PHARMACOLOGY

Effect of Hydrodynamic Environment on Tablet Dissolution Using Flow-Through Dissolution Apparatus

YAN WU, MS; EVONE S. GHALY, Ph D

The main objective of this research is to investigate the principles underlying the dissolution process, study the phenomena of drug release in laminar flow, and better understand the effect of hydrodynamic condition on drug dissolution, in order to predict drug dissolution from a solid dosage form. Two drug models were selected, theophylline (Class I) and naproxen (Class II), and were formulated into conventional tablets containing 105 mg theophylline or 300 mg naproxen using wet granulation method. Additionally theophylline (105 mg) and naproxen (300 mg) matrices containing 30% hydroxypropylmethylcellulose (HPMC) polymer were prepared by direct compression and tested for dissolution using both USP II and IV dissolution apparatus. Tablets were tested for dissolution (USP IV) using different cell diameter, flow rate, and different position of the tablet inside the cell. In general, the drug dissolution at a given time is a direct function of the flow rate, increasing the flow rate increases drug release. The use of a small cell resulted in faster drug dissolution and higher Reynold's Number than using a large cell. Tablet position in the cell, also has an effect on drug dissolution, inserting the tablet in a horizontal position inside the cell gave faster dissolution than a vertical position. The hydrodynamic conditions did not affect the drug dissolution from HPMC controlled release tablets indicating that the drug dissolution is controlled by the matrix. An equation to predict drug dissolution from conventional tablets was established: $Sh=-21.36+10.58Re^{1/2}$ where $R^2=0.98$. This study demonstrated that hydrodynamic conditions, and type of dissolution testing apparatus used have an effect on dissolution rate, mass transfer rate, and film thickness underlying dissolution process.

Key words: Dissolution model, Hydrodynamic condition, Dissolution, Theophylline, Naproxen, Flow-Through dissolution apparatus, USP IV dissolution apparatus

Sensitive and reproducible dissolution data derived from physicochemically and hydrodynamically defined conditions are necessary in order to compare variability in in vitro dissolution data and to be able to use such results as a surrogate for possible in vivo bioavailability, bioequivalence testing and in vitro/in vivo correlations (1-3).

The flow-through cell dissolution method presents a useful alternative to the other existing official compendia dissolution methods and had received wide acceptance in pharmaceutical research. The test product is placed in a small column or cell, which is continuously exposed to a homogeneous laminar flow. This system is thought to be a very good system that can simulate an in vivo environment (4-8).

Drug dissolution and gastrointestinal permeability are the fundamental parameters that control the rate and extent of drug absorption. The Biopharmaceutic Drug Classification system defined four class of drug based on aqueous solubility and intestinal permeability. The permeability of both class I and class II drugs is high, which means in-vitro/in-vivo correlation may be expected. For Class I drug, if 85% of the drug is released within 15 minutes, this can ensure good bioavailability; for class II drug which is of low solubility and of high permeability characteristics, appropriate designed dissolution tests can provide a picture of the in vivo performance (2).

Efficient simulation of the in vivo dissolution process of oral dosage forms is beneficial for pharmaceutical scientist interested in product development, quality control, manufacturing, and research applications. There is several issues that should be considered, such as the media composition and volume, hydrodynamics, and interpretation of the data (9-12)

The objectives of this research are to understand the principles underlying the dissolution process; evaluate the dissolution profiles of two classes of drugs (class I and II) from conventional and matrix tablets using USP IV dissolution apparatus under variable conditions such as:

Address to correspondence: Evone S. Ghaly. Ph D, School of Pharmacy, University of Puerto Rico, PO Box 36506, San Juan, P.R.00936-5067

different flow rate; diameter of the cell and position of the tablet and additionally, to develop a model to predict drug dissolution.

Materials

Theophylline anhydrous, USP, lot No. 88135 (Knoll AG, BASEF Pharm., Minden, Germany); Naproxen, Lot No. 37943 (donated by Mova Pharmaceutical, Cauguas, Puerto Rico); Lactose NF anhydrous, Impalpable, lot No. 8 NLO2C (Kraft Inc, New York, USA); Polyvinyl pyrrolidone, PVP, Plasdone K 29-32 (supplied by GAF Corporation, New York, USA); Ac-Di-Sol, Lot No. T844 (Donated by FMC, Philadephia, PA, USA); Hydroxypropylmethylcellulose, Methocel K4M, lot No. MM92030901K (Dow Chemical Co., Midland, MI) and Magnesium Sterate, lot No. 606-413 (Ruger Chemical Co, Irvington, New Jersey, USA).

Model

The model used in this study was:

$$J=0.62\ D^{2/3}\ n^{-1/6}C_s w^{1/2} \qquad (1)$$

where, J is the observed dissolution rate at a given speed of rotation, mg/(cm^{2}s); D is the diffusion in cm^2/second; V is linear velocity and C_s is the solubility of the solid. Both the weight dissolved and the remaining external surface area was calculated as a function of time. From the amount dissolved and the mean external surface area, the surface specific dissolution rate can be calculated for specific time intervals during the dissolution process.

