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PREPARATION AND IN-VITRO EVALUATION OF POWDER SOLUTION TABLETS OF VALPROIC ACID

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ABSTRACT

A tablet dosage form of liquid valproic acid (VPA) was formulated using powder solution technology as an alternative to the manufacturing of soft elastic gelatin capsules (SEGs). Mixing of liquid VPA with suitable adsorbents followed by blending with other excipients resulted in a non-adherent, free flowing powder. Tableting was achieved through standard direct compression. The tablets were acceptable in terms of physical properties. Film coated tablets (FCTs) and sugar coated tablets (SCTs) were also prepared. The in-vitro dissolution rates of these VPA tablets were significantly greater than that of a marketed SEG product. There was no significant change in the dissolution rates of the plain and FCTs after storage under accelerated stability conditions. Powder solution

technology was a viable alternative to the commercial preparation of SEGs.

INTRODUCTION

Valproic acid (VPA) is a branched chain fatty acid structurally unrelated to any other marketed drug[1]. Due to its broad spectrum of activity against seizures, VPA is widely prescribed. It is particularly effective in controlling seizures that commonly occur in populations with the highest incidence of epilepsy such as children and the elderly[2,3].

VPA is primarily administered orally. It is, therefore available in various oral formulations such as solutions, soft elastic gelatin capsules (SEGs), enteric coated capsules, and slow release preparations[1]. A number of techniques have been used to manufacture these oral dosage forms of VPA. However, there are no reports of "liquid" VPA being incorporated into a tablet dosage form.

Powder solution technology is an effective means to formulate liquid drugs or drug solutions into free flowing and readily compressible powders[4]. It is a relatively simple process in which drug dissolved in a suitable, non-volatile solvent(s) or liquid drug is converted into a dry, non-adherent powder by admixture with selected carriers (adsorbents) and coating materials. This approach is free from any drying

process[4]. The drug is in a thin film liquid or solution form, consequently enhancing its release rate. Since the rate limiting step for the absorption of water-insoluble drugs is dissolution, potentially better bioavailability is expected with powder solution dosage forms. Powder solution preparations of several water-insoluble drugs have exhibited faster dissolution than commercially available products including SEGs[4]. Considering the difference in production cost between SEGs and tablets, powder solution technology could be a viable alternative to SEGs.

The objectives of this study were to: (a) formulate a rapid-release tablet dosage form of liquid VPA using powder solution technology; (b) prepare film coated tablets (FCTs) and sugar coated tablets (SCTs) in addition to plain tablets; (c) compare in-vitro dissolution of these tablets with a marketed SEG; and (d) determine the effects of accelerated storage conditions on VPA dissolution from these tablets.

EXPERIMENTAL

Materials

The following materials were used as received: Valproic Acid (Sigma Chem. Co., St. Louis, MO 63178), 250 mg Valproic Acid SEGs (Depakene®, Abbott, N. Chicago, IL 60064, Lot # 39 058 AF Exp. July 1994), Avicel PH 101 & PH 200 and AC-DI-SOL, NF (FMC

Corporation, Philadelphia, PA 19103), Magnesium Oxide DC/EM, USP (Edward Mendell Co., Inc., Patterson, NY 12563), Methyl Cellulose 1500 cps (Dow Chemical USA, Midland, MI 48686), Starch 1500 (Colorcon, West Point, PA 19486), Magnesium Stearate (Mallinkrodt, St. Louis, MO 63147), Cab-O-Sil (Cabot Corporation, Tuscola, IL 61953), Talc (Penta Manufacturing Co., Fairfield, NJ 07007), Hydrochloric Acid and Sodium Chloride (Fisher Scientific, Fair Lawn, NJ 07410).

Methodology

(a) Mixing Process: Powder solution technology involves simple admixture of liquid drug or drug solution with suitable carriers. The present choice of carriers was based on a number of preformulation trials. Materials investigated included starches, silicas, dicalcium and tricalcium phosphate, magnesium oxide, and various forms of Avicel, either alone or in combination. The formulation selected for liquid VPA contained drug:Avicel PH 200:magnesium oxide in a ratio of 1:2:3. Mixing of liquid VPA with this formulation (using a glass beaker and metal spatula) resulted in a dry powder which was rendered non-adherent and free flowing by blending with Cab-O-Sil. Other tableting excipients were added to prepare a blend suitable for direct compression (Table 1).

