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Appendices

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Appendix 1

The modified Noyes-Whitney equation

The major factors involved in the rate of dissolution are incorporated and represented in the Noyes-Whitney equation:
(Fincher, 1968)

$$\text{Dissolution rate} = da / dt = KS (C_s - C) \text{ -----(equation 1)}$$

where **A** = amount of drug in solution
t = time
K = intrinsic dissolution rate constant
S = surface area
C_s = Concentration of the drug-solvent boundary on the surface of the particle which is approximately equal to the solubility of the drug in the solvent.
C = concentration of the drug in the dissolution medium at time t.

According to the dissolution layer theory , the dissolution rate constant is a function of two parameters (Ogato et al., 1979)

$$K = D / h \text{ -----(equation 2)}$$

Where D and h represent the diffusion coefficient and diffusion layer thickness, respectively .

From equation 1 and 2 , the dissolution can be defined by

$$dA / dt = DS (C_s - C) / h \text{ -----(equation 3)}$$

In examining equation 3 , the dissolution rate is noted to increase with

- a) increasing diffusion coefficient
- b) increased surface area
- c) increased solubility
- d) decreased diffusion layer thickness



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Appendix 2

Calculation of the data

1. Coefficient of determination

least squares method :

$$r^2 = \frac{[n\sum(xy) - \sum x \sum y]^2}{[n\sum x^2 - (\sum x)^2][n\sum y^2 - (\sum y)^2]}$$

2. Specific rate constant (K)

$$k = \frac{n\sum(xy) - \sum x \sum y}{n\sum x^2 - (\sum x)^2}$$

(k : were calculated from the slope of linear line)

$$k_{sk} = k \cdot s_y / x \sqrt{\frac{1}{\sum(x - \bar{x})^2}}$$

where :

x = time (day)

y = ln A/A₀

3. The extrapolated values of k at room temperature.

$$\ln k = \ln A - \frac{\Delta H_a}{R} \cdot \frac{1}{T}$$

Calculated the specific rate constant (k) at room temperature by substituted the T value in the above equation.

$$k \pm s_k = k \pm s_{y/x} \sqrt{1 + \frac{1}{n} + \frac{(x_0 - \bar{x})^2}{x^2 - \frac{(\sum x)^2}{n}}}$$

where :

x_0 = the extrapolated specific rate constant at room temperature

x = average specific rate constant of 45° c, 55° c and 65°c.

n = the observed values

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Appendix 3

Standard curve data of famotidine in 0.1 M phosphate buffer (pH 4.5)
at a wavelength of 265 nm. by UV spectroscopic method.

