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COMPARATIVE pH-GRADIENT DISSOLUTION OF SEVERAL ORAL DOSAGE FORMS OF IRON.

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ABSTRACT

A comparative pH - gradient dissolution study was conducted for several brands of oral iron dosage forms on the Canadian market. The commercially available dissolution apparatus employed in the study met the requirements of the variety of pH media conditions necessary for conducting dissolution of conventional, enteric coated and slow release iron preparations. The reproducibility of the dissolution system was evaluated using the USP's non- disintegrating salicylic acid tablets. Dissolution results are discussed in reference to a recent bioavailability report concerning oral iron preparations. The applicability of the procedure in studying the dissolution of solid dosage forms of iron is discussed.

INTRODUCTION

Recent reports (1,2) have indicated significant differences in bioavailablity of iron in oral ferrous sulphate preparations. This has provided the impetus to perform a comparative dissolution study of iron preparations. The investigation chose to employ and assess a dissolution method applicable to several oral dosage forms of iron, which is purported to mirror physiological media conditions in the gastrointestinal tract.

Dissolution studies (3,4) have been conducted on conventional and slow release iron preparations using simulated gastric juice, duodenal media and water. These studies show that the dissolution of iron may occur in various simulated physiological media and is pH dependent. Except for the dissolution requirements of the United States Pharamacopia (5) for ferrous gluconate capsules and tablets, there has been no official dissolution standards for other salts and dosage forms of iron.

The current investigation reports on a comparative pH - gradient dissolution study for several dosage forms of oral iron preparations on the Canadian market. The pH - gradient dissolution technique attempts to simulate pH changes that may be encountered in the gastrointestinal tract by conventional, slow release and enteric coated dosage forms of iron salts.

EXPERIMENTAL

Chemicals and Reagents: Ferric nitrate and potassium phosphate were ACS grade (Fisher, USA). Buffer solutions were prepared with distilled water.

Dissolution Apparatus and Conditions: A BIO-DIS DISSOLUTION TESTER, Van-Kel industries,inc., Model 14000. Dissolution tubes were attached to discs fitted with 74 micron mesh size filters.
Automated mode - program 10. Speed: 20.
Dissolution media was phosphate buffer adjusted with phosphoric acid or sodium hydoxide to the appropriate pH. Rows 1 to 5 contained the following pH of media: 1.5, 2.5, 4.5, 6.5 and 7.5, respectively.

Atomic Absorption Condition for Iron Analyses: The atomic absorption spectrophotometer was equipped with 4 inch (1 slot) standard burner head and a single element iron hollow cathode lamp. The instrument settings were: wavelength, 248 nm; spectral band width, 3 nm; lamp current, 30 mamp; air flow, 55; and acetylene flow 55 SCFH.

Iron Stock Solution: A standard solution containing 40.00 ppm of iron was prepared by dissolving 28.7 mg ferric nitrate in 50 mL of 50% nitric acid and making to volume (100 mL) with water.

Sample Preparation: The total contents of the dissolution tubes were filtered and transferred to 250 mL volumetric flasks, respectively. To each flask was added 2 mL of phosphoric acid and then made to volume with distilled water.

Procedure: The nebulizer flow, lamp position, fuel flow and burner head position were adjusted to maximum absorption. The absorbance of sample and standard solutions were determined using 10 read average mode and 1-sec integration time. Each solution was aspirated until a constant absorbance reading was obtained. Linear regression of absorbance - concentration for the standard was determined, correlation coefficient (r) was 0.99.

