temperature of Eudragit E 30 D formulations is less than 20°C, formation of a continuous film at room temperature or above is ensured (Lehmann and Dreher, 1973).

A property which has special significance to the formation of pigmented films such as employed here is the critical pigment volume concentration (CPVC). Above CPVC, pigmented films become proportionately more porous and permeable as the amount of insoluble additives incorporated in the formulations is increased. Below CPVC, however, the permeability of the films is essentially independent of additive concentration. Factors which influence the CPVC include deformability and glass transition temperature of the polymer, particle size of the emulsion spheres and the tendency of the pigments to remain deflocculated in the pigmented film.

Water vapor transmission

Water vapor transmission studies indicated that, at the quantities employed, incorporation of water-insoluble additives such as kaolin in Eudragit E 30 D formulations brought about a significant change in the water vapor permeabilities of the free films. The permeability constants of a series of films progressively increased as the amount of kaolin was increased relative to the Eudragit E 30 D resin in the final film (Table 1). Although the relationship between permeability and amount of kaolin in the films appears to be linear in nature, it is difficult to make a conclusive statement based on the small number of data points available.

The increase in the permeation of water vapor through the free films with increasing amounts of kaolin in the films is attributed to channels that may be formed among kaolin particles or at the interface between kaolin and the resin. It may also be due to weak spots that are formed as a result of the entrapment of kaolin particles during film formation. The existence of these weak spots and artifacts becomes apparent upon examination of the scanning electron microscopic photomicrographs of the various films (Fig. 1A–D). The

TABLE 1

WATER VAPOR TRANSMISSION THROUGH EUDRAGIT E 30 D FREE FILMS

Film composition	Permeability constant cm/h × 10^5
Eudragit E 30 D	1.21
Eudragit E 30 D : Kaolin (3 : 1)	1.51
Eudragit E 30 D : PEG 8000 (3 : 1)	8.56
Eudragit E 30 D : Kaolin (1 : 1)	1.93
Eudragit E 30 D : PEG 8000 (1 : 1)	38.80

