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RESEARCH PAPER

Multiple-Layer Compression-Coated Tablets: Formulation and Humidity Studies of Novel Chewable Amoxicillin/ Clavulanate Tablet Formulations

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ABSTRACT

The purpose of this study was to produce novel multiple-layer, compression-coated, chewable tablet formulations containing amoxicillin trihydrate, and clavulanic acid as potassium clavulanate, and to test in vitro *dissolution characteristics and the effect of humidity stability compared to Augmentin® chewable tablets as a reference. Double- and triple-layer tablets were manufactured on a laboratory scale by multiple-layer dry compression, and dissolution profiles of both active ingredients were determined. Tablets were subjected to stability evaluation in laboatory-scale humidity tanks maintained at constant humidity. Assay of content was determined by HPLC or UV spectroscopy. Physical characteristics of the powder mixture, such as angle of repose, and of tablets for hardness and friability, were also determined. Chewable tablets showed similar dissolution profiles in vitro for both active ingredients, compared to the marketed reference, Augmentin. The stability of clavulanic acid, but not amoxicillin, was increased in the novel triple or bilayer formulation. The tablets showed suitable friability, hardness, and angle of repose for starting materials to suggest that industrial scale-up is feasible. This approach to formulation of drugs containing multiple or moisture-sensitive ingredients has been shown to increase the stability of the central core drug without changing the dissolution pattern of the active ingredients. This formulation is expected to be bioequivalent in vivo based on these in vitro results.*

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INTRODUCTION

Amoxicillin is a semisynthetic broad spectrum antibiotic derived from ampicillin, which is in turn derived from the basic penicillin nucleus, 6-aminopenicillanic acid. It is used for a wide range of clinical indications (1) and is also available commercially as an oral antibacterial combination (2) containing the β-lactamase inhibitor, potassium clavulanate, the potassium salt of clavulanic acid. Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus* and is also a β-lactam, structurally related to amoxicillin and other penicillins, and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. It is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferring drug resistance to pencillins and cephalosporins.

The combination of amoxicillin trihydrate with potassium clavulanate is available commercially (Augmentin®) as both immediate-release (875, 500, and 250 mg amoxicillin, each containing 125 mg clavulanic acid) and chewable tablets (250 and 125 mg amoxicillin, each containing 125 and 62.5 mg clavulanic acid, respectively). Both amoxicillin trihydrate and potassium clavulanate will degrade quickly in solution and the latter, in particular, is extremely moisture sensitive (3,4). For this reason, a novel type of formulation was proposed which contained the clavulanic acid in a central protected core, surrounded by a hydrophobic stearic acid barrier layer, and further surrounded by a third amoxicillin drug layer. This design works particularly well with this formulation due to the small amount of potassium clavulanate present, relative to amoxicillin trihydrate. An alternative to this approach is a double-layer tablet, which is similar but contains stearic acid combined with the amoxicillin outer coat. The chewable formulation was chosen initially because it is more unstable than the immediate-release tablet, thereby presenting a greater formulation challenge. (Stability was evidenced by the packaging of Augmentin dosage forms—chewable tablets are individually packed in foil.) Schematic representations of these formulations are shown in Fig. 1.

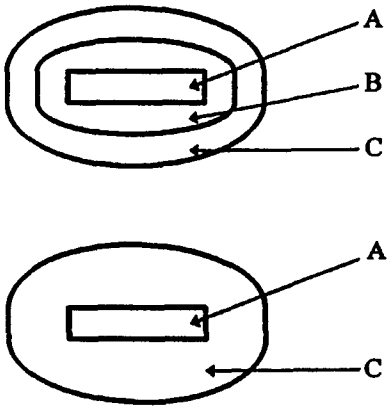

Figure 1. Schematic representation of triple- (top) and double-layer (below) tablets: A = clavulanic acid; B = stearic acid or Avicel layer; C = amoxicillin.