The linear velocity, V of the media in the area around the tablet is calculated as:

Media flow rate / media density / area for flow (2)

Where, area for flow is the sectional area of the cell minus sectional area of the tablet.

The Reynold's number which is the ratio of momentum forces to viscous forces in a moving fluid, commonly interpreted as the degree of turbulence in the fluid was calculated as follows:

$Re = d \times v \times r/h$

where, d is the diameter of the tablet; v is the linear fluid velocity around the object; r is the fluid density; h is the fluid viscosity.

Methods

Preparation of Tablet Formulations:

1. Theophylline tablets

Wet granulation method was used to prepare theophylline tablets where each tablet contains 105 mg theophylline, 6 mg polyvinyl pyrrolidone, 183 mg lactose, 3 mg Ac-Di-Sol and 3 mg magnesium stearate. The batch size was 1 kg, all ingredients were passed manually through a screen number 20 to break any agglomerates and magnesium stearate was passed through a screen number 30.

a. Blending:

In a V-blender, PK Reference number C419379 (Patterson Kelly Co., Division of Harsco Corporation, PA, USA), half of the lactose was added, followed by Ac-Di-Sol, Polyvinyl pyrrolidone, theophylline, and the remaining half of the lactose. The mixture was mixed for 20 minutes. The magnesium stearate was added and the mixture was mixed for further 5 minutes.

b. Wet granulation:

The mixture in the V-blender was transferred into a planetary mixer model A 120, serial number 1414996 (Hobart MFG Co., Ohio, USA), mixed for 1 minute and 220 ml distilled water was added over 7 minutes to obtain agglomerates of suitable consistency. The wet agglomerates passed manually through a screen number 8, and the granules were spread on paper lined trays and introduced in hot air conventional oven for drying at temperature of 39^{0}C over night. The dried granules were then passed through a screen number 12 and mixed with magnesium stearate for 5 minutes.

c. Compression:

The granules were compressed into tablets using Manesty B-3B rotary machine serial No. 1C186 (Manesty Machine Ltd, Liverpool, England) equipped with 11/32 inches flat faced punches. Target weight and hardness were 300 mg $\pm$ 5 mg and 6-8 Kp, respectively.

2. Naproxen Tablets

Wet granulation method was also used for preparation of Naproxen where each tablets contains 300 mg naproxen, 6 mg polyvinyl pyrrolidone, 3.2 mg Ac-Di-Sol and 3.2 mg magnesium stearate.

a. Blending

The same procedure described under blending of theophylline is used for naproxen except that half of the naproxen was introduced in the V-blender, followed by Ac-Di-Sol, polyvinyl pyrrolidone and the remaining half of naproxen and no lactose was added..

b. Wet granulation

The same procedure described under theophylline is used for naproxen except that 240 ml water over 8 minutes is used as a granulating liquid for naproxen instead of 220 ml water over 7 minutes in case of theophylline.

c. Compression

Granules were compressed into tablets at target weight and hardness of 312.4 mg $\pm$ 5 mg and 6-8 Kp respectively.

3. Tablets Theophylline-Hydroxypropylmethyl-cellulose (HPMC) Controlled Release

Direct compression method was used for preparation of theophylline-HPMC tablets, where each tablet contains 105 mg theophylline, 90 mg HPMC, 102 mg lactose and 3 mg magnesium stearate.

a. Blending

In a V-blender, PK reference number C413379 (Patterson Kelly Co., Division of Harso Corporation, PA, USA) lactose was added followed by theophylline and HPMC. The Mixture was mixed for 15 minutes and then magnesium stearate was added and mixed for further 5minutes

b. Compression

The mixture was compressed into tablets at target weight of 300 mg $\pm$ 5 % and 7-9 Kp, respectively.

4. Naproxen – Hydroxypropylmethyl cellulose Tablets

Direct compression method was used for preparation of naproxen-HPMC tablets where, each tablet contains 300 mg naproxen, 120 mg HPMC and 4 mg magnesium stearate.

a. Blending

In a V-blender, PK reference number C413379 (Patterson Kelly Co., Division of Harso).

