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THE EFFECT OF ADSORBED WATER ON COMPACTION PROPERTIES AND THE DISSOLUTION OF QUINACRINE HYDROCHLORIDE FROM COMPACTED MATRICES OF SOY PROTEIN

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ABSTRACT

Albuminoid proteins are a byproduct of soya bean processing and are widely employed as inexpensive food additives. Native (undenatured) commercial soy protein has been evaluated in this preliminary study as a tablet excipient since it is readily compressed and has considerable potential as a non-toxic

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tablet matrix. In addition, it provides an inexpensive model of albuminoid proteins obtained from other natural sources such as serum of various species.

Gravimetric measurement of water adsorption demonstrated the capacity of soy protein to equilibrate at various water concentrations when exposed to different relative humidities over a range of 15 - 80% R.H.

Mixtures (1:4) of quinacrine dihydrochloride and soy protein powders were exposed to various relative humidities and compressed into matrices under standardized conditions over a range of pressures from 60 to 230 MPa.

The protein compacts were directly affected by the initial water level of the powder, being stronger and more readily compressed with increased water adsorption. Although low water levels, <51% RH, resulted in relatively loosely compacted matrices, surprisingly the drug release rates into water at 37°C were somewhat slower. This unexpected result may be attributed to changes produced in the pore structure of the compacts by the soy protein swelling under these conditions.

INTRODUCTION

Soy protein is used as an ubiquitous food additive and is a major source of vegetable protein. It is thought that soy protein may also be used as a tablet excipient since preliminary experiments have shown that it is readily compressible. In addition, soy protein provides an inexpensible model of albuminoid proteins obtained from other natural sources.

The water vapor sorption properties of some tablet excipients have been investigated and no apparent difference in the mechanism of sorption between various starches and celluloses were found[1]. These investigators suggested that water sorbed to these polymeric materials may most likely exist in at least three states: tightly bound; less tightly bound; and bulk water.

Chowhan and et al.[2-5] discussed the interrelationships between moisture, crushing strength, friability, and in vitro dissolution in compressed tablets made from granules.

Native (undenatured) commercial soy protein isolate in the form of powder may have the ability to adsorb water vapor on the surface, and condensed water then may act as binder during a compressing process. The purpose of this study is to investigate the water vapor sorption properties of soy protein isolate (either in the form of powder or compact) and to determine the effect of initial surface water level on direct compaction properties and dissolution behavior of quinacrine dihydrochloride from directly compressed matrices of soy protein isolate.

MATERIALS AND EQUIPMENT

Soy protein isolate, Ardex-R®, ADM, Chicago, IL. Average particle size 16 μm (by optical microscope).
Lithium chloride, Fisher Scientific Company.
Calcium chloride dihydrate, USP, Fine granulated, Fisher Scientific Company.
Calcium nitrate tetrahydrate, Sigma Chemical Company.
Sodium nitrite, crystal, certified A.C.S., Fisher Scientific Company.
Ammonium chloride, certified A.C.S., Fisher Scientific Company.
Carver Laboratory Press, Fred S. Carver Inc., U.S.A., model 2702.
Quinacrine dihydrochloride hydrate, Aldrich Chemical Company, Inc., Average particle size 10μm (by optical microscope).
Vanderkamp® 600, Six spindle U.S.P. dissolution tester connected with a Van-kel circulator 2500 and an auto-sampling driving pump. Van-kel Industries, Inc., U.S.A.
Perkin-Elmer Lambda 3B UV/VIS spectrophotometer, 3600 data station, and 660 printer. Perkin-Elmer, U.S.A.
Erweka hardness tester, Erweka-Apparatebau, West Germany.

METHODS

Water Vapor Adsorption: Desiccators were preequilibrated with saturated salt solutions of lithium chloride, calcium chloride, calcium nitrate, sodium nitrite, and ammonium chloride to give relative humidities of 15%, 31%, 51%, 66%, and 80% respectively. Each desiccator contained two aluminum dishes (diameter 4.5 cm). One dish contained 500 mg of soy protein isolate powder and the other contained a 1.28 cm diameter, 500 mg, flat-faced soy protein isolate tablet, compressed at 170 MPa and maintained at the same pressure for 30 seconds. The desiccators were stored at room temperature of 21±2°C and the dishes weighed twice a day until equilibrium was reached.