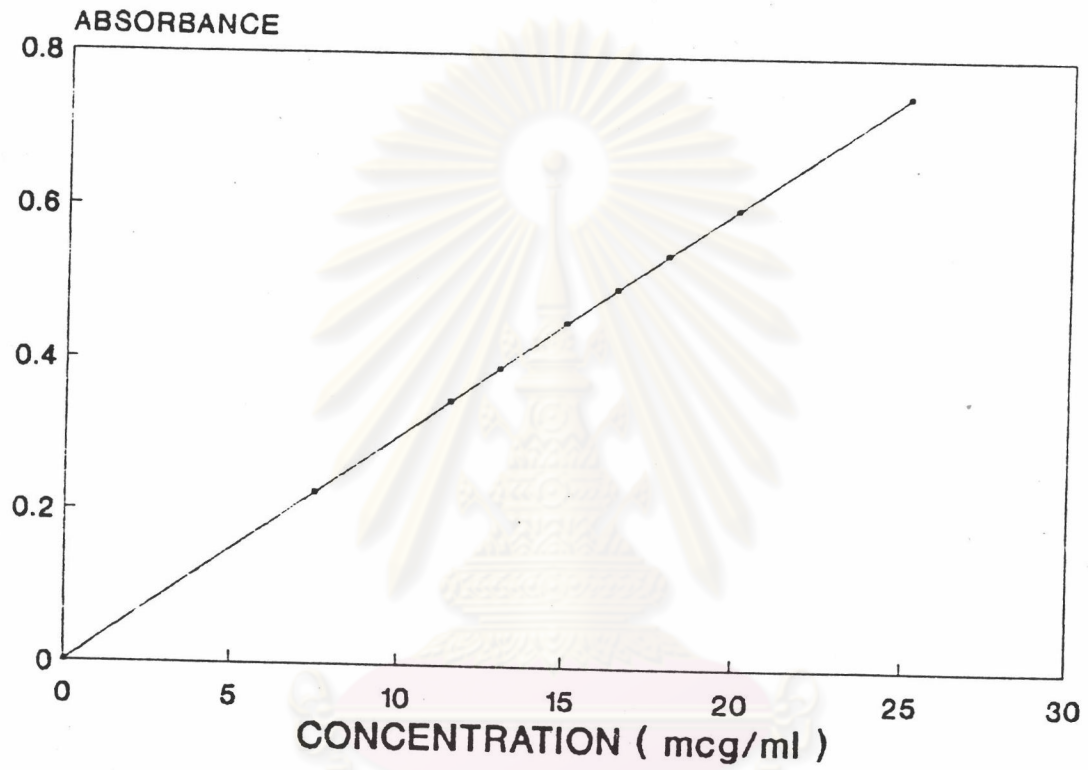
standard no.	concentration mcg/ml	Absorbance
1	0.00	0.000
2	8.00	0.252
3	10.00	0.307
4	12.00	0.362
5	14.00	0.418
6	16.00	0.473
7	18.00	0.529
8	20.00	0.584
9	22.00	0.639

Regression Output :

Constant	0.0123
Std Err of Y Est	0.0073
R Squared	0.9998
No. of Observations	9
Degrees of Freedom	7
X Coefficient (s)	0.0288
Std Err of Coef.	0.0004

Appendix 4

The calibration curve of famotidine in 0.1 M phosphate buffer pH 4.5.



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Appendix 5

Standard curve data of lyophilized famotidine in mobile phase of HPLC condition at a wavelength of 267 nm.

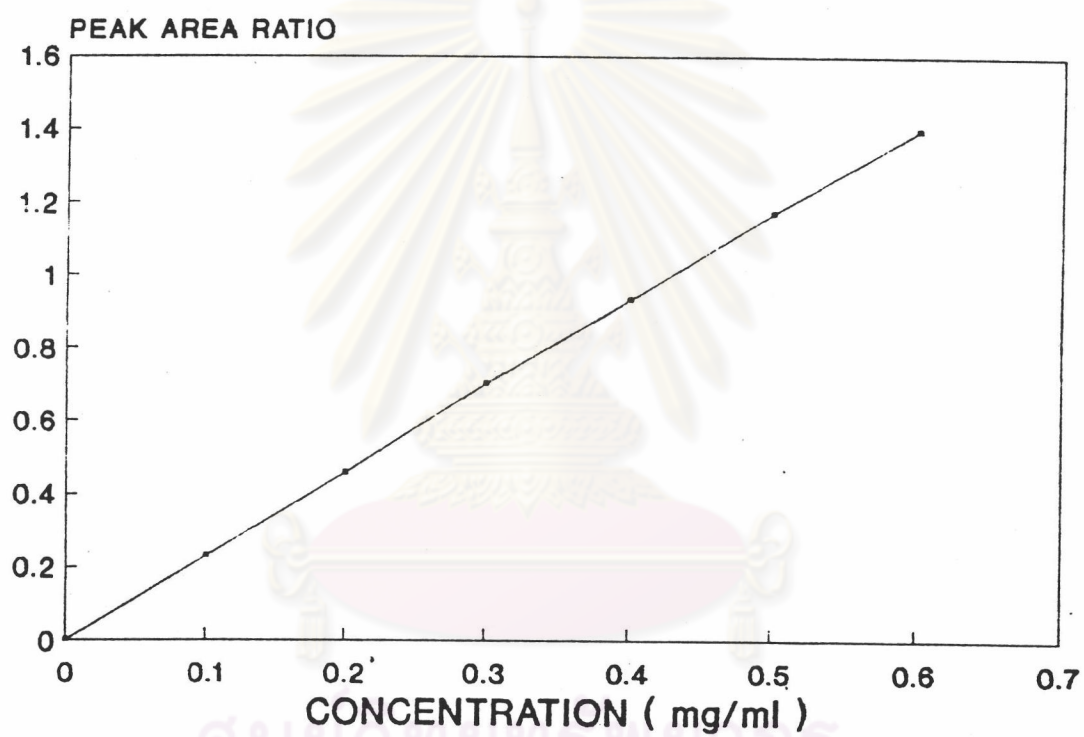
standard no.	concentration mg/ml	peak area ratio
1	0.00	0.0000
2	0.10	0.2292
3	0.20	0.4587
4	0.30	0.7007
5	0.40	0.9320
6	0.50	1.1712
7	0.60	1.3960