MATERIALS AND METHODS

Tablet Manufacture

Tablets were manufactured on a laboratory scale using a hydraulic press (Fred S. Carver, Inc., Summit, NJ). Core tablets were directly compressed first, then placed into a slightly larger die on top of half of the powder mixture for the middle layer formulation. The remaining powder mixture was sprinkled on top and compressed. The process was repeated again with a larger punch and die set to obtain the final tablet. All powders were compressed directly except for amoxicillin, which was previously roller compacted, and mannitol, which was granular. Tablets were compressed at 500, 500, and 3000 lb for each respective layer. Compression pressures were later found to be critical, as was the shape of the inner tablets. Scanning electron microscopy of the tablets provided information about how the tablet layers were bound together and where tablet weaknesses would occur and lead to fracture or splitting. Two different sets of punches and dies were used during the developmental process.

Assessment of Formulations

Good flow properties of powders are critical for an efficient tableting operation. When a heap of powder is allowed to stand with only gravitational force acting on it, the angle between the free surface of the heap and the horizontal can achieve a certain maximum for a given powder. This angle is the angle of repose. This angle was measured for each layer of powder mixture. The powder was poured through a wide-neck funnel and the circular fall pattern was traced on paper. The diameter of this circle was measured several times and a mean radius value (r) obtained. The height of the powder pile (h) was measured and the angle of repose (α) calculated from the following equation (5):

$$\tan \alpha = \frac{h}{r}$$

Measurements were made in triplicate for all tablets, including the core and middle layer tablets. For most pharmaceutical powders, the angle of repose ranges from 25 to 45°, with lower values indicating better flow characteristics. Values of ≤ 30° generally indicate a free-flowing material, angles ≥ 40° suggest a poorly flowing material (5).

To assess friability of the tablets, six dedusted tablets were weighed then placed in the laboratory VanderKamp friability tester (Van-Kel Industries, Edison, NJ) for 100 revolutions. The tablets were dedusted and reweighed. Normal friability limits define no more than 1% weight loss under these conditions.

The tablet hardness was measured by a strong Cobb hardness tester (Cleveland, OH). An average of six readings was taken as the final hardness, and the normal minimal hardness limits were greater than 5 kg, although chewable tablets may have been somewhat softer (6).

Dissolution Profiles

Dissolution tests were conducted according to the USP 22 paddle method (7) at 37°C, 75 rpm. Dissolution medium was 900 ml deionized deaerated water. Dissolution profiles of six tablets were determined over 50 min for immediate-release tablets. Five-milliliter samples were withdrawn with replacement via syringe with an inline filter (2 μm immersible filter). Samples were diluted 1:5 for amoxicillin analysis by UV spectroscopy at 270 nm, and undiluted samples were derivatized to provide the clavulanic acid samples for analysis by UV spectroscopy at 310 nm (8).

Dissolution profiles of the chewable tablet formulations were determined for Augmentin initially as crushed and uncrushed tablets. Tablets were crushed using an EZ-Swallow® Pill Crusher (American Medical Industries, Highland Park, IL) a small device which can uniformly crush tablets and minimize human error compared to grinding tablets using a mortar and pestle. All further dissolution profiles were determined using crushed tablets because it was anticipated this would more closely mirror an in vivo absorption profile for chewable tablets.

Dissolution profiles were determined, with 3-ml samples withdrawn for UV analysis and replaced at 6, 12, 20, 30, 40, and 50 min. Amoxicillin samples were analyzed directly at 270 nm. For clavulanic acid, a derivative of each sample was formed. From each sample 400 μl was first added to 100 μl imidazole reagent and allowed to stand at room temperature for 10 min in order to form the derivative (8). A further 2 ml water was then added to provide the sample for UV spectroscopic detection of clavulanic acid at 310 nm. Imidazole reagent was prepared by making 8.25 g imidazole up to 24 ml with deionized water. HCl (5 M) was added to pH 6.8 and the solution was made up to 40 ml with deionized water. Both calibration curves constructed for UV analysis gave a correlation coefficient of greater than 0.999 and were linear over the range of 0–200 μg/ml for clavulanic acid and 0–50 μg/ml for amoxicillin.