(b) Tableting: Tablets containing 125 mg of VPA were

TABLE 1

Composition of the Core VPA Tablets

INGREDIENT	QTY/TAB (mg)
Valproic acid	125
Magnesium oxide, DC/EM	375
Avicel, PH 200	250
Cab-O-Sil	37.5
Methyl cellulose, 1500 cps	100
Avicel PH 101	75
AC-DI-SOL	50
Starch 1500	17.5
Magnesium stearate	10
Talc	10

prepared using a Stokes single punch press installed with ½ inch diameter round, standard concave tooling. Compression was performed at a constant pressure and at a speed of approximately 60 tablets/min. Hardness, thickness, weight variation, content uniformity, disintegration, and friability of the tablets were evaluated by standard procedures.

(c) Film Coating: Aqueous film coating was performed in a 12 inch diameter Hi-coater, round, stainless steel, perforated pan (Model HCT-30, Vector Corporation, Marion, IL 52302). Opadry yellow (Colorcon, West Point, PA 19103) with 12.5% w/w solids was used as a coating polymer. Conditions during coating are listed in Table

2. Film coating was continued until a weight gain of approximately 3.5% was achieved.

(d) Sugar Coating: A spraying method was used in the pan described earlier. The process involved a sealing coat of Opaseal clear (Colorcon, West Point, PA 19103); subcoating with simple syrup containing gelatin, acacia, PEG 400, and sugar, and a dusting powder containing calcium carbonate, talc, and corn starch; coloring using Opalux (Colorcon, West Point, PA 19103) mixed with simple syrup, and polishing using a solution of carnauba wax and beeswax in isopropyl alcohol. Coating conditions are listed in Table 2. A weight gain of approximately 100% was obtained by this process.

(e) Dissolution Testing: No official method for VPA dosage forms is described. Dissolution tests were performed using U.S.P. apparatus II (rotating paddle) at 100 rpm (Model 72, Hanson Research, Chatsworth, CA 91311). One 250 mg SEG or two 125 mg tablets of VPA were placed in 900 ml of 0.1 *N*, pH 1.2 HCl at 37 ± 0.5°C. Approximately 1 ml samples were withdrawn every 15 min for 1 hr through 10 μ filters attached to the sampling probe. Samples were assayed for VPA content immediately after the test using fluorescence polarization immunoassay (TD_x, Abbott Diagnostics Division, Irving, TX 75015). Data were compared by one-way analysis of variance using the 5% level of significance ($P < 0.05$).

TABLE 2

Conditions for Film and Sugar Coating

PARAMETER	FILM COATING	SUGAR COATING
Load Size	700 g	500 g
Pan Speed	16 rpm	24 rpm
Spay Gun Type	Atomized	Atomized
Nozzle Diameter	1.8 mm	1.8 mm
Spay Rate	5 ml/min	10 - 15 ml/min
Inlet Temperature	60 - 65°C	80 - 85°C
Exhaust Temperature	30 - 35°C	40 - 45°C
Air Pressure	2 kg/cm^2	2 kg/cm^2

(f) Accelerated Stability Studies: These studies were performed with plain tablets, FCTs, and SCTs. Tablets were packaged in amber glass containers with 1 g silica-gel packets and cotton. These containers were stored at 45°C and 40°C/75% relative humidity (RH) for 1, 2, and 3 months. Dissolution tests were performed on the stored samples.

RESULTS AND DISCUSSION

A combination of liquid VPA and adsorbents in the ratio stated earlier followed by the addition of Cab-O-Sil yielded a dry, non-sticking, free flowing powder. After the addition of suitable excipients, direct compression yielded sufficiently hard tablets without compaction problems. The physical properties of the

TABLE 3

Physical Properties of Core VPA Tablets

PHYSICAL PROPERTY	MEAN ± S.D.
Average Weight (g)	1.041 ± 0.037
Content Uniformity (%)	99.02 ± 3.19
Thickness (mm)	6.39 ± 0.25
Hardness (kg)	13.83 ± 2.4
Disintegration (min)	10.8 ± 1.48
Friability (%) After 4 min	0.125
After 10 min	0.43

tablets are presented in Table 3. The tablets had acceptable uniformity in weight, VPA content and thickness, sufficient hardness, low friability, and good disintegration.