RESULTS AND DISCUSSION

Dissolution of film or sugar coated iron tablets are usually performed in simulated gastric juice (pH 1.2), whereas the enteric coated are normally exposed to acidic pH prior to conducting the dissolution in water or simulated intestinal juice (pH 7.4). Slow release tablets ideally require exposure to a stepwise increase in pH

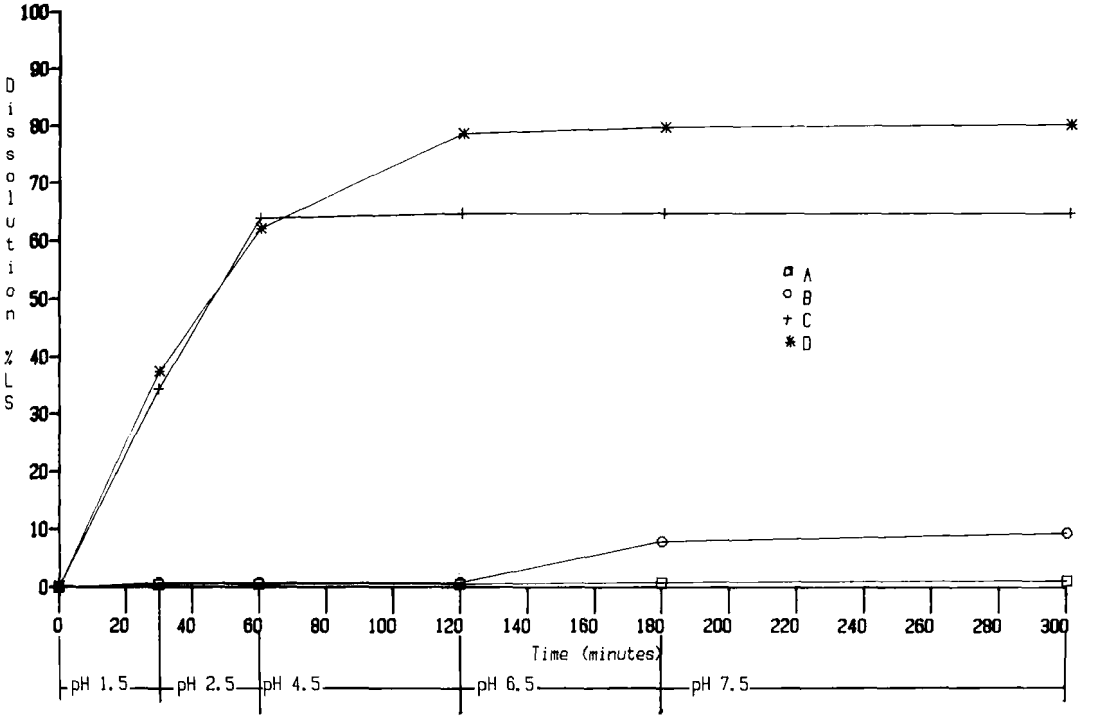

Fig. 1 pH Gradient Dissolution-Ferrous Sulfate Tab

from 1.2 to 7.5 over a set time period to simulate the gastrointestinal tract's changes in pH.

The official (USP and BP) (6) rotating basket and rotating paddle dissolution methods were not chosen as they are not easily adapted to changes in the pH of media. Instead a dissolution system was employed that would satisfy the variety of pH media conditions necessary for conducting dissolution of conventional, enteric coated and slow release dosage forms of oral iron preparations. The commercially available "BIO-DIS DISSOLUTION TESTER" (7) was chosen for this study as it provides automatic changes in pH of media with minimal operator involvement and is applicable to the evaluation of several types of dosage forms.

The reproducibility of the dissolution system was examined using non-disintegrating salicylic acid tablets that are recommended as calibrator standards for the USP rotating basket and paddle dissolution methods. Dissolution of six individual salicylic acid tablets were conducted in phoshate buffer (pH 7.4) using the first three rows of tubes in the apparatus, corresponding to the time intervals 30, 30 and 60 minutes. The average percent (mean $\pm$ relative SD) and the precision for six (6) individual tablet determinations in percent labeled claim of salicylic acid were,