HPLC Analysis

A sensitive HPLC method with UV detection (8) was used to assess humidity stability, with some modifications. Two dedicated systems were used to analyze separate drug levels due to the large sample number and instability of both compounds. Calibration curves for both analytes were linear through 0.5–300 μg/ml for amoxicillin and 0.5–150 μg/ml for clavulanic acid (both correlation coefficients >0.99). The lower limit of quantitation was 0.5 μg/ml for both amoxicillin and clavulanic acid. For both active drugs, interday coefficients of variation were less than 10% at both low and high concentrations. Amoxicillin samples were analyzed directly using acetaminophen (1 μg/ml) solution as an internal standard. Clavulanic acid samples were derivatized as described previously, and sulfadiazine solution (0.5 mg/ml) was used as an internal standard. For amoxicillin, 0.005 M potassium phosphate solution containing 5% methanol was degassed and pumped using a Waters (Milford, MA) M-45 solvent delivery system. A similar mobile phase, containing 6% methanol and adjusted to pH 3.6 with phosphoric acid, was used to carry clavulanic acid samples to be injected using a Waters Wisp 710A autosampler onto a reversed-phase column C18, 25 cm, 100A Rainin Microsorb-MV®, (5 and 8 μm, respectively, for amoxicillin and clavulanic acid). The UV absorbance of amoxicillin was recorded at 229 nm and clavulanic acid derivative was recorded at 310 nm. Data were recorded and analyzed with a Shimadzu CR501 Chromatopac.

Humidity Stability

Both amoxicillin and clavulanic acid degrade rapidly when exposed to moisture (3,4). Standard glass aquari-

ums (50 × 26 × 30 cm) were sealed with a plastic cover to form humidity tanks. A saturated solution of calcium sulfate dihydrate provided 75% relative humidity (RH) conditions. The solution was prepared using deionized water and filled to about 1 in. depth in the bottom of each tank. Both humidity and temperature were monitored daily using a hand-held humidity meter (VWR Scientific, San Francisco, CA). A plastic rack was placed in the tank to hold Petri dishes containing either triple-layer, bilayer, or Augmentin tablets 7 cm above the surface of the solution.

Chewable tablets were exposed to 75% RH. Two tablets from each formulation were removed at various time points up to 50-hr, and crushed and powdered as above. The powder was transferred to a 500-ml flask and made up to volume with deionized water. After the mixture was stirred for 30 min, three 5-ml aliquots were transferred to test tubes and centrifuged for 10 min. This solution was diluted 1 ml in 5 ml with water and used for HPLC sample preparation.

RESULTS AND DISCUSSION

Compression pressure was found to be a critical factor in chewable tablet formulation, and the final pressures used were the result of a balance struck between the manufacture of a tablet that was soft enough to easily chew, even upon triple compression, but hard enough to withstand transport. If the initial core was tableted at high pressure, the subsequent layers were not cohesive. Minimizing this initial tableting pressure increased the pressure difference between initial and final compression pressures, and produced good tablets.

Scanning electron microscopy of cross sections of the tablets gave further information about how the tablets bonded together. Figure 2 shows a triple-layer tablet under high magnification. Note that the layers did not directly bond to each other, but a viable gap could be detected all around each surrounding layer. For conventional triple-layer tablets, for which the same size punches and dies are used with several powder fills, the layers must bond in order for the tablet to have integrity. For the type of core tablets described herein, it is thought that similar material in each layer promotes interlayer bonding. These SEM results, however, indicate that for a triple-layer tablet of the type described in this paper, the important factor is how well the layer sticks to itself. This is consistent with a previous description of this approach to tablet formulation as being "likened to a peanut in a shell" (9). Centering of core tablets is critical, and badly centered tablets will result in cracks in the outer surface, as indicated in Fig. 3, which shows an example of a badly centered tablet. Misalignment appears to cause unwanted additional pressure at opposite edges and cracks can be seen beginning to form. By changing the shape of both the inner and outer punches and dies, the appearance of cracks in the tablets on storage was eliminated. Inner punches with more rounded edges than depicted in Fig. 4 provided a tablet "lip" or edge which was reduced around two-thirds in size, as can be seen by comparing Fig. 4 from initial inner punches to Fig. 3 from final inner punches.