Dissolution: 72 g of soy protein isolate powder was mixed with 18 g of quinacrine hydrochloride. The mixture was spread evenly in six round plastic dishes of diameter 8.8 cm, 15 g each, and individually kept in desiccators of known humidities of 15%, 31%, 51%, 66% and 80%, at room temperature (21±2°C) for four days.

Tablets (500 mg) were prepared by directly compressing the powder mixtures containing different levels of adsorbed water, as described, and applying six different compression pressures ranging from 60 MPa to 230 MPa for 30 seconds. Immediately after the tablets were prepared, the thickness and the dissolution behavior were determined.

Dissolution tests were performed following the USP XXI specified dissolution method II. The stirring rate and temperature were set up to 50±1 rpm and 37±0.5°C respectively. Distilled water (1L) was employed as the dissolution medium. Six dissolution tests were run simultaneously. Samples were taken automatically, carried through Tygon™ tubing from the dissolution vessels to flow-through cells in the spectrophotometer and back to the dissolution vessels by a pump. Assays were carried out automatically at a wavelength of 425 nm.

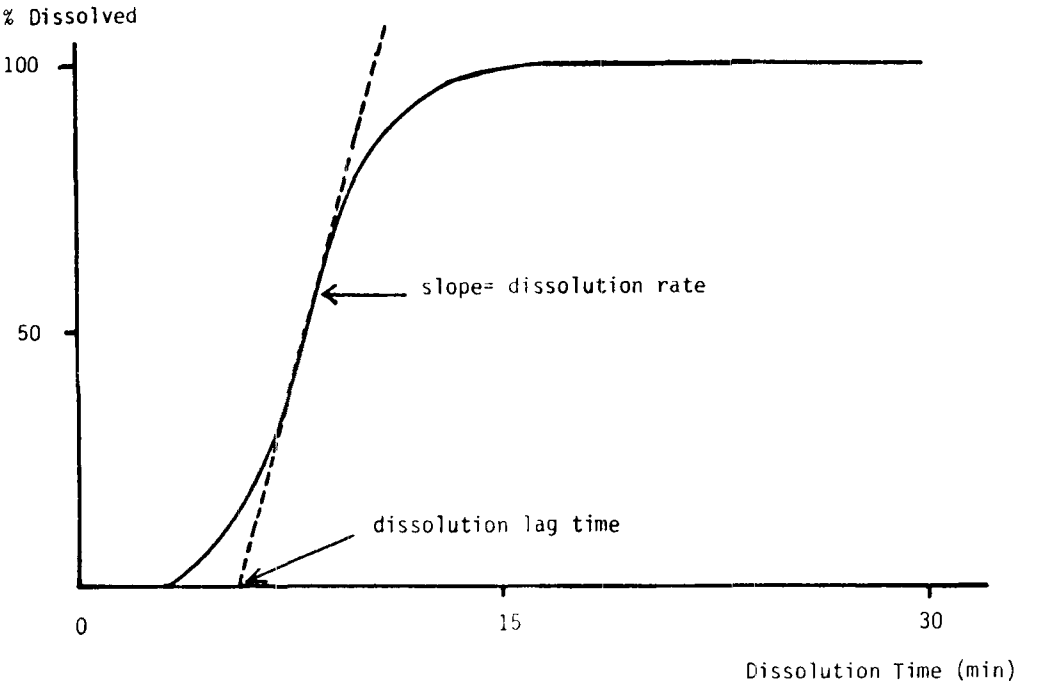

FIGURE 1

General Form of Computer - generated Dissolution Curve

A general form of the computer-generated dissolution curve is shown in Figure 1. Lag times and dissolution rates were determined from the linear portions of the curves, the former being the X-intercept and the latter being the slope.

Hardness tests: Tablets for hardness tests were prepared in the same manner as described above. Measurements were made with the Erweka hardness tester immediately after tablets were made, using the average of three runs.

RESULTS AND DISCUSSION

Water vapor adsorption curves of soy protein isolate powder and compacted matrices are shown in Figure 2. Both powder and compacted matrices of soy