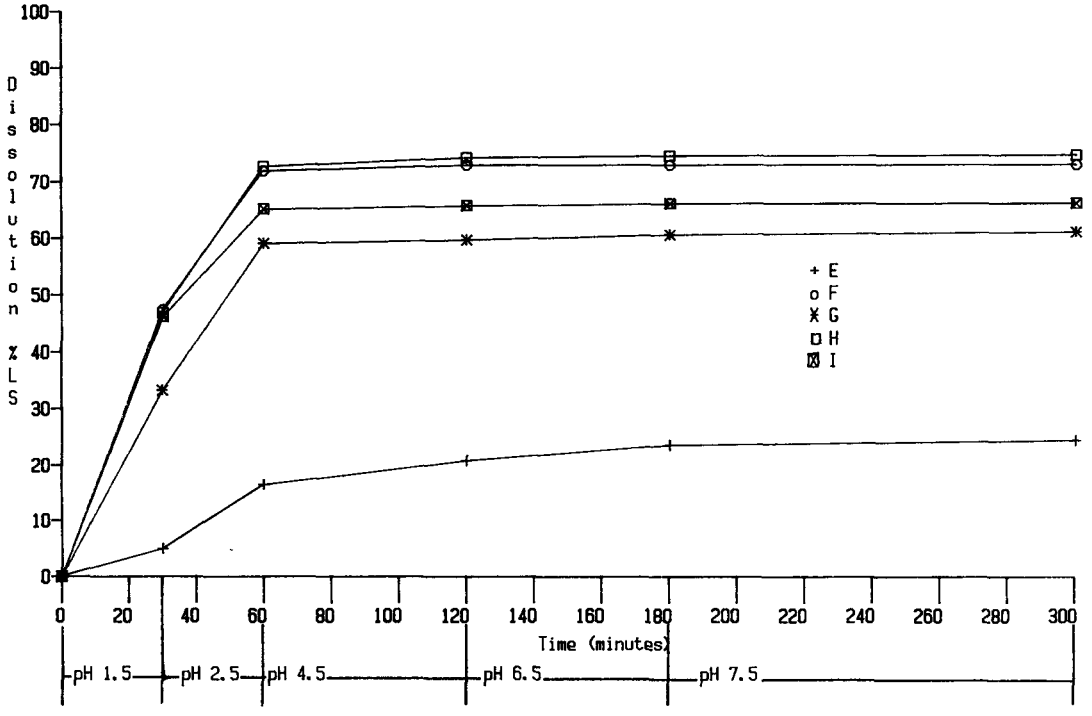

Fig. 2 pH Gradient Dissolution-Ferrous Gluconate Tab

respectively: 1st row 36.80 ± 0.60%; 2nd row 29.64 ± 3.7% and 3rd row 31.39 ± 3.8% for the Bio-Dis apparatus.

Dissolution was conducted for five hours using the Bio - Dis dissolution tester on each iron preparation. A dissolution program was chosen where six individual dosage units of the same preparation are exposed to intervals of discrete pH over 5 hours as follows: pH 1.5 (0.5h), pH 2.5 (0.5h), pH 4.5 (1.0h), pH 6.5 (1.0h) and pH 7.5 (2.0h).

Typical cumulative dissolution curves for ferrous sulphate and ferrous gluconate preparations, are shown, respectively, in figures 1 & 2. Figure 1 compares the dissolution profiles for the film, enteric coated and slow release tablets of ferrous sulphate. The dissolution of the film coated tablets occurs mainly within the pH range 1.5 - 2.5 during the first one (1) hour interval and accounts for about 200 mg of FeSO4 or about 70% of the labeled strength. Less than 1% ferrous sulphate was released in the next four(4) hours from the remaining residue in the basket when exposed to media in the pH range 4.5 - 7.5 (see Table 1).