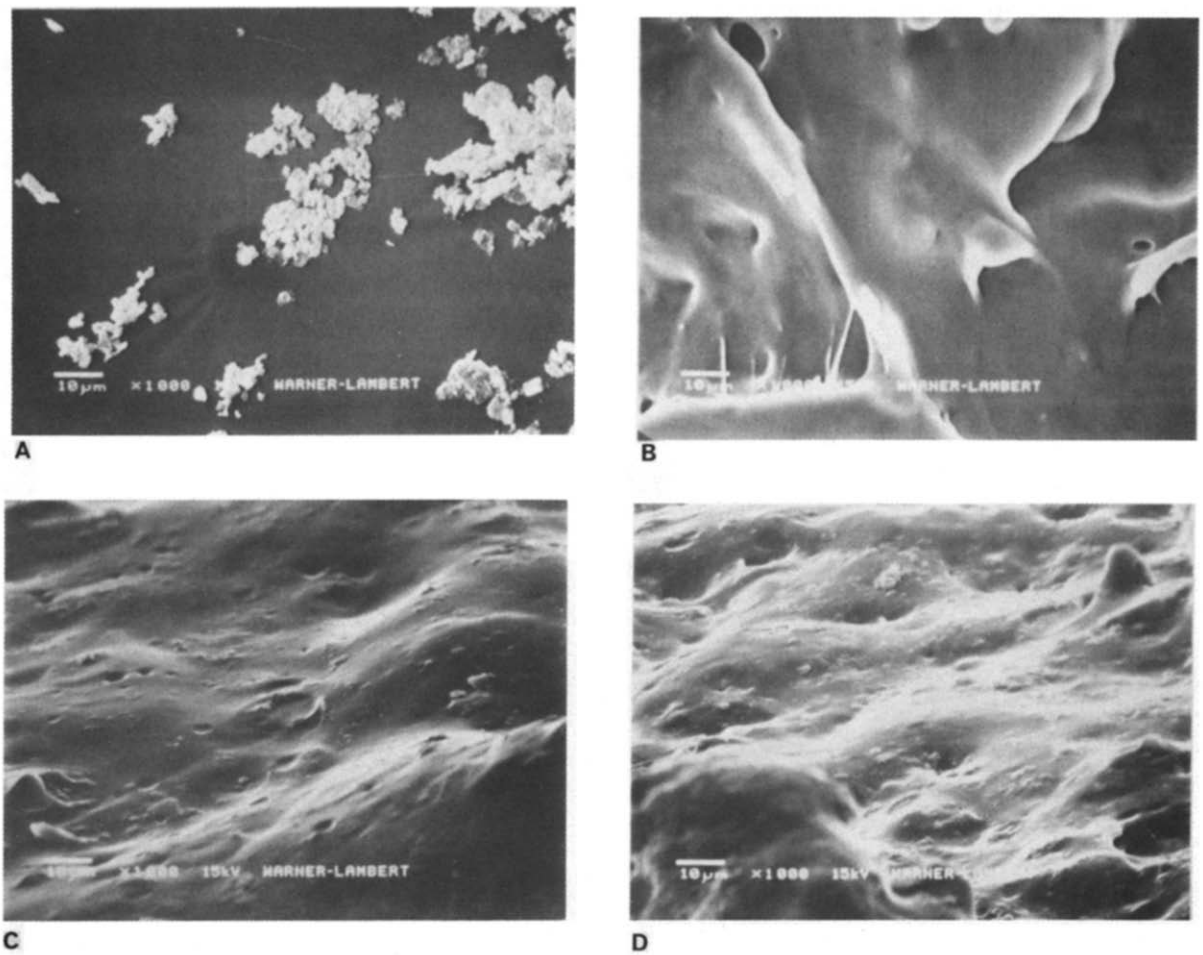

Fig. 1. Scanning electron photomicrographs of (A) kaolin, and free films composed of different ratios of kaolin to Eudragit E 30 D resin: (B) 0 : 1, (C) 1 : 3, (D) 1 : 1.

photomicrographs show the gradual transformation of a smooth film when Eudragit E 30 D was used alone, to films with a lot of identations and ridges as the ratio of kaolin to Eudragit E 30 D is increased. This observation is consistent with the properties of pigmented films (Porter, 1982). Although they are highly impermeable to moisture below the critical pigment volume concentration (CPVC), above CPVC, pigmented films become more porous as the amount of pigments incorporated in the formulations is increased, thereby leading to a corresponding increase in water vapor permeability. When polyethylene glycol 8000 was incorporated in Eudragit E 30 D formulations in quantities similar to that of kaolin, it provided films that were more permeable (Table 1). The permeability, however, does not appear to be linearly related to PEG content. It is apparent, therefore, that the use of kaolin and other water-insoluble additives in Eudragit E 30 D formulations instead of the hydrophilic film-formers offers better protective coating for moisture-sensitive drugs.

Coating process

Like with any other aqueous polymeric dispersions or latex, a special advantage of Eudragit E 30 D as a coating material is that water is only a dispersion medium rather than a solvent for the

TABLE 2

RELEASE RATES OF DIPHENHYDRAMINE HYDROCHLORIDE PELLETS OBTAINED FROM THE SAME BATCH, COATED TO 20% WEIGHT INCREASE WITH KAOLIN/EUDRAGIT RESIN (2 : 3)

Time (h)	Percent released						
	No. 1	No. 2	No. 3	No. 4	No. 5	X *	S_X **
1	14.1	14.9	14.4	15.1	15.1	14.7	0.45
2	34.6	35.2	34.7	35.1	35.1	34.9	0.27
4	54.9	55.3	54.6	54.9	55.2	55	0.28
6	67.8	68.1	67.2	67.4	67.6	67.6	0.35
8	76.6	76.7	75.8	76.0	76.4	76.3	0.39
10	83.0	83.3	81.8	82.1	82.8	82.6	0.63
12	87.9	87.9	86.5	86.8	87.3	87.3	0.63

* X = mean.