In addition to plain tablets, FCTs and SCTs were prepared. In-vitro dissolution tests were conducted on fresh samples of these tablets and compared with the marketed SEG (Fig. 1). For VPA tablets each data point represents the mean of at least three determinations; whereas, for SEGs each data point represents the mean of six determinations. The VPA tablets exhibited faster dissolution than the SEG. As expected for SCTs, VPA release was delayed until the coating disintegrated to expose the core. After 1 hr, the percent VPA dissolved from plain, FCTs, and SCTs was 98.0 ± 3.7%, 94.3 ±

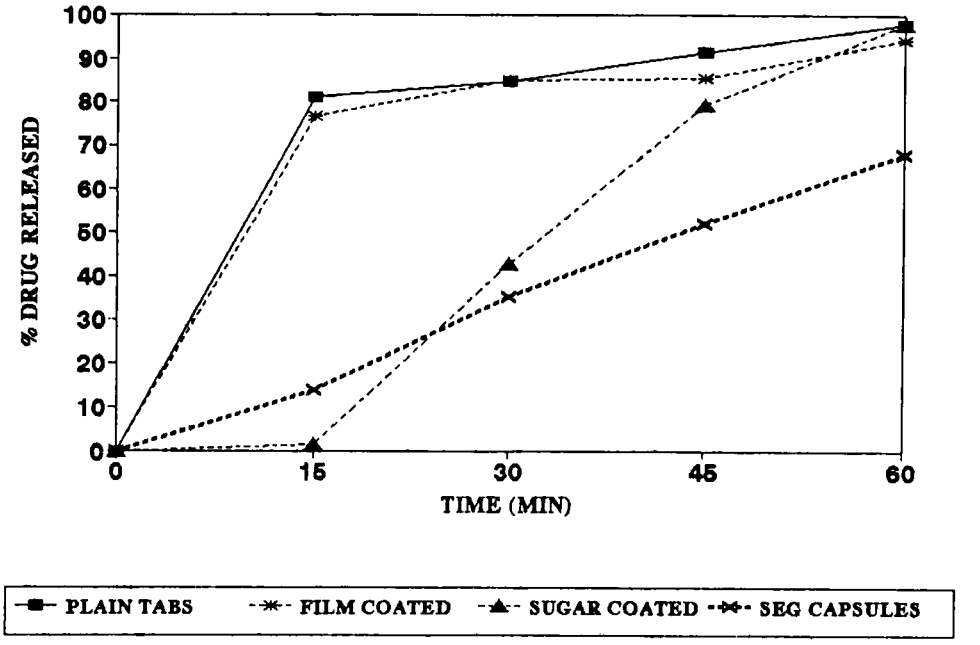

FIGURE 1

Dissolution Profiles of Freshly Prepared Plain, Film Coated, and Sugar Coated Tablets and a Commercial SEG of VPA.

2.9%, and 97.9 ± 5.2%, respectively. These percents were not significantly different, but were significantly greater than that of the SEG (68.0 ± 4.8%).

Dissolution tests were also performed on tablet samples exposed to accelerated storage conditions. Figs. 2a and 2b depict the dissolution profiles of freshly prepared plain tablets and plain tablets stored for 1, 2, and 3 months at 45°C and at 40°C/75% RH. Release rates were very similar and there was no