In contrast the slow release tablets exhibit an extended dissolution over the pH range from pH 1.5 - 4.5, within the initial two (2) hour period and accounts for

Table 1a

Dissolution of Ferrous Sulphate (300 mg) Tablets

Brand	Dosage Form	pH 1.5 (30 min.)		pH 2.5 (30 min.)		pH 4.5 (60 min.)	
		Mean (%)	S.D.	Mean (%)	S.D.	Mean (%)	S.D.
A	ECT	00.54	0.06	0	0	0	0
B	ECT	00.85	0.13	0	0	0	0
C	FCT	34.40	2.40	29.60	2.70	0.82	0.32
D	SR*	37.34	2.58	24.73	3.90	16.63	4.40

* Label strength 160 mg ferrous sulphate per tablet (slow release).

Table 1b (continued...)

Brand	pH 6.5 (60 min.)		pH 7.5 (120 min.)		Cumulative (300 min.)
	Mean (%)	S.D.	Mean (%)	S.D.	Mean (%)
A	0.30	0.06	0.27	0.07	1.09
B	7.12	1.15	1.44	0.21	8.69
C	0	0	0	0	64.70
D	1.34	0.80	0.66	0.44	80.77

about 125 mg of FeSO4 or 80% of the labeled strength. At the higher pH's 6.5 & 7.5, the dissolution rates of the slow release tablets were similar to the film coated tablets as less than 1% ferrous sulphate was released (see Table 1).

The A and B enteric coated brands exhibited poor dissolution performance of 1% and 8% cumulative dissolution, respectively, in contrast to the film or slow release brands. Cumulative dissolution data after 300 minutes (Table 1) indicate about a 7 and 60 fold increase, respectively, in dissolution of the film coated (C) to the B and A enteric coated tablets. This investigation found an order of ranking of

Table 2a

Dissolution of Ferrous Gluconate (300 mg) Tablets

Brand	Dosage Form	pH 1.5 (30 min.)		pH 2.5 (30 min.)		pH 4.5 (60 min.)	
		Mean (%)	S.D.	Mean (%)	S.D.	Mean (%)	S.D.
E	SCT	04.90	3.40	11.60	3.50	4.30	3.00
F	SCT	47.39	1.20	24.57	2.00	0.99	0.27
G	SCT	33.21	12.90	25.85	11.72	0.60	0.31
H	FCT	46.89	02.30	25.90	2.16	1.52	0.20
I	FCT	46.12	03.56	19.04	1.80	0.57	0.26

Table 2b (continued...)

Brand	pH 6.5 (60 min.)		pH 7.5 (120 min.)		Cumulative (300 min.)
	Mean (%)	S.D.	Mean (%)	S.D.	Mean (%)
E	2.70	0.90	0.80	0.36	24.30
F	0		0		72.95
G	0.9	1.1	0.49	0.55	61.05
H	0.28	0.10	0		74.67
I	0.38	0.52	0		66.11

products based on a comparison of cumulative dissolution data similar to a recent bioavailability study by Walker et al. (1) which employed AUC plasma level data.

Generally, the enteric coated dosage forms studied show a significant tablet - to - tablet dissolution variation at each pH interval as evidenced by the standard deviations determined for each product. Similar vaiations were encountered for the ferrous gluconate preparations. These tablet - to - tablet variations are attributed to the products as the relative standard deviations determined in the reproducibility tests for the apparatus were found to range only from $\pm$ 0.6% to $\pm$ 3.8%.

The sugar and film coated ferrous gluconate preparations show (Figure 2) significantly higher values for cumulative dissolution in contrast to the enteric coated preparations. This is primarily attributed to the disintegration of the sugar or film coated tablets in the acidic pH, which allows contact and dissolution of the ferrous gluconate with the dissolution media.

CONCLUSION

In summary the pH gradient dissolution method is reproducible, discriminating and will be of direct application in the quality control of solid dosage forms containing iron compounds. Generally, the gradient dissolution technique appears applicable to those dosage forms that release the drug over a pH gradient. Our preliminary findings indicate that the technique shows good prospects for developing an invitro - invivo correlation for solid dosage forms containing iron salts.

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