** S_X = standard deviation.

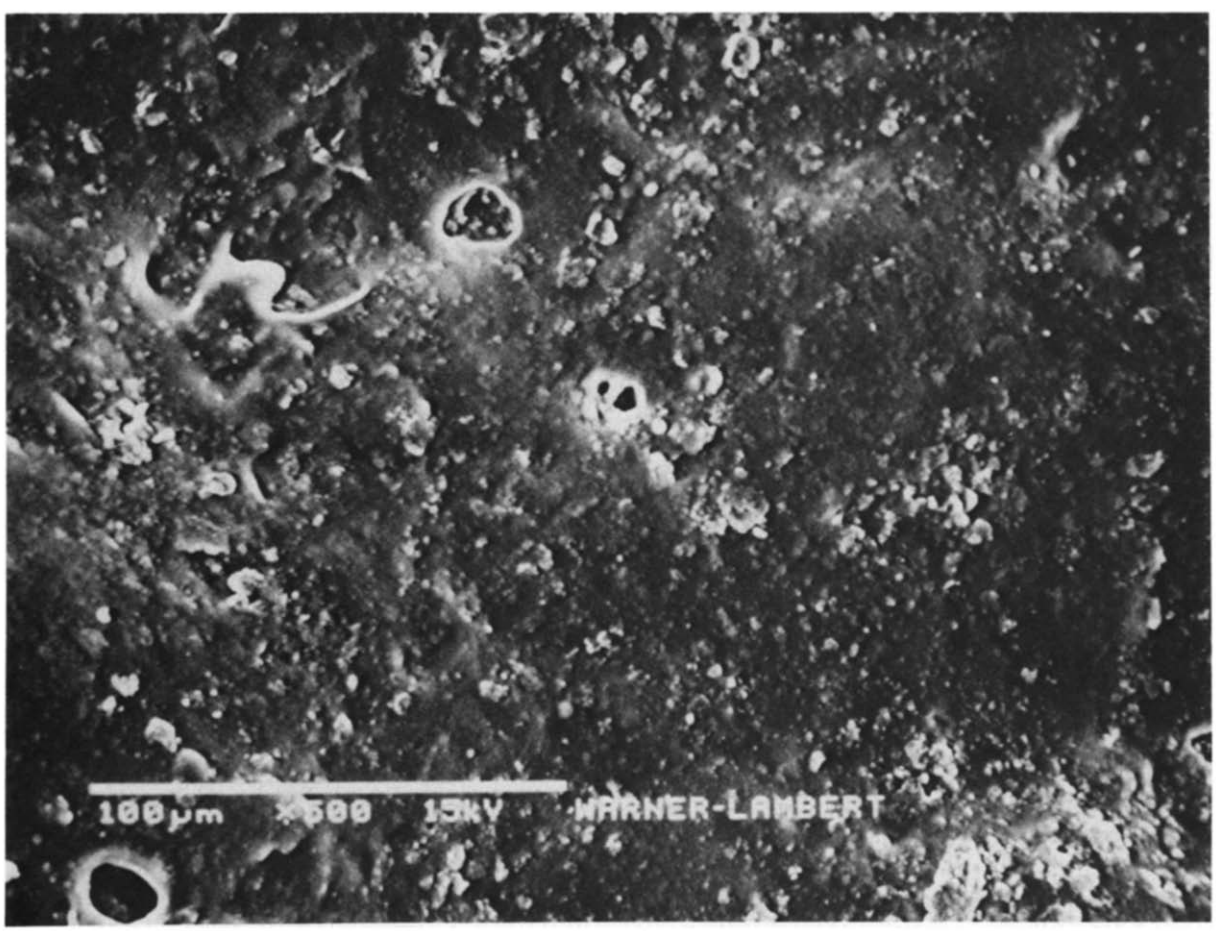

Fig. 2. Scanning electron photomicrograph of the surface of diphenhydramine pellet after dissolution.

polymer and therefore is not retained by the acrylic resin during film formation. When the liquid formulation is sprayed into the dry air stream (fluidizing air) of the coating equipment, the water evaporates rapidly. The short drying time, therefore, enables the aqueous dispersion to be processed, in most cases, without special sealing of the pellet cores against water. During coating, the bed temperature should be kept around 26°C, especially when the coating is done in small size fluidized bed equipment. Not only is this temperature high enough to drive off the water at a reasonable rate but it is within the necessary temperature range for the formation of a continuous film that is free from cracks as cited earlier. If the product temperature is maintained very high, the coating material becomes tacky due to the low glass transition temperature of the polymer and can lead to an undesirable agglomeration of the pellets. With large fluidized bed equipment like the Glatt CPCG-5, product temperature is not as critical due to the high fluidization air volume and efficient mixing that is normally employed. Assay of coated pellets revealed that the procedure is highly reproducible. Dissolution studies also showed that pellets sampled from the same batch provided similar release profiles as shown in Table 2. The ratio of kaolin to Eudragit E 30 D resin in the film coat of these particular pellets was 2 : 3, although other ratios which provide different release patterns have also been prepared.