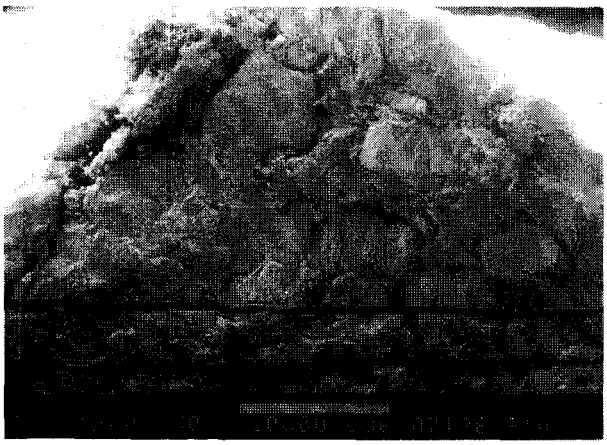

Figure 2. Scanning electron microscope detail of triple-layer tablet (30× magnification) shows no direct bonding between layers.

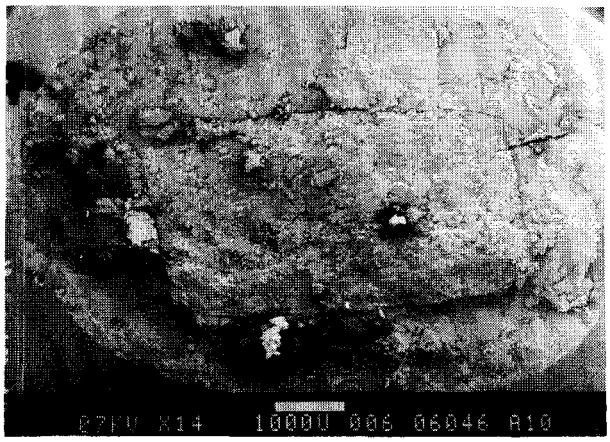

Figure 3. Scanning electron microscope detail of a misaligned core in a bilayer tablet (14× magnification) shows cracks forming at edges.

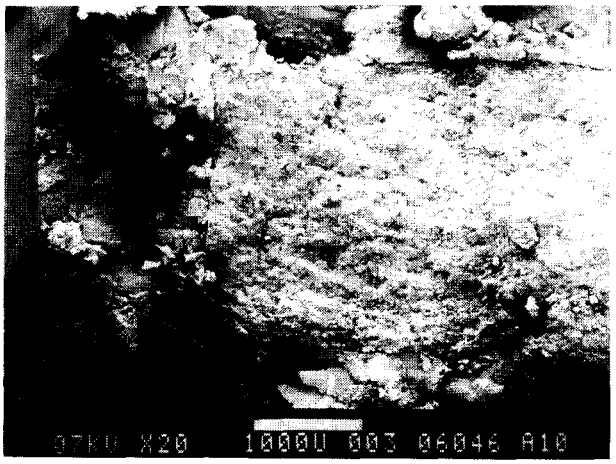

Figure 4. Scanning electron microscope detail of a bilayer tablet (20× magnification).

Table 1 lists formulations studied. The first formulation is simply a bilayer tablet consisting of a clavulanic acid-containing core with an outer surrounding layer containing amoxicillin. Two triple-layer formulations are reported: the first contains a middle layer of Avicel PH112, with lubricant, separating the two active ingredients, and the second has 20% stearic acid in this middle Avicel PH112 layer to act as a tableting lubricant and hydrophobic barrier to moisture penetration. Because stearic acid itself provides sufficient lubrication, extra lubricant was not added.