Corporation, PA, USA) HPMC was added followed by naproxen and the mixture was blended for 15 minutes. Magnesium stearate was added and mixed for further 5 minutes.

b. Compression

The mixture was compressed into tablets at target weight of 424 mg $\pm$ 5 % and target hardness of 7-9 Kp, respectively

Dissolution Testing

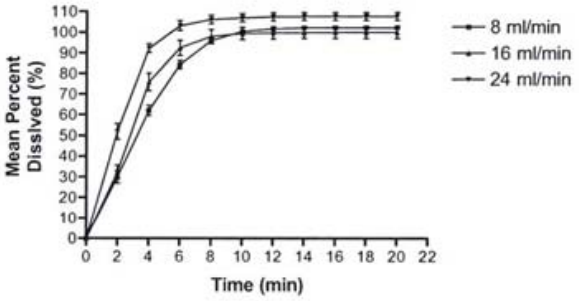
Dissolution testing was performed for both theophylline and naproxen tablets using flow-through cell dissolution method (Apparatus IV, Distec, Flow-Through dissolution, serial No. PV-20020424, North Brunswick, N.J., U.S.A.). Six cells were operated in parallel, and the flow rate of each cell was checked prior to each experimental run to ensure that the variability was less than 5%. The temperature of the Flow Cell unit bath was kept at 37.5 ± 0.5°C. Both 12 and 22.6 mm cells were used during the study. Each cell was prepared by placing a 5 mm ruby bead in the apex of the cone to protect the inlet tube then a total of 2.5 g of 1 mm glass beads were placed in each 12 mm cell, and 8.0 g of 1 mm glass beads were placed in each 22.6 mm cell, the tablets vertically or horizontally were positioned in each cell on the layer of beads. Distilled water and phosphate buffer pH 6.4 were used as a dissolution medium for theophylline and naproxen tablets respectively. The sampling intervals of theophylline were 0-2 minutes, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16, 16-18, and 18-20 min, and the sampling intervals of naproxen were 0-5 minutes,5-10, 10-15, 15-30, 30-45, 45-60, 60-90 and 90-120 min; the elution from each cell was collected. Concentration of the drug in each sample was determined by measuring the absorbance at maximum wavelength of 272 nm and 332 nm for theophylline and naproxen respectively. Dissolution experiments were run in triplicate.

Additionally, theophylline and naproxen controlled release tablets were tested for dissolution using USP II dissolution apparatus at 50 rpm, 100 and 150 rpm. Also, they were tested for dissolution using USP IV at flow rates of 8 ml / minute, 16 and 24 ml / minute.

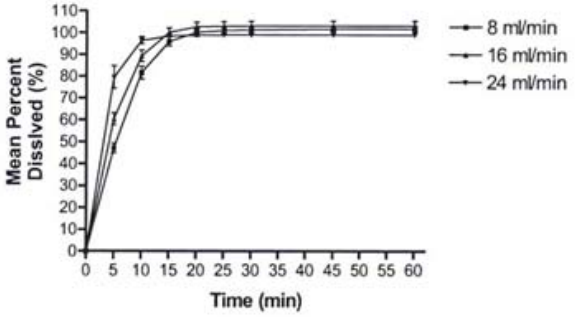
Results Ans Discussion

Figures 1 and 2 show the dissolution profiles of the theophylline tablets in distilled water using USP IV small cell and large cell at different flow rate. The percent of drug dissolved at 4 minutes using the 12 mm cell and flow rate of 8 ml per minute was 62% while the percent drug dissolved was 92.17% when the flow rate was increased to 24 ml/minute. The same results were true for the large

Figuere 1. Dissolution Profiles Of Theophylline Tablets Using Usp Iv And 12 Mm Cell



Figuere 2. Dissolution Profiles Of Theophylline Tablets Using Usp Iv And 22.6 Mm Cell



cell (22.6 mm). The amount of drug dissolved at a given time is a direct function of the flow rate; as the flow rate increased, drug dissolution is increased. ANOVA analysis showed significant difference between tablets tested for dissolution using flow rate of 8 ml/min versus 24 ml/min, for both small and large cells as shown in Table 1..

In order to calculate the Reynold's number, the following value were measured: for theophylline r = 0.977 g/cm3 at 37°C distilled water; h=0.00697 g/cm per second at 37°C distilled water; d=0.94cm and for naproxen, r = 0.9992 g/cm3 at 37°C phosphate buffer PH 6.4; h=0.01167 g/cm per s at 37°C phosphate buffer PH 6.4; d=0.94 cm.

Table2 shows the Reynold's number and mean dissolution rate using two size of cells. In general, as the flow rate increased, the Reynold's number increased, and the mean dissolution rate increased. Comparing the two type of cell under the same flow rate, such as at 8 ml/min, the Reynold's number using the small cell is 41.15, while the large cell Reynold's number is 5.42. These data indicate that as the diameter of cell increased, the Reynold's number decreased. At the same flow rate, the mean dissolution rate in small cell is 1.86±0.01 mmol/min per cm^2 while in large cell is 1.15±0.06 mmol/min per cm^2, indicating that as the diameter of the cell increased, the mean dissolution rate decreased. .