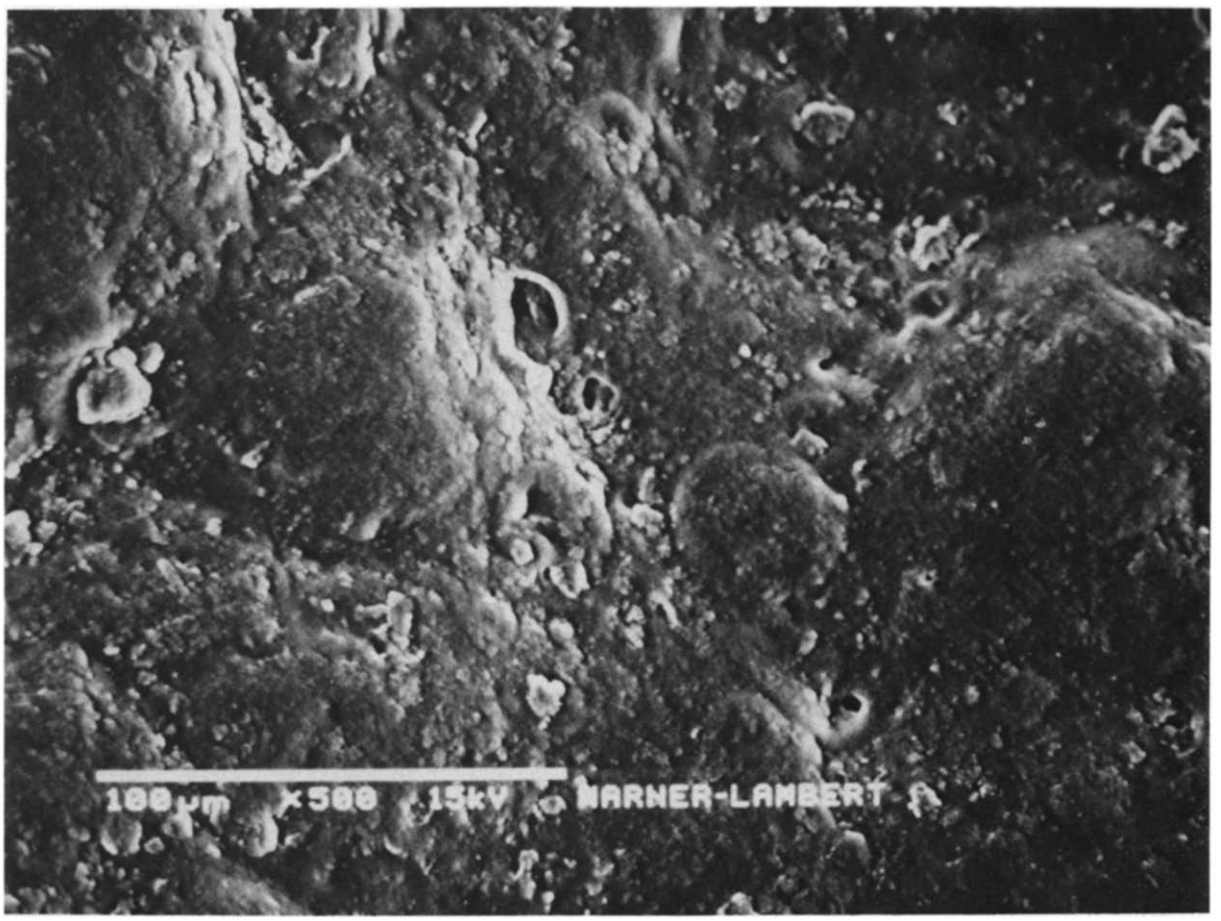

Fig. 3. Scanning electron photomicrograph of the surface of diphenhydramine pellet before dissolution.