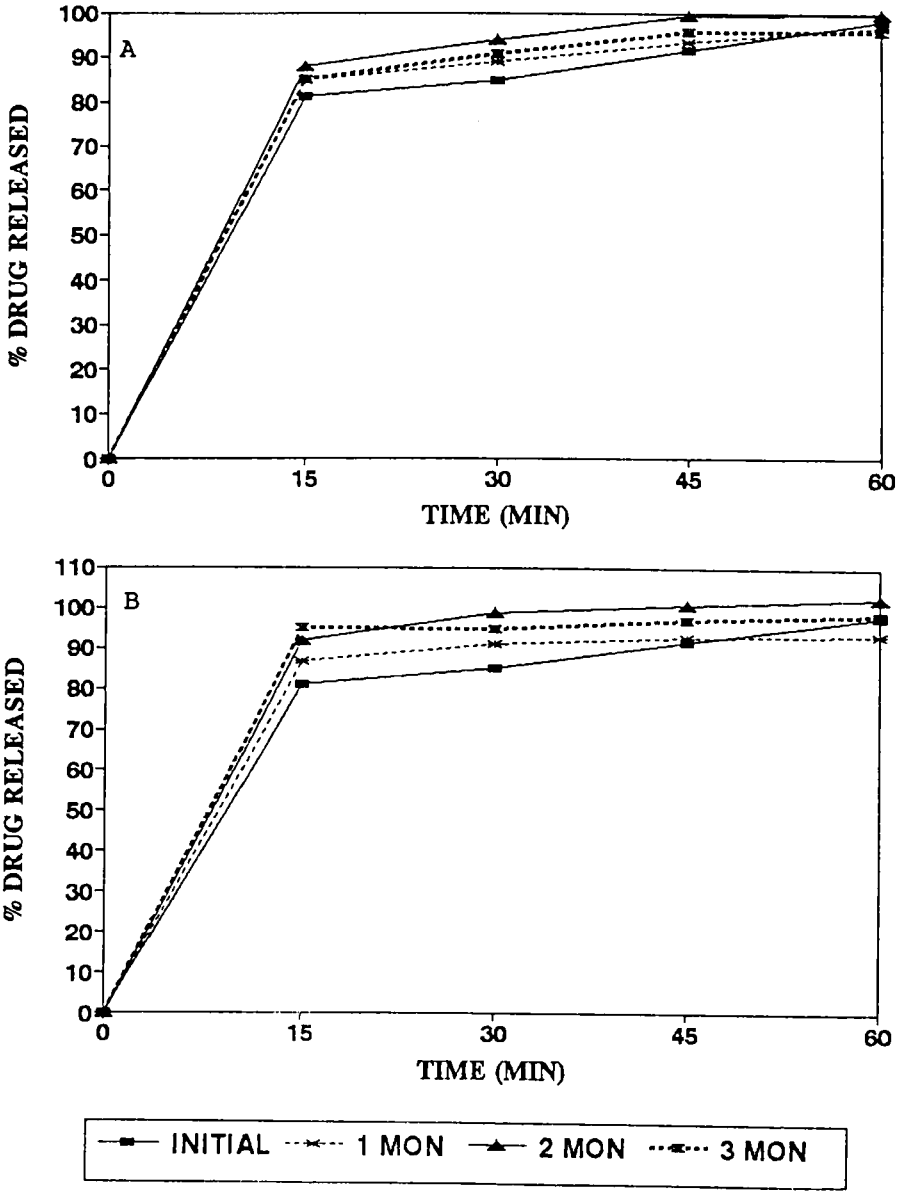

FIGURE 2

Dissolution Profiles of Freshly Prepared Plain VPA Tablets and Plain Tablets Stored for 1, 2, and 3 Months at (a) 45°C and (b) 40°C/75% RH.

detectable increase or decrease in dissolution rate with storage time. These results indicated that the plain VPA tablets were not adversely affected by the accelerated storage conditions for at least 3 months.

Figs. 3a and 3b are dissolution profiles of freshly prepared FCTs and FCTs exposed to 45°C and 40°C/75% RH for up to 3 months. The samples exposed to the accelerated storage conditions released greater than 90% of their VPA at the end of 1 hr. While FCTs stored at 40°C/75% RH for 2 months appeared to have a faster release rate than the initial sample, the difference was statistically insignificant. As with plain tablets, there was no detectable change in dissolution rate with storage time. This indicated that the FCTs were not adversely affected by the accelerated storage conditions for at least 3 months.

For SCTs stored at 45°C (Fig. 4a), the dissolution rate decreased as the exposure time increased. After 2 and 3 months of storage, the decrease in the percent VPA released at 1 hr was significant compared to the freshly prepared SCTs. For SCTs stored at 40°C/75% RH (Fig. 4b), the percent VPA released from the 1 month sample was not different from that of the freshly prepared sample at 1 hr. However, the 2 and 3 month samples failed to release any detectable amount of VPA. These SCTs passed the content uniformity test with 95.9