Regression Output :

Constant	- 0.003
Std Err of Y Est	0.0043
R Squared	0.9999
No. of Observations	7
Degrees of Freedom	5
X Coefficient (s)	2.3376
Std Err of Coef.	0.0082

Appendix 6

The calibration curve of lyophilized famotidine in mobile phase of HPLC condition.



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Appendix 7

Solubility of famotidine in various solvents at 20 °c (Pepcid prescribing information , 1990).

Solvent	Solubility Term	
	Approximate	Definite (mg/ml)
Dimethyl Formamide	Soluble	568
Glacial Acetic Acid	Freely Soluble	498
Methanol	Slightly Soluble	5.2
Water	Slightly Soluble	0.74
Acetone	Practically Insoluble	0.41
Ethanol 100%	Practically Insoluble	0.36
Chloroform	Insoluble	< 0.1
Ethyl Acetate	Insoluble	< 0.1

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Appendix 8

The equilibrium aqueous solubility of famotidine (mg/ml) from various ratios of famotidine-mannitol physical mixtures and solid dispersions at 37.0 ± 0.5 °c.

drug-carrier ratio	physical mixture					solid dispersions				
	n1	n2	n3	mean	SD	n1	n2	n3	mean	SD
1:1	1.420	1.414	1.427	1.42	0.007	2.907	2.880	2.894	2.89	0.013
1:2	1.487	1.474	1.467	1.48	0.010	3.340	3.367	3.354	3.35	0.013
1:5	1.787	1.800	1.794	1.79	0.007	3.834	3.854	3.814	3.83	0.020
1:10	1.800	1.827	1.774	1.80	0.027	3.960	3.974	3.987	3.97	0.013
1:20	1.790	1.793	1.783	1.79	0.005	4.218	4.192	4.201	4.20	0.014
1:30	1.813	1.820	1.807	1.81	0.007	4.121	4.123	4.118	4.12	0.007
1:40	1.843	1.850	1.857	1.85	0.007	4.142	4.157	4.159	4.15	0.009

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Appendix 9

The equilibrium aqueous solubility of famotidine (mg/ml) from various ratios of famotidine-sorbitol physical mixtures and solid dispersions at 37.0 ± 0.5 °c.

drug-carrier ratio	physical mixture					solid dispersions				
	n1	n2	n3	mean	SD	n1	n2	n3	mean	SD
1:1	1.360	1.360	1.387	1.37	0.014	1.534	1.520	1.467	1.51	0.035
1:2	1.454	1.334	1.340	1.38	0.067	1.580	1.574	1.600	1.58	0.014
1:5	1.340	1.400	1.414	1.38	0.039	1.667	1.700	1.714	1.69	0.024
1:10	1.510	1.500	1.490	1.50	0.010	1.740	1.667	1.680	1.70	0.039
1:20	1.527	1.517	1.523	1.52	0.005	3.040	3.033	3.020	3.03	0.010
1:30	1.550	1.550	1.543	1.55	0.004	3.047	3.034	3.027	3.04	0.010
1:40	1.597	1.583	1.567	1.58	0.015	3.087	3.100	3.114	3.10	0.013