Scanning electron microscopy

Scanning electron microscopic examination revealed that the surface morphology of diphenhydramine hydrochloride pellets that released their contents during dissolution was roughly the same as of those which were not subjected to dissolution (Figs. 2 and 3). This observation suggests that the physical adsorption of kaolin to the matrix is permanent and will withstand the rigorous mixing in the gastrointestinal tract.

The technique was also used to evaluate the homogeneity of the coating materials using line scan and point analysis.

Line scan analysis

A series of line scans (about 90 μm in length) on a cross-section of a pellet including the drug layer, film coat and drug layer/film coat interface revealed conclusively the applicability of the technique for the characterization of the components of the pellet. Not only did the procedure show, respectively, the direct relationship between the silicon and chlorine levels and the exposed surface of the coating material and the drug layer, but it also demonstrated clearly the homogeneity of the components of the pellet. The line scans labeled Drug Layer 1, Drug Layer 2, Interface

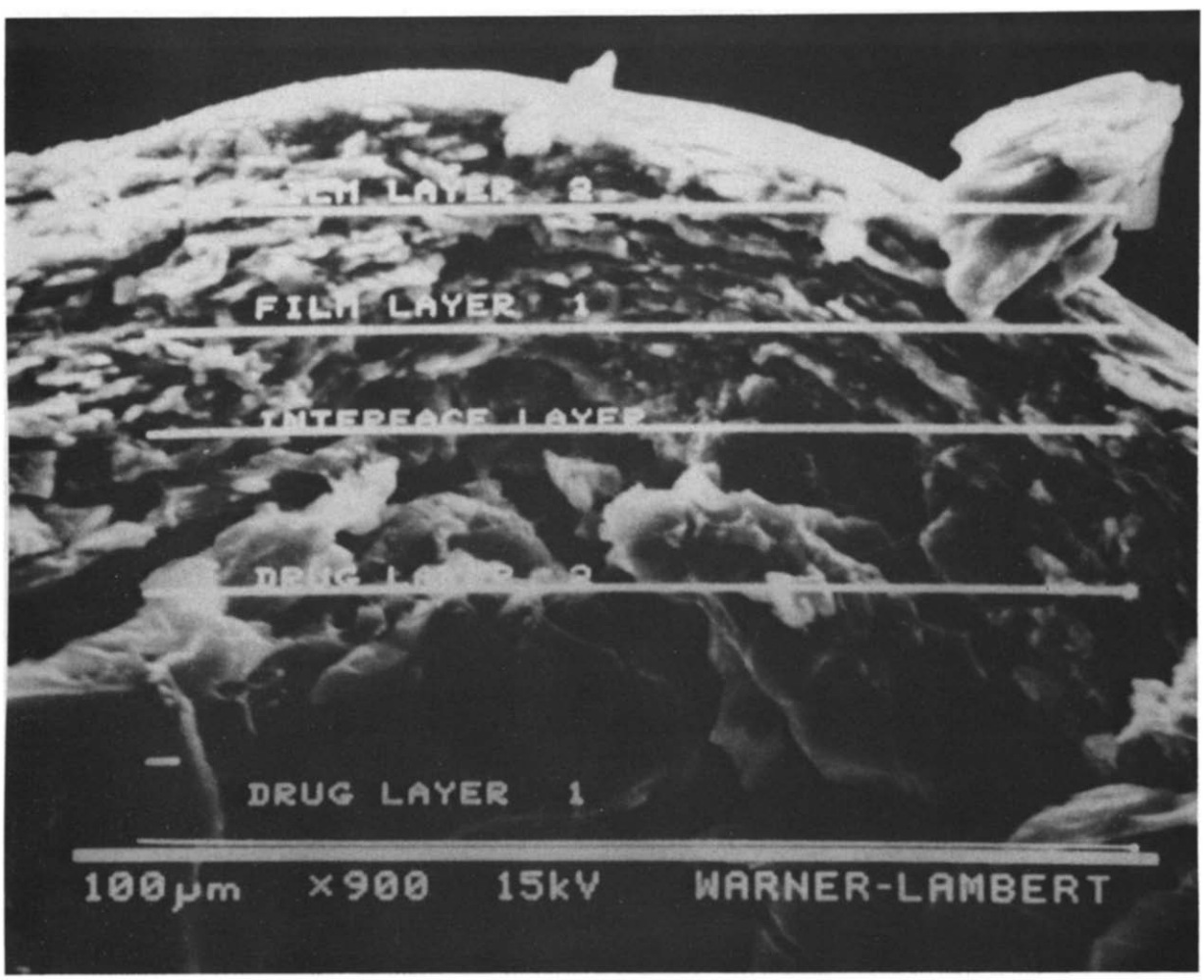

Fig. 4. Scanning electron photomicrograph of a sectioned pellet depicting traces of a series of line scans.

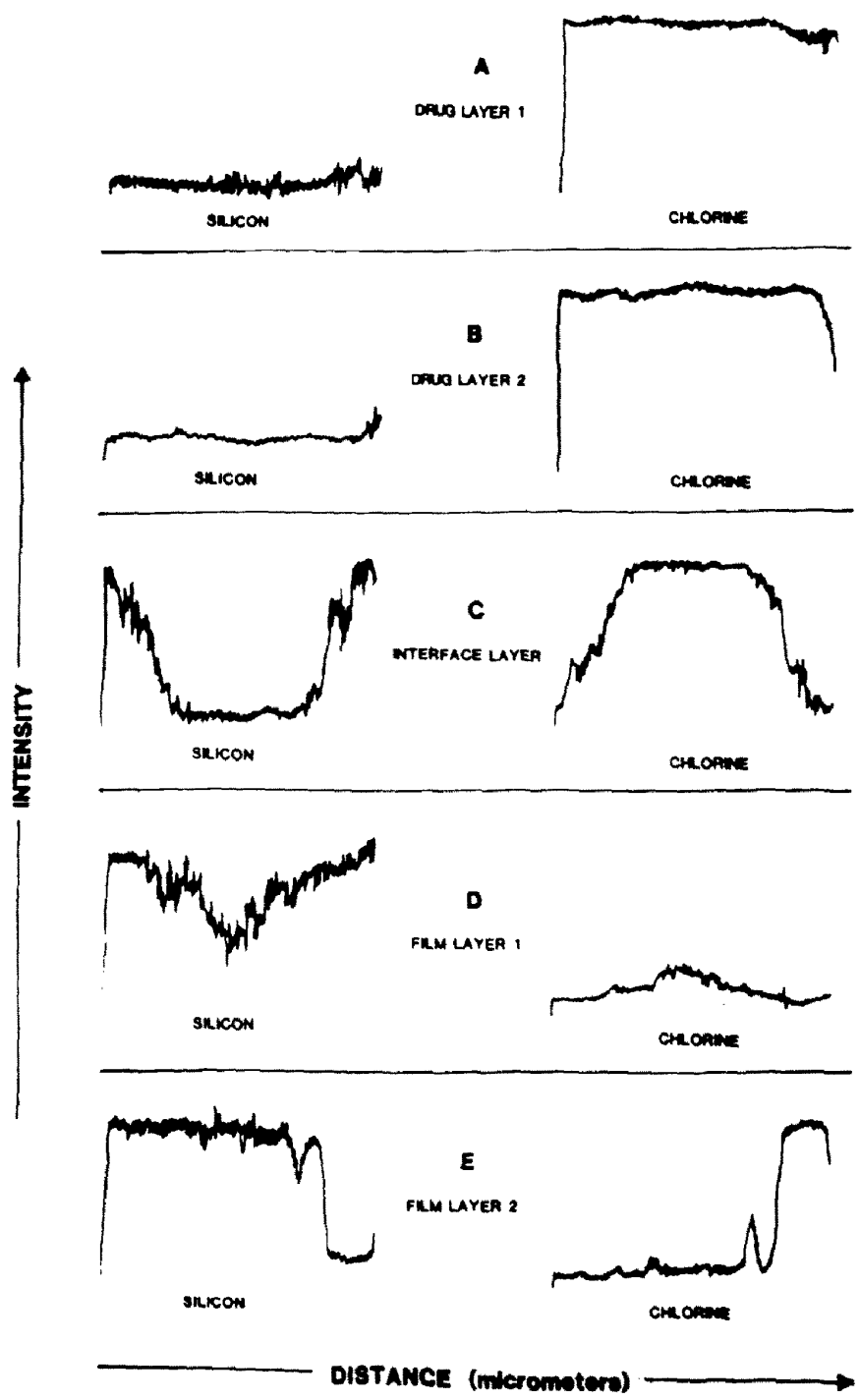

Fig. 5. Silicon and chlorine distribution across a sectioned pellet.