Table 2. Reynold's Number and Dissolution Rate of Theophylline Tablets Using Small and Large Cell Size and Different Flow Rate

Experiments	Reynold's number	Mean Dissolution Rates and 95% confident intervals, (mmol/min per cm^2)
Theophylline 8 ml/min 12 mm cell	41.15	1.86 ± 0.11
Theophylline 16 ml/min 12 mm cell	82.30	2.39 ± 0.2
Theophylline 24 ml/min 12 mm cell	123.45	3.18 ± 0.17
Theophylline 8 ml/min 22.6mm cell	5.42	1.15 ± 0.06
Theophylline 16 ml/min 22.6mm cell	10.83	1.48 ± 0.07
Theophylline 24 ml/min 22.6 mm cell	16.25	2.63 ± 0.14

Table 1. ANOVA Analysis of Theophylline Dissolution Data Using USP IV and 12 mm Cell

Min.	8ml/min	16ml/min	24ml/min	SS	MS	F	P	
2	24.7	38.7	59.5	876.8	438.4	12.6	0.007	S
	35.1	27.4	47.8	209.2	34.9			
	29.7	30.8	48.3	1086.1				
4	57.5	84.2	96.2	1376.0	688.0	23.7	0.001	S
	66.0	69.9	89.1	174.4	29.1			
	62.5	73.4	91.2	1550.4				
6	80.5	99.7	105.7	539.3	269.6	11.3	0.009	S
	87.9	87.9	98.5	143.5	23.9			
	84.5	89.4	105.4	682.8				
8	93.1	104.5	108.2	176.4	88.2	5.3	0.05	NS
	98.1	94.3	102.2	100.9	16.8			
	96.4	95.1	108.0	277.3				
10	98.5	105.4	109.0	102.9	51.4	3.7	0.091	NS
	102.0	96.1	103.1	84.0	14.0			
	100.5	96.5	108.8	186.9				

ANOVA Analysis of Theophylline Dissolution Data Using USP IV and 22.6 mm Cell

Min.	8ml/min	16ml/min	24ml/min	SS	MS	F	P	
5	49.1	64.3	83.1	1594.0	797.0	20.4	0.002	S
	42.9	55.1	86.2	234.7	39.1			
	49.4	61.6	69.3	1828.7				
10	83.0	94.0	97.4	330.2	165.1	9.0	0.016	S
	75.6	85.0	98.6	110.7	18.5			
	85.2	88.7	93.3	440.9				
15	98.6	103.8	99.0	27.4	13.7	1.6	0.275	N
	91.9	99.6	99.6	50.9	8.5			
	97.4	97.4	97.0	78.3				

The same results were true for naproxen as shown in Figures 3 and 4. As the flow rate increased, drug dissolution increased. The percent drug dissolved at 5 minute of testing dissolution using flow rate of 8 ml/minute was19.53%, while percent drug dissolved at a flow rate of 24 ml/minute was 37.12%. These data indicated that as the flow rate increased, the drug release increased and also that the small diameter cell method gave higher dissolution than the larger cell.

Table 3 shows that as the flow rate increased, the Reynold' s number increased, and the mean dissolution rate of naproxen increased. Comparing the two cells, the Reynold's number obtained by using small cell was larger than the Reynold's number obtained by using the large diameter cell and consequently, the drug dissolution for tablets tested in the small diameter cell is higher than those of the same composition, but tested for dissolution in the large cell.

Figure 5 shows the drug dissolution of theophylline tablet inserted in the cell at different position: horizontal or vertical. The percent drug dissolved at 2 minutes of testing dissolution was 27.27 % when the tablet was inserted horizontally while the percent drug dissolved was 16.77% when the tablet was inserted vertically. These data indicated that when the tablet was inserted horizontally in the cell, the drug dissolution was higher than vertical inserted tablet. Student's t-test analysis (Table 4) supported these data and showed significant

Figure 3. Dissolution Profiles of Naproxen Tablets Using USP IV and 12mm Cell

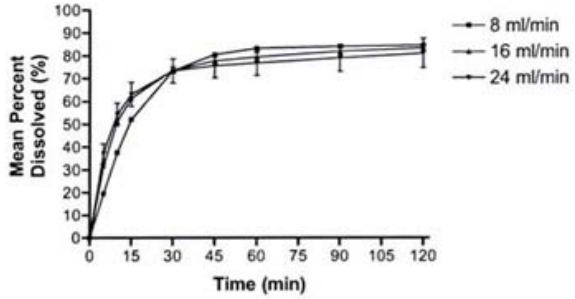


Figure 4. Dissolution Profiles of Naproxen Tablets Using USP IV and 22.6 mm Cell

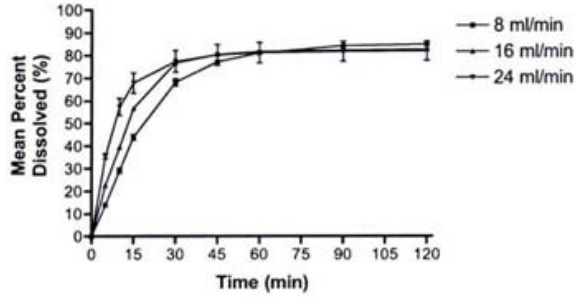


Figure 5. Effect of Tablet Position on Theophylline Dissolution Rate Using USPIV

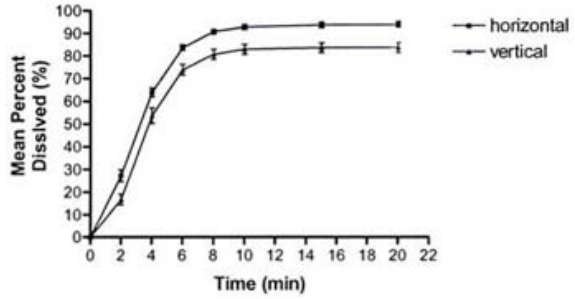


Table 3. Reynold's Number and Dissolution Rate of Naproxen Tablets Using Small and Large Cell Size and Different Flow Rates