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Appendix 10

The equilibrium aqueous solubility of famotidine (mg/ml) from various ratios of famotidine-xylitol physical mixtures and solid dispersions at 37.0 ± 0.5 °c.

drug-carrier ratio	physical mixture					solid dispersions				
	n1	n2	n3	mean	SD	n1	n2	n3	mean	SD
1:1	1.150	1.153	1.157	1.15	0.003	1.267	1.260	1.273	1.27	0.007
1:2	1.290	1.300	1.313	1.30	0.012	1.327	1.337	1.320	1.33	0.008
1:5	1.340	1.350	1.323	1.34	0.012	1.362	1.370	1.358	1.36	0.006
1:10	1.407	1.393	1.417	1.40	0.013	1.372	1.386	1.377	1.38	0.007
1:20	1.493	1.483	1.500	1.49	0.008	1.540	1.527	1.660	1.57	0.013
1:30	1.593	1.593	1.613	1.60	0.034	1.687	1.714	1.667	1.69	0.023
1:40	1.876	1.876	1.912	1.89	0.005	2.013	1.975	1.982	1.98	0.021

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Appendix 11

Dissolution data of pure famotidine powder in 0.1 M phosphate buffer pH 4.5 at 37.0 ± 0.5 °C.

Time (min)	% Famotidine dissolved								
	n1	n2	n3	n4	n5	n6	Mean	S.D	% C.V
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00
1	29.892	28.592	31.029	30.542	28.755	27.780	32.76	4.31	13.18
3	64.817	65.633	63.511	64.654	63.511	61.388	66.58	3.24	4.86
5	80.323	81.960	85.705	81.792	84.072	79.000	82.15	2.22	2.71
7	84.313	86.611	88.742	85.299	87.591	86.902	90.36	1.83	2.02
9	88.974	89.651	94.567	90.781	91.941	93.045	96.56	2.06	2.14
11	95.289	96.458	96.665	94.982	95.495	95.298	101.88	4.13	4.05
15	100.163	100.359	100.240	101.488	100.860	99.683	106.68	1.29	1.22
20	101.794	101.644	101.218	101.656	101.678	100.985	108.09	1.46	1.34

Appendix 12

Dissolution data of famotidine from 1:10 famotidine - mannitol physical mixtures in 0.1 M phosphate buffer pH 4.5 at 37.0 ± 0.5 °C.

Time (min)	% Famotidine dissolved								
	n1	n2	n3	n4	n5	n6	Mean	S.D	% C.V
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00
1	44.188	42.401	32.816	34.116	40.289	47.112	40.15	4.78	11.91
3	70.426	64.164	68.573	73.307	65.960	68.899	68.56	2.73	3.98
5	83.020	81.953	85.240	88.529	90.452	91.936	86.36	4.03	4.66
7	98.777	90.359	93.335	100.396	98.247	100.718	96.97	3.53	3.64
9	99.427	94.234	96.897	100.565	99.385	101.378	98.70	2.29	2.32
11	100.731	95.676	99.658	101.222	101.343	101.386	100.01	1.87	1.87
15	101.875	98.267	100.634	101.544	101.675	101.719	100.95	1.17	1.62
20	102.044	98.582	100.797	102.374	102.333	102.540	101.45	1.30	1.28

Appendix 13

Dissolution data of famotidine from tablets of famotidine - mannitol solid dispersions in 0.1 M phosphate buffer pH 4.5 at $37.0 \pm 0.5^\circ \text{C}$.