Layer, Film Layer 1 and Film Layer 2, are depicted on the photomicrograph of a sectioned pellet in Fig. 4. The corresponding silicon and chlorine levels expressed as a function of a given location on the sliced pellet are given in Fig. 5 and are described below.

Drug Layer 1 (Fig. 5A). This line, which is 34.1–68.2 μm beneath the surface of the coated pellet, traverses only the drug layer. As a result, a high and constant level of chlorine is detected. No significant level of silicon was observed.

Drug Layer 2 (Fig. 5B). Since this line also resides mostly in the drug layer, once again an even distribution and high level of chlorine and no detectable level of silicon were found. On the right side, where the line barely touches the film coat, a slight rise in silicon level with a drop off in the chlorine was observed.

Interface Layer (Fig. 5C). This line bisects the drug layer/film coat interface twice. The whole field of view is of a nodule on the pellet, so the curvature observed along this line is not representative of the whole pellet. As the scan penetrates the drug layer moving from left to right, the levels of silicon and chlorine interchange positions. Initially, the silicon levels were high due to the partial exposure of the film coat. At this point, no detectable level of chlorine was observed. This situation was followed by a gradual increase in the level of chlorine and simultaneous decrease in the amount of silicon present. This portion of the pellet comprises the first interface. Moving further to the right brought about the drug layer. Here, consistent with earlier findings, a high and uniform distribution of chlorine and little trace of silicon were detected. Following the drug layer, the line scan reached the second interface, in which a gradual drop off in chlorine and an increase in silicon level were observed. Finally, the line penetrated the film coat where a high level of silicon was detected with no noticeable quantities of chlorine.

Film layer 1 (Fig. 5D). Although this line resides mostly on the film coat, a portion also passes through the film coat/drug layer interface. Consequently, at the interface, a slight increase in chlorine and a corresponding decrease in silicon level were observed. Because the two interfaces mentioned earlier are very close to each other, silicon and chlorine did not reach, respectively, the minimum and maximum levels described above.

Film Layer 2 (Fig. 5E). The position of this line is exactly opposite to Drug Layer 1 in that it exclusively covers the film coating. High and constant levels of silicon with no detectable quantities of chlorine were observed. The sudden rise in chlorine level and drop off in silicon level is due to a drug layer fragment formed during sectioning and lodged on the film coat. The position and size of the fragment is clearly shown in Fig. 4.

Point analysis

In addition to line scan analysis, the scanning electron microscope along with energy dispersive X-ray spectrometer has the added feature of scanning pinpoint locations on any given surface. Therefore, after the initial spectra and line scan were generated, specific points on the surface of the pellet were scanned. Data from each point were collected for 200 live seconds and reported as weight percent. The determination by weight is done automatically through the spectrometer's computer and is based on the integrated peak intensities rather than peak heights. The solid state silicon detector converts, through various transducers and amplifiers, a well-defined X-ray line into a broad gaussian peak. The width of the peak varies with the energy of the incident X-rays and has a direct effect on peak heights. Two X-ray lines of the same intensity (or number of photons

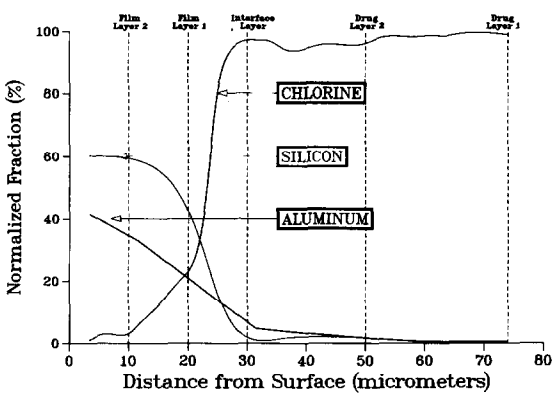

Fig. 6. Distribution of chlorine, silicon and aluminum in a sectioned pellet as a function of distance.

per second) but of different energies are shown as gaussian peaks of equal areas but different heights.