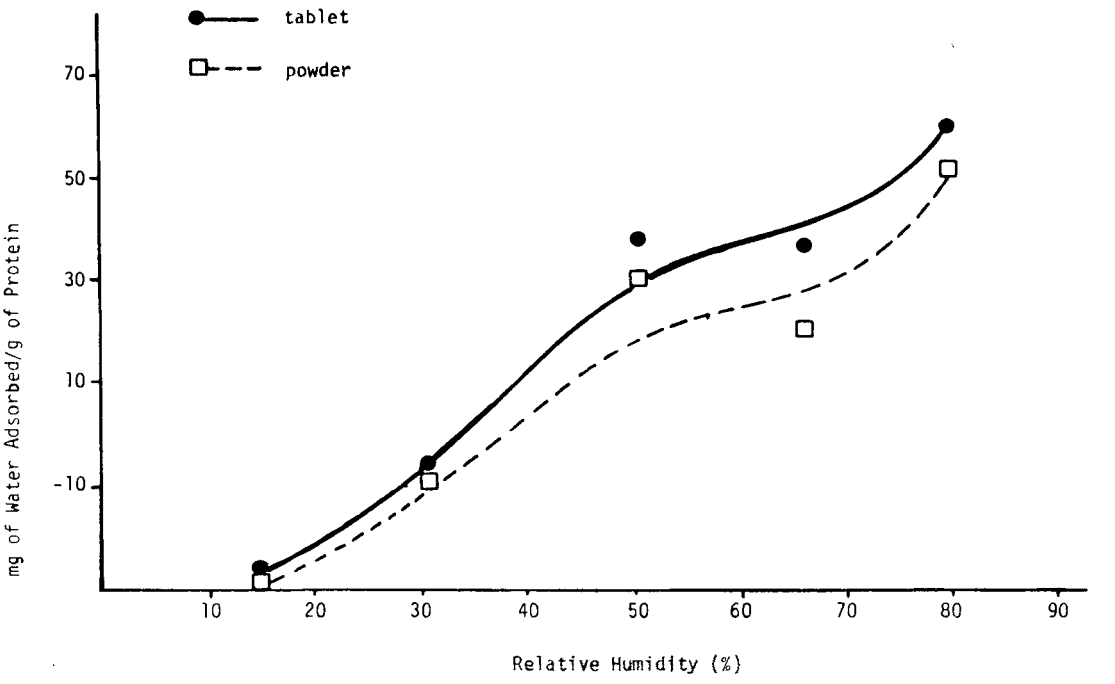

FIGURE 2

Water Vapor Adsorption Isotherms of soy Protein Isolate Powder and Tablet

protein isolate showed similar types of adsorption behavior initially, indicating capillary condensation[6,7].

Adsorbed surface water may act as a binder during the compression process. Powders with higher initial surface water levels should have improved binding, resulting in a decrease in tablet volume and an increase in strength. This idea is supported by the results shown in Figure 3, and Table 1.

In other words, interparticular spaces decreased as initial surface water increased even though the same compression pressure was employed. Figure 3 also indicates a direct relationship between the tablet thickness (compressibility) and initial surface water content. The slopes of the lines were