Time (min)	% Famotidine dissolved								
	n1	n2	n3	n4	n5	n6	Mean	S.D	% C.V
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00
1	8.773	12.671	4.874	3.249	5.686	9.747	7.50	3.20	42.75
3	76.899	84.409	82.123	78.205	80.164	90.450	82.04	4.49	5.47
5	97.037	101.482	97.226	95.411	93.788	97.104	97.00	2.35	2.42
7	100.783	103.455	102.606	98.659	99.967	100.687	101.02	1.60	1.58
9	102.749	104.454	103.765	100.615	101.766	102.979	102.72	1.26	1.23
11	105.213	105.620	105.254	103.231	103.408	105.607	104.72	1.01	0.96
15	105.074	105.646	105.441	104.878	105.056	106.776	105.48	0.64	0.60
20	106.401	109.978	106.444	105.225	106.057	106.968	106.86	1.53	1.43

Appendix 14

Dissolution data of famotidine from tablets of commercial product brand A in 0.1 M phosphate buffer pH 4.5 at $37.0 \pm 0.5^\circ \text{C}$.

Time (min)	% Famotidine dissolved								
	n1	n2	n3	n4	n5	n6	Mean	S.D	% C.V
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00
1	19.170	20.794	31.029	25.668	30.217	27.942	25.80	4.48	17.37
3	87.185	86.042	89.960	85.879	83.919	85.879	86.47	1.83	2.11
5	101.823	100.021	100.530	102.306	99.194	102.306	101.30	1.19	1.18
7	103.143	102.149	100.538	104.772	100.502	104.445	102.59	1.70	1.65
9	105.121	102.000	101.524	104.962	100.344	103.981	102.99	1.81	1.75
11	105.964	103.153	101.695	105.640	101.983	103.675	103.69	1.64	1.58
15	105.991	104.147	101.702	104.034	101.167	104.507	103.59	1.66	1.60
20	106.996	104.489	101.869	104.376	102.642	105.178	104.26	1.67	1.60

Appendix 15

Dissolution data of famotidine from tablets of commercial product brand B in 0.1 M phosphate buffer pH 4.5 at 37.0 ± 0.5 ° C.

Time (min)	% Famotidine dissolved								
	n1	n2	n3	n4	n5	n6	Mean	S.D	% C.V
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00
1	0.162	1.137	0.000	3.574	1.625	0.487	1.16	1.12	96.52
3	47.378	67.140	51.131	71.551	62.729	56.032	59.32	7.96	13.41
5	91.252	98.385	91.436	94.979	91.827	86.236	92.853	3.44	3.73
7	95.838	98.600	94.880	95.992	94.129	96.185	95.94	1.29	1.34
9	100.284	99.793	101.117	98.477	101.505	98.346	99.92	1.11	1.11
11	101.485	107.688	102.649	99.994	103.202	99.208	102.371	2.55	2.49
15	103.015	107.618	103.206	99.994	106.049	100.400	103.41	2.51	2.43
20	105.695	108.525	103.921	100.258	105.314	101.108	104.14	2.60	2.50

Appendix 16

Dissolution data of famotidine from tablets of commercial product brand C in 0.1 M phosphate buffer pH 4.5 at 37.0 ± 0.5 ° C.

Time (min)	% Famotidine dissolved								
	n1	n2	n3	n4	n5	n6	Mean	S.D	% C.V
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00
1	4.224	5.686	4.874	6.498	5.361	9.097	5.96	1.45	24.38
3	78.248	80.699	79.882	80.208	78.738	79.065	79.47	0.79	1.00
5	105.634	92.253	96.332	96.661	92.732	96.654	96.71	4.06	4.20
7	106.216	105.338	100.129	97.192	96.182	98.493	100.59	3.58	3.56
9	107.450	106.405	99.860	97.397	98.505	101.809	101.90	3.53	3.46
11	107.545	106.495	100.730	98.417	99.205	102.199	102.43	3.21	3.13
15	107.801	107.235	102.419	99.440	99.415	102.589	103.15	3.09	3.00
20	108.544	108.139	103.297	100.138	100.604	103.632	104.06	3.04	2.93

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