Generally, areas are compared and concentrations determined using appropriate standards. Standards for this type of analysis must represent the unknown material in form and composition. Since proper standards were not available, a standardless semi-quantitative technique was employed. The procedure compared the intensities of the X-rays of the elements and generated relative fractions which are summed to equal 100 to reflect the percent composition (Table 3). Since the entire spectrum up to the accelerating voltage of the S.E.M. is read at one time and the analysis performed only on the identified peaks, the drug layer and film-coat composition is evaluated by observing the relationship between kaolin (film-coat) and chlorine (drug layer). Due to differences in the molecular weights, however, the peak intensities and hence the concentrations by weight are different as shown in Fig. 6.

A general equation (Hren et al., 1979) which relates the measured X-ray intensity, I, of a characteristic line of energy, E, and the composition of the area of the specimen where the electron beam strikes is given by:

$$I\,dt = e(E,\alpha) \cdot k \cdot c \cdot n\,dt$$

where e = the efficiency of response of the detector system, c = the concentration in weight per-

TABLE 3

RELATIVE CONCENTRATIONS BY WEIGHT OF ALUMINUM, SILICON AND CHLORINE AS A FUNCTION OF DISTANCE FROM THE SURFACE

	Distance from surface (μm)	Aluminum (%)	Silicon (%)	Kaolin * (%)	Chlorine (%)
Drug Layer 1	73.84	0.46	0.58	1.04	98.96
	65.12	0.11	0.28	0.39	99.61
	63.95	1.19	0.90	2.09	97.91
	60.47	0.44	0.27	0.71	99.29
	59.30	0.83	0.99	1.82	98.18
	57.56	1.03	0.84	1.87	98.13
	52.33	0.63	0.79	1.42	98.58
	51.16	1.71	1.29	3.00	97.00
	50.00	1.81	2.56	4.37	95.63
Drug Layer 2	42.44	2.18	1.74	3.92	96.08
	36.05	3.63	3.21	6.84	93.16
	34.30	1.09	0.96	2.05	97.96
	31.41	1.46	1.08	2.54	97.46
	31.40	2.08	1.67	3.75	96.25
Interface Layer	26.74	5.53	6.30	11.83	88.17
	24.42	1.10	1.41	2.51	97.49
	23.26	27.93	43.98	71.91	28.09
Film Layer 1	19.19	29.00	47.06	76.06	23.94
	13.37	33.85	57.86	91.71	8.29
	11.64	35.20	55.99	91.19	8.81
	11.63	35.32	58.79	94.11	5.89
Film Layer 2	10.47	38.50	60.47	98.97	1.03
	5.81	36.99	59.11	96.10	3.90
	3.50	38.83	60.56	99.39	0.61
	3.49	39.02	60.02	99.04	0.96

* Aluminum + silicon = kaolin.

cent, n = the number of electrons bombarding in dt, α = the angle of incident X-ray beam entering the detector, and k = the X-ray time generation constant. When comparing two X-ray lines, the equation is reduced to:

$$\frac{C_1}{C_2} = k_{12} \cdot \frac{I_1}{I_2}$$

where k_{12} represents various correction factors. It is apparent from these equations that the concentration (in weight percent) of a given element in a given specimen is proportional to the intensity of the X-rays which in turn is related to the recorded peak areas.

Conclusion

Although incorporation of hydrophilic polymers into Eudragit E 30 D sustained release formulations has been the generally recommended approach, incorporation of insoluble pharmaceutical excipients not only opens up a new avenue, but also appears to have a decided edge in a number of ways. It offers a better protective potential for moisture-sensitive bioactive agents. It combats the tackiness problem that is frequently observed with Eudragit E 30 D formulations better. Moreover, preliminary indications are that it provides a more stable film-coating. Since the pH independence of the coating material is kept intact with a proper choice of additive, pH-sensitive additives should be avoided if the same release profile throughout the pH gradient of the gastrointestinal tract is desired. Additives such as talc and magnesium trisilicate have been tested and provided comparable modified release behavior.

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