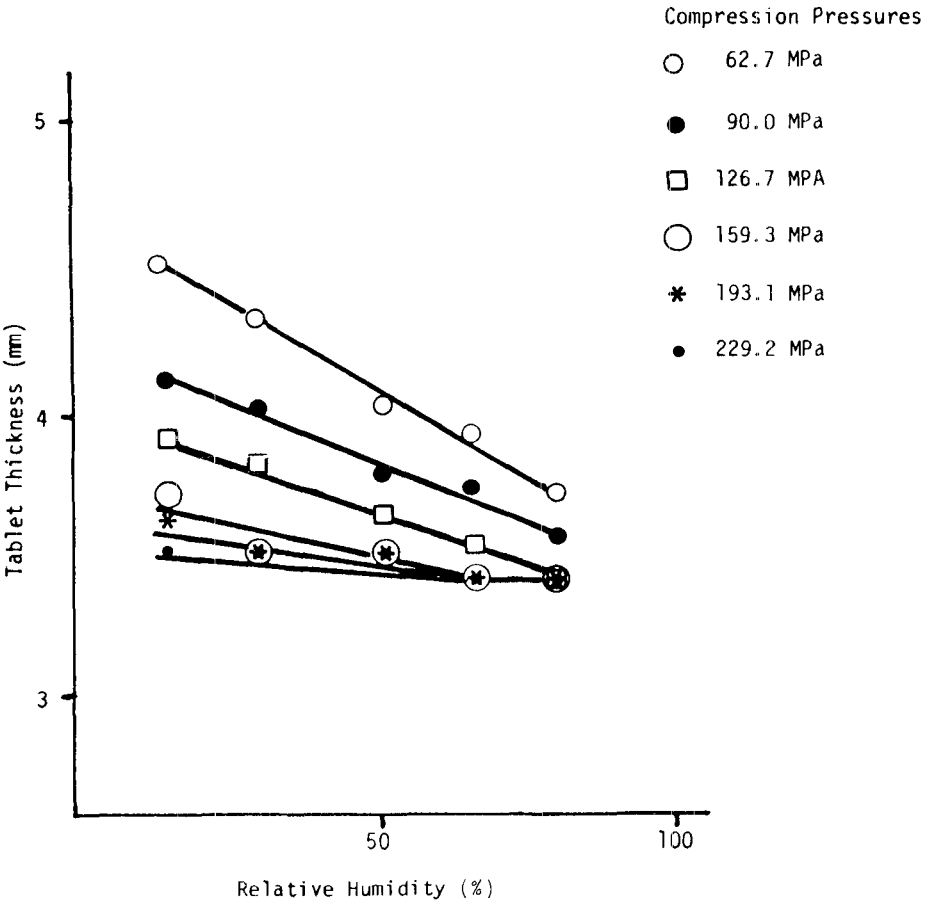

FIGURE 3

Effect of Adsorbed Water on Compressibility of Quinacrine/Soy Protein Isolate Tablets

greater at low compression pressures ($\leq$ 130 MPa), which may be an indication of lowered compressibility of the powder mixture with a lower level of adsorbed water. As binding improves, harder matrices are produced, Table 1.

Similar results were found by Nystrom and Glazer[8] with polyvinylpyrrolidone which had a better binding effect during the direct compression process. This effect was attributed to the hygroscopic nature of polyvinylpyrrolidone,

TABLE 1

EFFECT OF ADSORBED WATER AND COMPRESSION PRESSURE ON TABLET HARDNESS

	Force required to break the tablet$^{\Delta}$(N) Compression Pressure* (MPa)					
Relative Humidity (%)	66.1	95.3	129.7	162.7	192.2	224.1
15	4.4	37.5	58.5	71.4	87.6	105
31	4.9	21.3	59.3	87.8	101	118
51	28.7	66.4	76.8	133	109	>147
66	77.5	132	144	>147	>147	>147
80	130	143	>147	>147	>147	>147

*Average compression pressure.
$^{\Delta}$Force greater than 147 N could not be measured.

leading to an increased number of liquid bridges in the compacts. Bangudu and Pilpel[9] also studied the effect of moisture (pre-existing in the granules) on tablet strengths. Tablets made of mixtures with 2-4% of water were stronger than tablets made of mixtures without additional moisture.

With the same initial surface water content, an increase in compression pressure decreases the interparticular volume, resulting in thinner compacted matrices until a limiting volume was reached, Figure 4. Loosely compacted beds were weaker, Table 1.

There is a general tendency for the dissolution lag time to increase with increased compression pressures, Figure 5. This was true for all initial surface water levels. However, the trend was not the same in all cases since the initial increase was much sharper at higher water levels. Lag times vary according to the initial rate of liquid penetration into the compacted matrix. The liquid penetration rate is dependent upon pore size of the matrix and