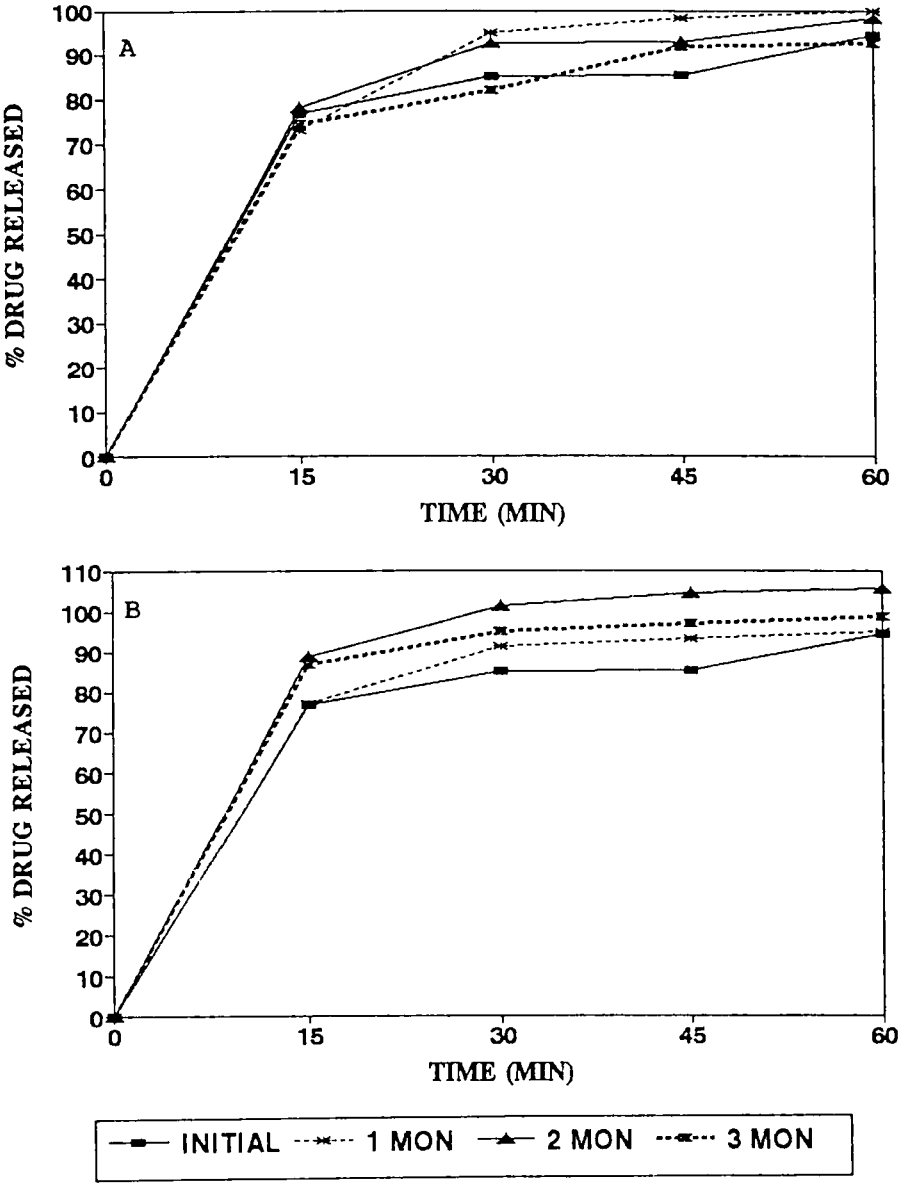

FIGURE 3

Dissolution Profiles of Freshly Prepared Film Coated VPA Tablets and Film Coated Tablets Stored for 1, 2, and 3 Months at (a) 45°C and (b) 40°C/75% RH.