Experiments	Reynold's number	Mean Dissolution Rates and 95% confident intervals, (mmol/min per cm^2)
Naproxen 8 ml/min 12 mm cell	24.58	0.42 ± 0.01
Naproxen 16 ml/min 12 mm cell	49.16	0.61 ± 0.02
Naproxen 24 ml/min 12 mm cell	73.74	0.79 ± 0.05
Naproxen 8 ml/min 22.6mm cell	3.24	0.29 ± 0.01
Naproxen 16 ml/min 22.6mm cell	6.47	0.44 ± 0.01
Naproxen 24 ml/min 22.6 mm cell	9.71	0.74 ± 0.06

differences at 2 minutes, 6 , 8, 10, 15 and 20 minutes. However, there was no significant differences in

Table 4. Student's t Test Analysis of Theophylline Dissolution Data Using USP IV and Different Tablet Position

Time (minute)	Horizontal	Vertical	t	P	
2	28.5	20.3	2.905	0.0439	S
	31.1	17.9			
	22.2	12.1			
4	65.8	57.8	2.594	0.0604	NS
	66.0	56.4			
	59.9	47.0			
6	85.4	77.5	3.707	0.0207	S
	84.3	74.3			
	81.3	69.5			
8	92.2	84.3	4.113	0.0147	S
	91.5	81.1			
	88.7	76.7			
10	94.2	86.5	3.913	0.0173	S
	93.6	83.4			
	90.5	78.9			
15	95.4	87.2	3.991	0.0163	S
	94.5	84.0			
	91.2	79.6			
30	95.5	87.3	4.016	0.0159	S
	94.7	84.1			
	91.5	79.6			

dissolution data when naproxen tablets was inserted in the cell at different positions (horizontal or vertical) as shown in Table 5.

Figures 6 and 7 show the dissolution profile at different rotational speed for both theophylline and naproxen based HPMC tablets. ANOVA analysis (Table 6) showed significant differences in drug dissolution at all time of testing dissolution of theophylline-HPMC tablets as the rotational speed increased. For naproxen-HPMC tablets, ANOVA analysis (Table 7) showed significant differences in drug dissolution as rotational speed increased only at 300 and 360 minutes of testing dissolution.

Figures 8-9 show the dissolution profiles for theophylline and naproxen-HPMC using U.S.P. Apparatus IV at different flow rates. Increasing the flow rate did not affect the drug dissolution and ANOVA analysis supported the dissolution data and indicated no significant differences as the flow rate increased (Tables 8-9). A possible explanation is that the drug dissolution from matrix tablets is not only related to drug transport through the static diffusion layer but also associate with the drug delivery mechanism from the dosage form. In general, the drug

Table 5. Student's t Test Analysis of Naproxen Dissolution Data Using USP 4 at Different Tablet Position

Time (minute)	Horizontal	Vertical	t	P	
5	27.3	24.9	0.3404	0.7507	NS
	26.7	32.0			
	31.7	31.7			
10	51.6	48.6	0.05604	0.9580	NS
	53.2	54.3			
	52.9	54.5			
15	65.2	62.8	0.1783	0.8672	NS
	64.7	66.3			
	64.8	66.2			
30	78.7	77.1	0.8038	0.4666	NS
	77.0	80.5			
	79.2	80.2			
45	83.6	83.6	1.352	0.2478	NS
	82.5	87.3			
	85.3	85.9			
60	85.3	86.1	1.525	0.2019	NS
	84.5	89.1			
	87.6	88.0			

Figure 6. Dissolution Profile of Theophylline-HPMC Tablets Using USP II

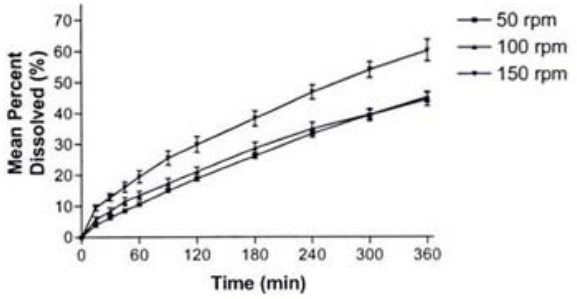
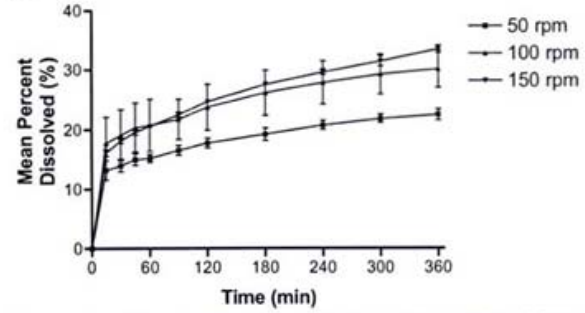