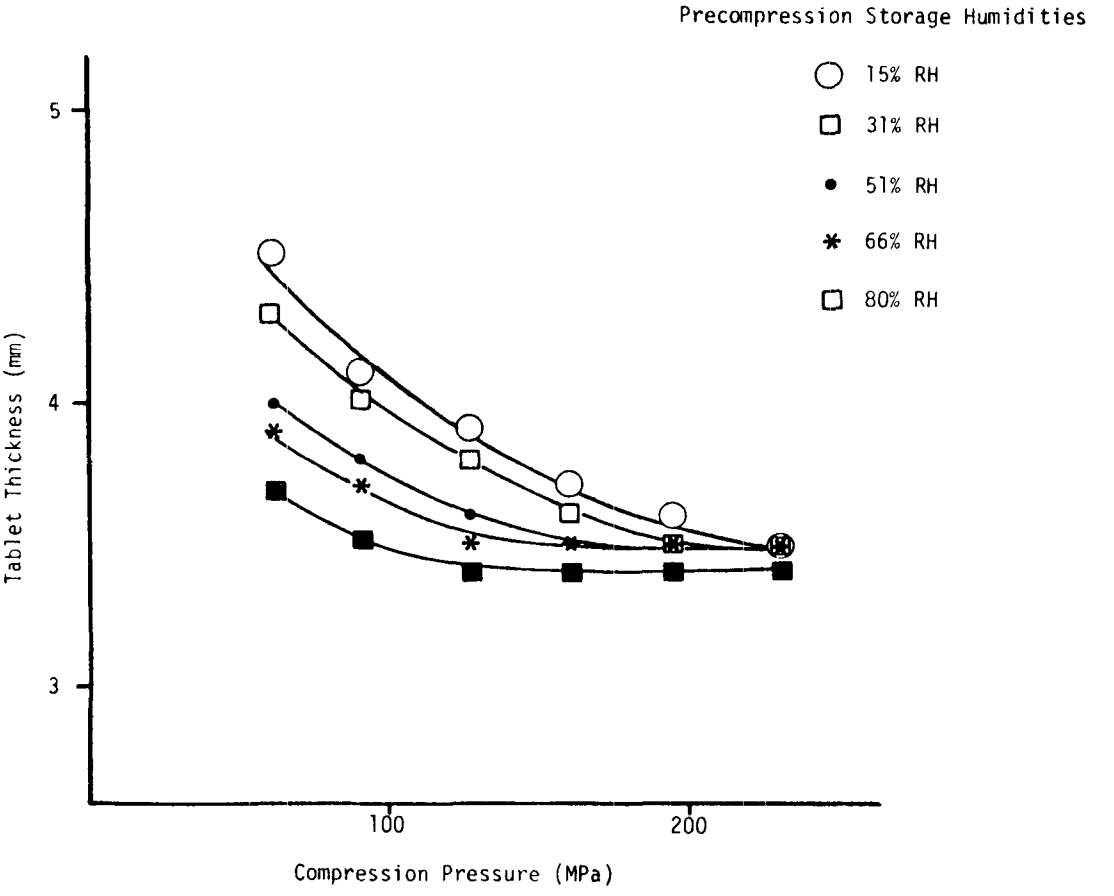

FIGURE 4

Effect of Compression Pressure on Compressibility of Quinacrine/Soy Protein Isolate Tablets

wettability of the solid surface by the penetrating liquid[10,11]. In this study compacts with lower initial surface water content showed shorter lag times under similar compressional conditions. This may indicate that the pore size is a dominant parameter controlling the initial penetration rate of water into the compacts.

Higher compression pressures cause particles to bind more strongly, thus decreasing the dissolution rate of drugs from compacts. This was only observed