Table 2 lists physical characteristics of the formulations studied; namely the angle of repose, friability, and hardness of each tablet layer. Flow properties of the core were marginal, as shown by the angle of repose of around 34°. This could be easily improved by dry granulating the clavulanic acid layer, although if flow was sufficiently good in industrial-scale equipment, this extra step would be unnecessary. Flow properties of all other layers were good (around 30° or less).

Core tablets showed no weight loss during friability testing, and indeed tended to show marginal weight increases. This may have been due, in part, to the tablets picking up atmospheric moisture during the friability test, because a controlled humidity environment was not available for this equipment. The friability of the middle layer containing Avicel PH112 was not good but was

Table 1

Chewable Tablet Formulations

Formulation	Bilayer	Triple Layer (Avicel)	Triple Layer (Stearic Acid)
Core[a]	Clavulanic acid	Clavulanic acid	Clavulanic acid
Middle	–	Avicel PH112	Avicel PH112 + 20% stearic acid
Outer[a]	Amoxicillin	Amoxicillin	Amoxicillin

[a]Active ingredients only are listed. Formulation includes other excipients.

Table 2

Angle of Repose, Friability, and Hardness Measurements

Formulation	Angle of Repose (α°)	Friability (% Weight Loss)	Hardness (kg)
1. Core	34.6	0	4.4
Middle	–	–	–
Outer	31.2	0.4	13.0
2. Core	34.6	0	4.4
Middle	31.7	16.8	4.0
Outer	31.2	0.4	13.0
3. Core	34.6	0	4.4
Middle	29.4	2.6	6.3
Outer	31.2	1.2	16.2

significantly improved with the addition of 20% stearic acid. It was noted that when Avicel PH112 was substituted with Avicel CE, a brand of microcrystalline cellulose cocrystallized with guar gum for chewable tablet formulation, friability was increased. Final friability levels with the outer amoxicillin-containing layer included were well under the recommended 1% weight loss limits. All tablet hardness measurements were above the minimum 4 kg limit, and were comparable to those of Augmentin.

Figures 5 and 6 illustrate the large difference in dissolution profiles between crushed and uncrushed or whole Augmentin chewable tablets. Both active ingredients dissolve faster from crushed tablets, as expected. Initial attempts to mirror the dissolution profiles of Augmentin chewable tablets failed because the main diluent of these tablets (colloidal silicon dioxide) is much less wettable than the microcrystalline cellulose used in the new formulations. Clavulanic acid was available commercially as a 1:1 mixture with either Avicel PH112 or Syloid, and the former was selected because of better flow properties and ease of handling. However, when the chewable tablets are crushed to simulate chewing, the dissolution profiles between products are very similar (Figs. 7 and 8), and this is thought to be more significant in terms of in vivo correlation. Figure 7 depicts very similar dissolution profiles for both triple-layer formulations compared to Augmentin, for both active ingredients. The fact that clavulanic acid was protected as a core tablet created concern that dissolution would be delayed. This concern was unfounded, partly because of the rapidly disintegrating Avicel diluent used. Figure 8 also shows that dissolution profiles of bilayer tablets are very close for both amoxicillin and clavulanic acid. All formulations complied with USP dissolution limits.

Figure 9 shows a similar humidity stability profile for amoxicillin from triple-layer tablets compared to Augmentin, but indicates a stability-enhancing effect for clavulanic acid contained in the triple-layer formulations. Clavulanic acid degrades very rapidly under these conditions, especially for Augmentin tablets in which content drops to below 40% in only 10 hr. The triple-layer tablets take an additional 10 hr to degrade to this level. It is believed that this difference may be extrapolated in terms of predicted shelf life.