Figure 7. Dissolution Profile of Naproxen-HPMC Tablets Using USP II



dissolution from theophylline or naproxen matrix tablets using apparatus 2 at 150 rpm was higher than the drug dissolution obtained by using USP IV at flow rate of 24 ml/minute. The percent drug dissolved from theophylline-HPMC matrix at 30 minutes of testing dissolution using USP II apparatus at 150 rpm was 12.6 % while the percent drug dissolved was 9.22% when USP IV apparatus was used at a flow rate of 24 ml/minute. The same results were true for naproxen-HPMC matrix.

Table 6. ANOVA Analysis for The Dissolution Data of Theophylline-HPMC Tablets Using USP II

Min	50 rpm	100 rpm	150 rpm	SS	MS	F	P	
	4.2	5.4	8.5	50.6	25.3	13.1	0.007	S
	3.7	7.4	8.7	11.6	1.9			
15	3.8	4.0	11.5	62.2				
	6.6	8.5	11.7	69.1	34.5	12.9	0.007	S
	5.8	10.3	11.7	16.0	2.7			
30	6.4	6.5	15.2	85.1				
	8.9	11.6	14.6	89.3	44.6	10.11	0.012	S
	7.9	13.7	14.5	26.5	4.42			
45	8.7	9.3	19.4	115.8				
	11.0	13.7	17.7	121.3	60.6	10.3	0.012	S
	9.9	15.7	17.2	35.4	5.9			
60	11.0	10.9	23.3	156.7				
	15.4	17.9	23.6	181.3	90.7	11.9	0.008	S
	14.1	19.6	22.8	45.9	7.6			
90	15.5	14.6	30.1	227.2				
	19.3	22.0	27.8	204.9	102.5	10.9	0.01	S
	17.4	23.0	26.8	56.4	9.4			
120	19.7	18.1	35.0	261.3				
	26.4	29.9	37.1	246.0	123.0	11.72	0.0085	S
	24.6	31.1	34.7	62.94	10.49			
180	27.7	25.1	43.2	308.9				
	33.6	36.2	47.3	325.3	162.6	14.33	0.005	S
	31.1	37.7	42.6	68.1	11.4			
240	35.6	31.0	50.8	393.4				
	40.5	39.9	56.8	426.3	213.1	16.4	0.004	S
	42.3	36.8	49.1	78.0	13.0			
300	35.5	42.1	56.6	504.3				
	45.9	45.3	65.7	476.2	238.1	12.1	0.008	S
	47.4	42.3	53.7	119.5	19.9			
360	40.4	48.4	61.7	595.7				

The dimensionless model was used to describe the effect of hydrodynamic conditions on conventional tablet dissolution. A linear relationship was obtained by plotting Sherwood number versus Reynold's number (Figure 10). The equation obtained is as follow:

$Sh = 21.36 + 10.58\ Re^{0.5}$ with $r^2 = 0.98$

The above equation can be used to predict mass transfer

Table 7. ANOVA Analysis for The Dissolution Data of Naproxen-HPMC Tablets Using USP II

	50 rpm	100 rpm	150 rpm	SS	MS	F	P	
	10.1	26.5	16.2	32.1	16.0	0.7	0.523	N
	15.6	13.5	15.1	132.9	22.2			
15	13.9	13.2	17.0	165.0				
	11.9	27.6	18.3	44.1	22.0	1.1	0.386	N
	14.7	15.0	17.3	118.0	19.7			
30	15.4	14.6	18.7	162.1				
	13.3	28.6	19.7	51.1	25.5	1.42	0.313	N
	14.9	16.6	18.8	107.8	18.0			
45	16.7	16.0	20.3	158.9				
	14.0	29.4	20.3	59.3	29.6	1.52	0.292	N
	15.4	16.2	20.1	116.8	19.5			
60	16.3	16.6	21.3	176.0				
	15.1	28.5	21.9	63.7	31.9	2.6	0.151	N
	16.6	18.6	22.5	72.7	12.1			
90	17.9	18.2	23.3	136.5				
	16.2	31.4	24.4	84.0	42.0	2.7	0.146	N
	18.0	19.9	24.3	93.3	15.5			
120	19.0	19.9	25.2	177.2				
	17.4	33.7	27.0	118.9	59.5	3.9	0.084	N
	19.4	22.7	27.5	92.7	15.4			
180	20.9	22.1	28.1	211.6				
	19.6	35.1	29.3	131.9	66.0	4.8	0.058	N
	20.6	24.4	29.0	83.6	13.9			
240	22.1	24.0	30.5	215.6				
	20.6	36.0	29.8	153.7	76.8	6.1	0.036	S
	21.8	26.5	32.3	75.4	12.6			
300	23.0	25.4	32.3	229.1				
	20.8	36.5	32.3	191.0	95.5	8.5	0.018	S
	22.5	27.1	34.2	67.5	11.2			
360	24.1	26.8	33.9	258.4				

rate of tablets at different rotational speed (USP II) or at different flow rates (USP IV).