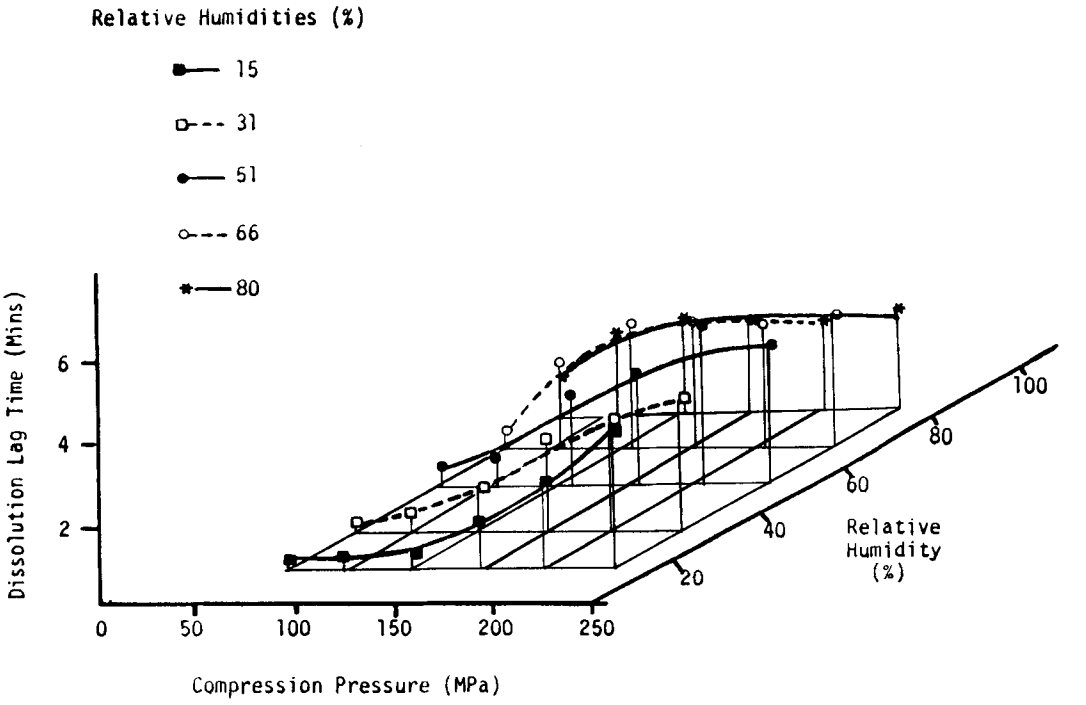

FIGURE 5

Effect of Adsorbed Water and Compression Pressure on Dissolution Lag Time

in the present study in tablets made at humidities higher than 50% RH. At lower humidity levels, the dissolution rates initially increased with increasing compression pressure, reached a maximum and then decreased, Figure 6. Similar results were found by Ganderton et al.[12] from a study of the dissolution rate of phenindione tablets prepared by wet granulation. Ibrahim[13] also observed an increase in dissolution rate with increased compressional force. However, in both of those studies, wet granulation was employed and the increase in dissolution rate was due to an increase in effective surface area. In this study, no granulation was employed. The initial increase in dissolution rate with an increase in compression pressure may be explained by the swelling properties of soy proteins. At low pressure there was enough space between particles to accomodate the swelling. The

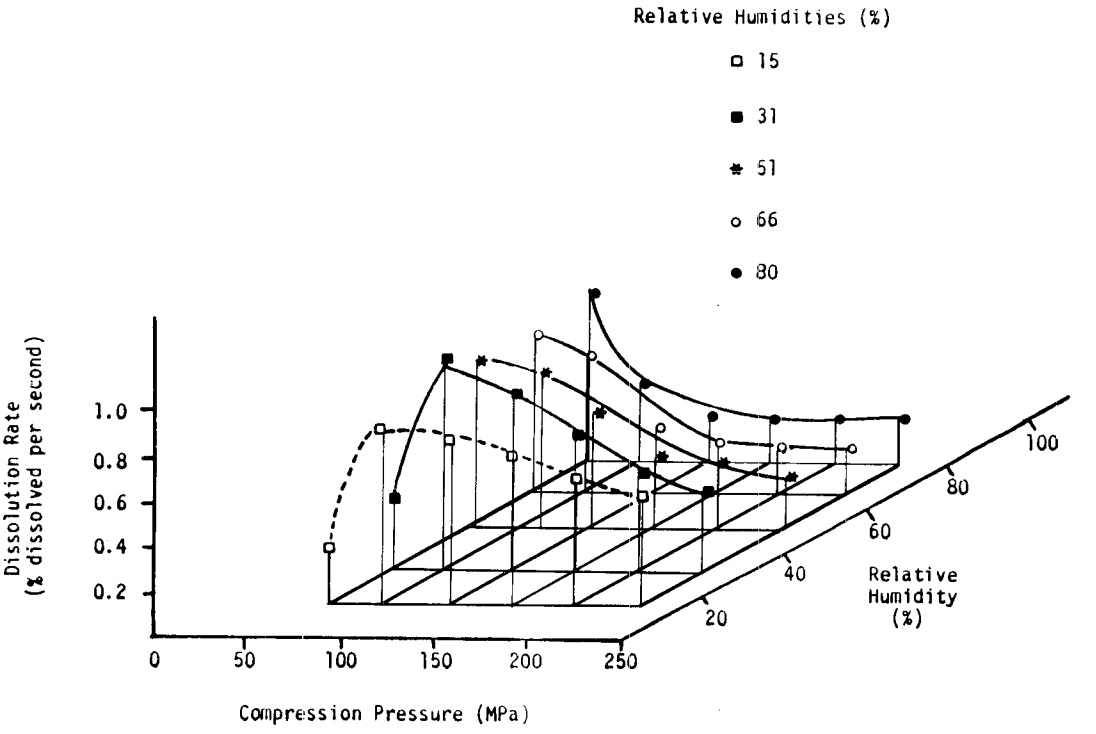

FIGURE 6

Effect of Adsorbed Water and Compression Pressure on Dissolution Rate

tablets did not therefore disintegrate to their primary particles although this occurs at higher compression pressures. Further studies are required in this area.

CONCLUSION

This study shows that soy protein isolate can be employed as an inexpensive excipient (filler/binder) in tablet manufacturing by direct compression since the compacted matrices are relatively strong and release the drug quickly. This study indicates that soy protein isolate adsorbs water vapor from the atmosphere which may cause some stability problems. Soy

protein either as a powder or in the compressed form should be stored under controlled humidity conditions. Tablets prepared under similar conditions from the same batch of soy protein isolate, but stored at different humidity levels will posses different physical properties, directly affecting the dissolution profiles of incorporated drug.

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