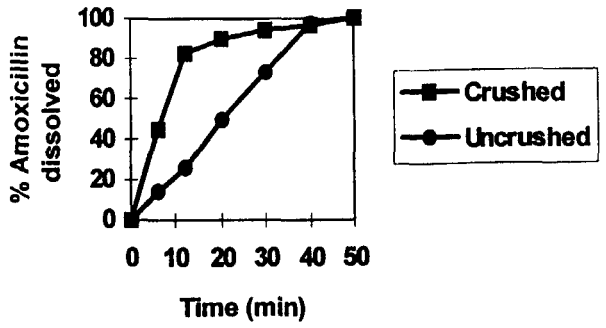

Figure 5. Dissolution profile of amoxicillin from crushed and uncrushed Augmentin 250 mg chewable tablets.

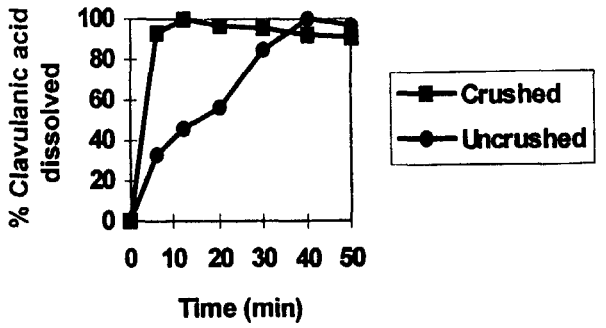

Figure 6. Dissolution profile of clavulanic acid from Augmentin 250 mg chewable tablets.

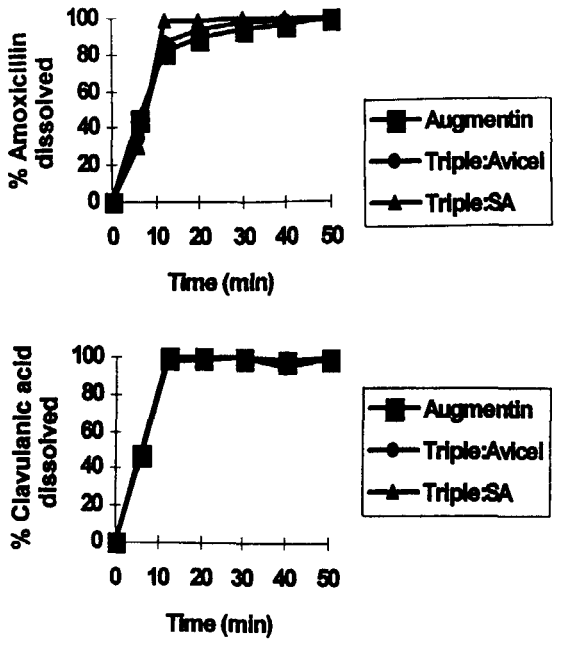

Figure 7. Dissolution profiles of amoxicillin and clavulanic acid from triple-layer tablet formulations compared to Augmentin 250 mg chewable tablets.

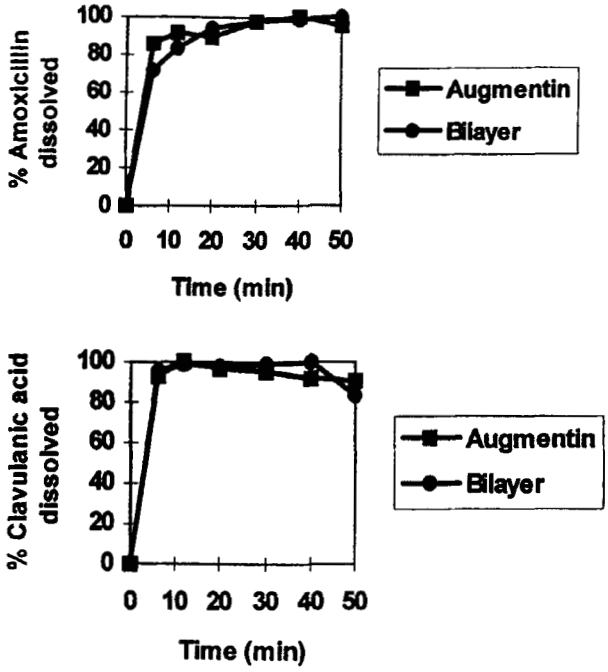

Figure 8. Dissolution profiles of amoxicillin and clavulanic acid from bilayer tablets compared to Augmentin 250 mg chewable tablets.