Summary And Conclusion

The amount of drug released from conventional tablets at a given time is a direct function of the flow rate, with an increase in the flow rate, the diffusion layer thickness decreased, resulting in an acceleration of drug release.

Figure 8. Dissolution Profiles of Theophylline-HPMC Tablets Using USP IV

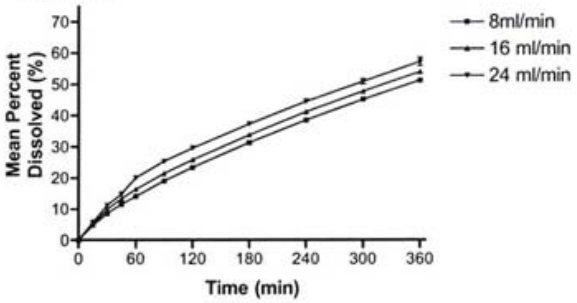
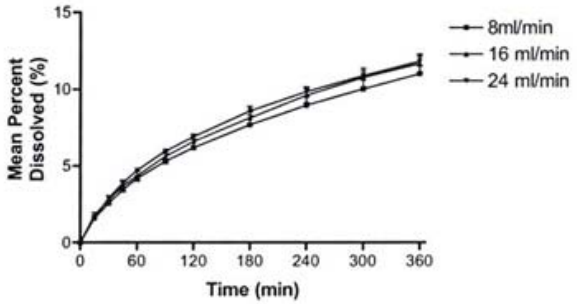


Figure 9. Dissolution Profiles of Naproxen-HPMC Tablets Using USPIV



The diameter of the cell is another variable that should be considered for conventional tablet dissolution with drug released from a small cell faster than drug released from large one. As the cell diameter increased, a decrease of Reynold's number was observed.

The drug dissolution from HPMC tablets did not show a significant differences as the rotational speed (USP II) or flow rate (USP IV) were varied, indicating that the drug release from matrix tablets is not only dependent on drug transport through the stagnant aqueous diffusion layer formed at the surface of the tablets but also, associated with the drug delivery mechanism from the dosage form.

Additionally, an equation using dimensionless numbers (Reynold's and Sherwood) for prediction of drug dissolution from conventional tablets was developed.

Resumen

El objetivo principal de esta investigación es determinar los principios fundamentales del proceso de disolución, estudiar el fenómeno de liberación de droga en flujo laminar, y tener un mejor conocimiento sobre el efecto de las condiciones hidrodinámicas en la disolución de la droga, con el propósito de predecir la disolución de la droga de un forma de dosificación sólida. Dos modelos de drogas fueron seleccionados, Teofilina (Clase I) y Naproxen

Table 8. ANOVA Analysis for The Dissolution Data of Theophylline- HPMC Tablets

Using USP IV

Min	8 ml/min	16 ml/min	24 ml/min	SS	MS	F	P	
	4.9	5.0	5.03	0.09134	0.04567	4.122	0.0747	NS
	44.8	85.1	5.06	0.06648	0.01108			
15	54.66	04.96	4.90	0.1578				
	8.60	9.17	9.56	0.7265	0.3632	4.623	0.061	NS
	8.75	9.26	8.80	0.4714	0.07857			
30	8.35	8.86	9.31	1.198				
	12.45	12.84	13.41	0.6618	0.3309	0.6522	0.5543	NS
	12.68	13.60	13.02	3.045	0.5074			
45	14.06	12.36	14.23	3.706				
	16.03	16.65	16.23	0.4553	0.2276	1.566	0.2836	NS
	16.44	16.48	17.33	0.872	0.1453			
60	16.08	16.12	16.65	1.327				
	20.80	21.78	21.64	0.3903	0.1951	1.075	0.399	NS
	21.31	21.50	21.84	1.089	0.1815			
90	22.02	21.09	22.08	1.479				
	25.14	26.32	27.17	2.19	1.095	3.781	0.0866	NS
	25.78	25.93	25.79	1.738	0.2896			
120	25.38	25.38	26.91	3.927				
	34.37	34.16	34.43	1.079	0.5396	5.333	0.05	NS
	33.55	33.81	34.81	0.6071	0.1012			
180	34.18	33.61	34.76	1.686				
	39.95	40.49	39.74	2.441	1.221	0.1393	0.2954	NS
	39.48	39.95	42.60	4.867	0.8112			
240	40.21	40.95	41.11	7.308				
	47.68	48.17	47.34	0.05375	0.02687	1.505	0.8727	NS
	47.13	47.50	48.18	1.157	0.1929			
300	47.62	47.56	48.18	1.211				
	53.74	54.26	53.22	0.1951	0.09754	0.2783	0.7663	NS
	54.29	53.62	54.54	2.102	0.3504			
360	53.65	54.08	54.96	2.298				