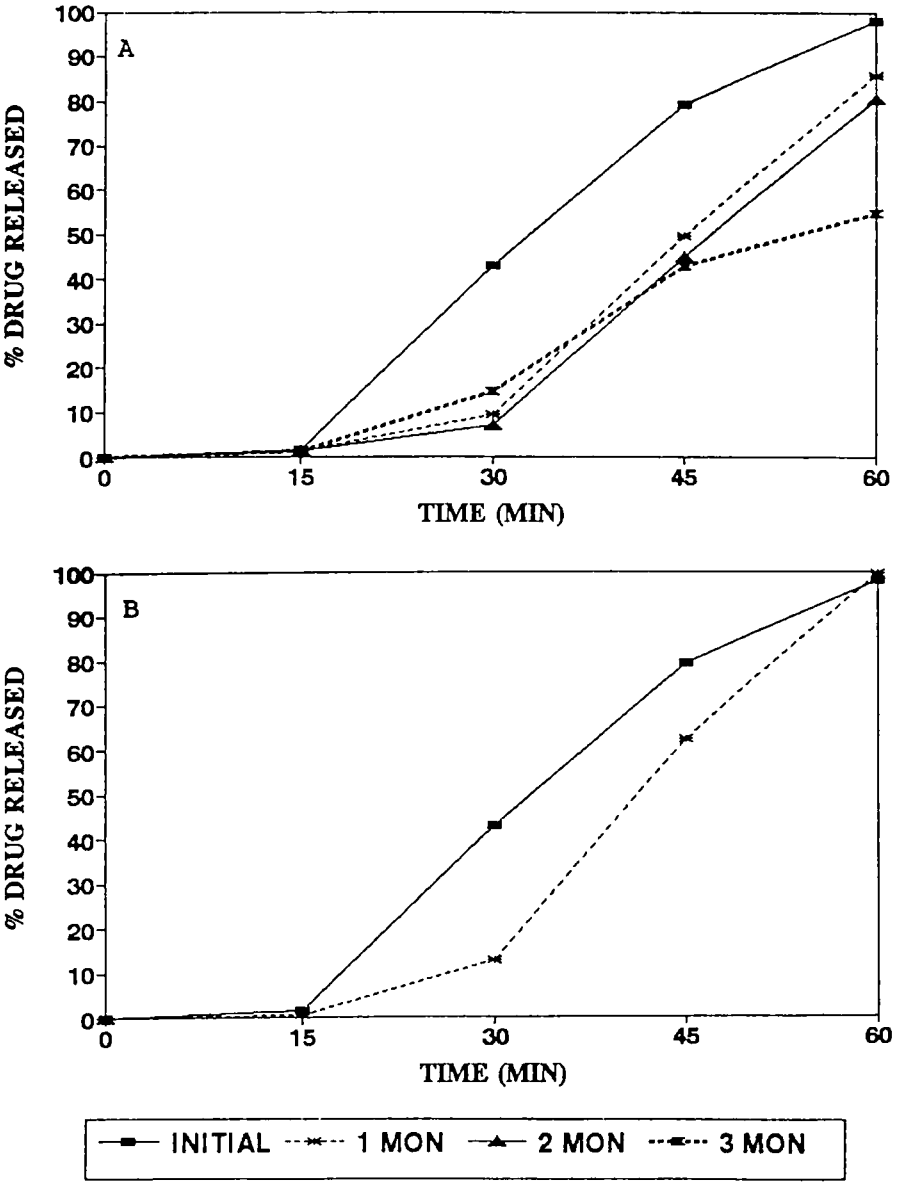

FIGURE 4

Dissolution Profiles of Freshly Prepared Sugar Coated VPA Tablets and Sugar Coated Tablets Stored for 1, 2, and 3 Months at (a) 45°C and (b) 40°C/75% RH.

± 2.6% of the VPA present after storage for 3 months at 40°C/75% RH. Thus, the poor dissolution results appeared to be a sugar coating disintegration problem, especially since most or all of the core tablets were still dry at the end of the dissolution test. These results may be due to the adherence of the sealing coat[5,6] or subcoat[7,8] to the tablet core. An interaction between gelatin and calcium carbonate in the subcoat leading to the insolubility of the sugar coat under accelerated storage conditions has been reported[9]. Excessive drying of the gelatin layer also causes sugar coating disintegration problems[10].

The physical appearance of the tablets stored under both accelerated conditions did not change. This also suggested that the various VPA tablets were stable under these storage conditions for at least 3 months. Plain tablets were also exposed to ambient atmospheric conditions for 3 months. During this time, there were no significant tablet weight changes indicating that neither moisture absorption nor VPA evaporation occurred. The VPA content of these tablets ranged from 89.6 - 97.6%, with a mean of 93.7 ± 3.5% after 3 months. The VPA blend (with tableting excipients) was also stored at room temperature for 3 months and the mean VPA content was 96.6 ± 1.9% with a range of 95.5 - 97.8%. This suggested that there was no interaction

between the drug and excipients leading to significant drug decomposition.

CONCLUSIONS

The results of this study demonstrated that the dissolution rates of freshly prepared plain and coated VPA tablets were significantly greater than those of the marketed SEG. After 3 months under accelerated storage conditions the dissolution rates of plain and FCTs were not altered, but SCTs exhibited poor dissolution, especially after 2 months of storage. Since the content uniformity test revealed more than 90% VPA in these stored SCTs and since the coating was intact at the end of the dissolution test, the dissolution problem was due to the physical instability of the sugar coat. Although plain tablets were stable, FCTs were best since they masked the characteristic odor of VPA. Thus, powder solution technology appeared to be a viable alternative to the much more expensive and highly specialized commercial preparation of SEGs.

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