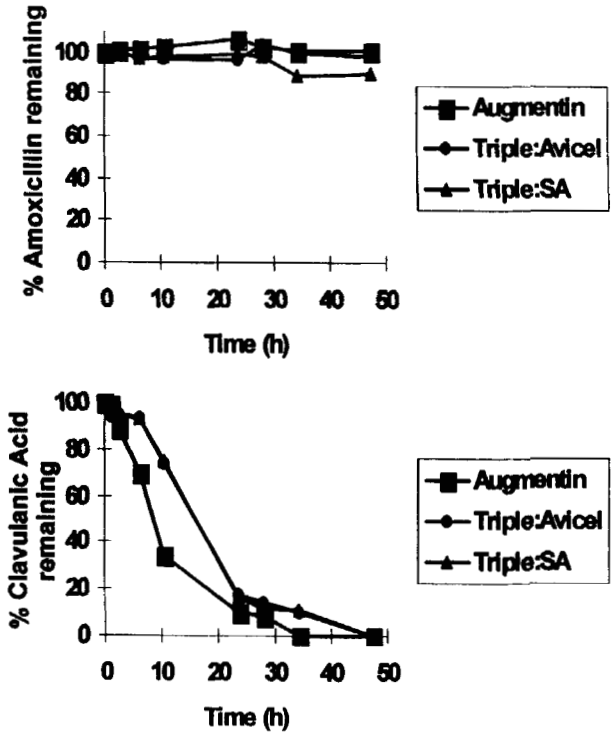

Figure 9. Effect of 75% relative humidity on amount of remaining clavulanic acid and amoxicillin in triple-layer tablets compared to Augmentin 250 mg chewable tablets.

Bilayer tablets also show a similar humidity stability profile for amoxicillin when compared to Augmentin (Fig. 10). Figure 11 shows increased stability for bilayer tablets compared to Augmentin. These results show that even without stearic acid present, and without three separate layers, placing the clavulanate in a core increases stability. These results are quite different from those of Crowley (10), who concluded that intimate mixing of clavulanate and amoxicillin results in increased stability of both materials. Figure 12 indicates the color change associated with the degradation of clavulanic acid. The triple-layer stearic acid formulation is seen on the far right and retains a white color in the outer layer, and both Augmentin and a generic single-layer tablet containing the same ingredients as in the triple-layer stearic acid tablet but not intimately mixed, are dark yellow-orange. These pictures reinforce the data collected above, indicating a stability-enhancing effect of this type of formulation over conventional single-layer tablets. This effect is presumably seen only in the presence of moisture because both ingredients are relatively stable when dry.

The chewable tablets studied show similar crushed in vitro dissolution profiles, and similar in vivo profiles were expected. These products were shown to be bioequivalent by monitoring urinary excretion rates in a single-dose study in healthy human volunteers (11). One disadvantage of using triple-layer core tablets lies in the equipment used. Three separate tooling sets are required in place of one, and tablet manufacture involves multiple steps. This type of approach could conceivably be applied to a number of formulations for which moisture-

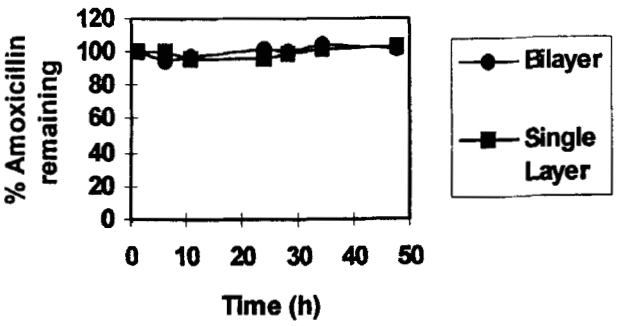

Figure 10. Amoxicillin remaining after exposure of bilayer and single-layer tablets to 75% relative humidity.