(Clase II). Ambas drogas fueron formuladas en tabletas convencionales conteniendo 105 mg de Theofilina o 300 mg de Naproxen utilizando el método de granulación húmeda. En adición, matrices de "Theophylline" (105 mg) y Naproxen (330 mg) que contenían 30% del polímero hidroxipropimetillcelulosa (HPMC) fueron preparadas por compresión directa y analizadas por disolución utilizando los aparatos I y IV de disolución USP. Las tabletas fueron analizadas para disolución (USP IV) utilizando diferentes diámetros de celda, diferentes razón de flujo y diferentes posiciones de la tableta dentro de la celda. En general, la disolución de la droga a un tiempo determinado es función directa de la razón de flujo, al aumentar la razón de flujo la liberación de la droga aumenta. El uso de una celda pequeña resulta en una rápida disolución de la droga y en un alto número de Reynold que al utilizar una celda grande. La posición de la tableta dentro de la celda también tiene un efecto en la disolución de la droga, al insertar la tableta en la celda en posición horizontal se produce una disolución mucho más rápida que la tableta colocada en posición vertical. Las condiciones hidrodinámicas no afectan la disolución de la droga de tabletas HPMC de liberación controlada indicando que la disolución de la droga está controlada por la matriz. Se estableció una ecuación para predecir la disolución de la droga de tabletas convencionales: $Sh=-21.36+10.58Re^{1/2}$, donde $R^2=0.98$. Este estudio ha demostrado que las condiciones hidrodinámicas, y el tipo de aparato de disolución utilizado tiene un efecto en la razón de disolución, la razón de transferencia de masa y el espesor de la capa, importantes en el proceso de disolución.

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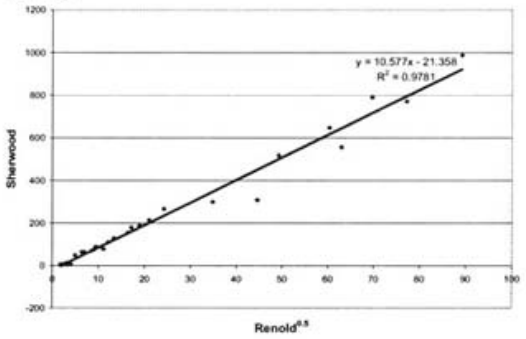
Table 9. ANOVA Analysis for The Dissolution Data of Naproxen-HPMC Tablets

Using USP IV

	8 ml/min	16 ml/min	24 ml/min	SS	MS	F	P	
	1.6	2.2	1.8	0.0531	0.0265	0.57	0.592	N
	1.6	1.6	1.8	0.2775	0.0463			
15	1.5	1.5	1.5	0.3306				
	2.4	3.3	3.0	0.1699	0.0849	1.0	0.441	N
	2.6	2.6	3.1	0.5421	0.0904			
30	2.7	2.5	2.6	0.7120				
	3.2	4.2	3.9	0.313	0.157	1.37	0.323	N
	3.5	3.5	4.2	0.684	0.114			
45	3.7	3.4	3.7	0.997				
	3.9	4.9	4.6	0.4	0.2	1.7	0.265	N
	4.2	4.2	5.0	0.8	0.1			
60	4.5	3.9	4.6	1.2				
	5.0	6.3	5.8	0.661	0.3	2.1	0.2	N
	5.3	5.3	6.3	0.942	0.2			
90	5.6	5.2	5.9	1.603				
	6.0	7.4	6.7	0.8	0.4	2.1	0.2	N
	6.1	6.3	7.2	1.1	1.2			
120	6.5	6.2	6.8	1.9				
	7.6	8.9	8.0	1.3	0.6	2.7	0.150	N
	7.7	7.8	9.0	1.4	0.2			
180	7.8	7.7	8.7	2.7				
	8.9	10.6	9.3	1.3	0.6	2.7	0.229	N
	9.1	9.4	10.2	2.0	0.3			
240	9.0	8.9	10.1	3.3				
	9.9	11.9	10.3	1.3	0.7	1.4	0.309	N
	10.1	10.5	11.2	2.8	0.5			
300	10.0	9.9	11.2	4.1				
	10.9	12.8	11.2	1.1	0.6	1.2	0.360	N
	11.2	11.5	12.2	2.8	0.5			
360	10.9	10.7	12.1	4.0				

Figure 10. Plot of Sherwood Number Versus Reynold's$^{0.5}$ Number



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