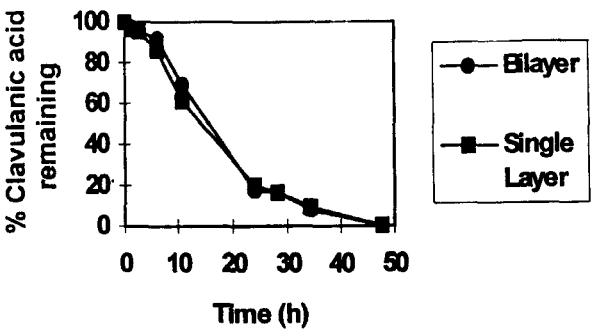

Figure 11. Clavulanic acid remaining after exposure of bilayer and single-layer tablets to 75% relative humidity.

sensitive ingredients are to be used and incompatible excipients or actives should be separated.

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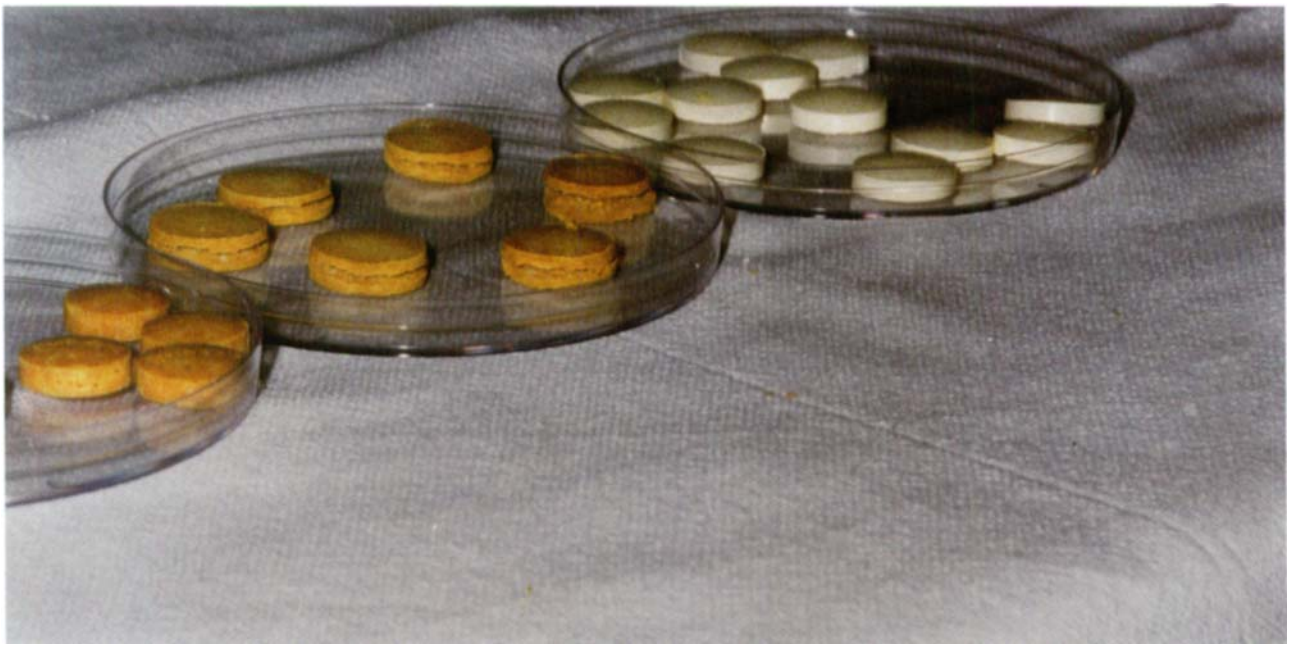

Figure 12. Effect of high humidity on tablets containing amoxicillin and clavulanic acid. Orange color is associated with clavulanic acid degradation. Right: triple-layer stearic acid formulation; center: Augmentin® 250 mg chewable; left: single-layer formulation containing all ingredients of triple-layer stearic tablets.