CHAPTER IV
RESULTS AND DISCUSSIONS

Results

The presentation of this section is divided into three parts. Part 1 described the characteristics of drugstores and aspirin samples. Part 2 showed the results of quality determination. Part 3 analyzed the factors relating to the drug quality.

1. Characteristics of the Drugstores and Aspirin Sample

From 96 drugstores surveyed, 66 (68.8%) of the stores were located in the city area, i.e., in districts 1 to 4. The majority of them were legal drugstores (76, 79.2%). This number is proportional to the population of drugstores in Phnom Penh city. Pharmacists were identified by means of the question, "Are you the pharmacist?" We found that, among 96 drugstores, only nine sellers (9.4%) were registered pharmacists. All of them were in Legal A stores. Only one was a nurse in Legal C store, and the rest were drug sellers without professional training.

About half of the sellers (55, 57.3%) did not ask any question when the researcher requested 100 the uncoated tablets of aspirin. Among those who asked, the only question was "for whom." Furthermore, the majority of the sellers (79, 82.3%) did not give any advice accompanying their dispensing procedure. Among the advice given were take the medication immediately after meal and followed by plenty of water. There was no statistical difference in giving advice across types of drugstores. All pharmacists in this sample collecting were found to give advice.

With regard to the condition of the stores, only two (2.1%) were air-conditioned. Even though all stores were found to have appropriate cabinets in which the drugs are kept, most of the stores (87, 90.6%) did not arrange their items appropriately. Unfortunately, the data collection method, which the researchers went in and out of the store in short time, did not allow the investigators to adequately observe light exposure

and moisture level in the stores throughout the day. The information regarding characteristics of the drugstores is shown in Table 3.

Table 3. Characteristics of the drugstores

Variable	Number (percent)
Location of the store	
City area	66 (68.8)
Out-skirt area	30 (31.3)
Type of the store	
Legal drugstore	76 (79.2)
Legal A	54 (56.3)
Legal B	12 (12.5)
Legal C	10 (10.4)
Illegal drugstore	20 (20.8)
Illegal A	9 (9.4)
Illegal B	3 (3.1)
Illegal C	8 (8.3)
Type of seller	
Pharmacist	9 (9.4)
Nurse	1 (1.0)
Normal seller	86 (89.6)
Drugstores with air-condition	2 (2.1)
Drugstores with appropriate cabinets	96 (100.0)
Drugstores with appropriate item categorization	9 (9.4)

Table 4 exhibited the characteristics of 96 aspirin sample. The majority of the samples were imported from Thailand (62 from 96 or 64.4%), followed by Vietnam (21 from 96 or 21.9%). The rest were imported from India (9 from 96 or 9.4%), Malaysia (3 from 96 or 3.1%) and USA (1 from 96 or 1.0%). None of the sample which contained 325mg or 300mg strength was locally made. The average price of 100 tablets was 3993.75 ± 486.62 Riels (approximately US$1).

About half (52 of 96, 54.67%) of the sample were packed in blister strips. For those not in blister packages, i.e., needed to be transfer from big containers, the storage conditions were inappropriate. All of them were kept in plastic containers without desiccant. More than half of these bottles (33 of 44, 75%) were without caps. When dispense, near half of store personnel did not use medicine tray to count them (18 of 44, 40.91%). The most frequently found method was pouring the drugs directly onto hands, and transferring them to small clear plastic bags (not medicine pouches). If not enough, the seller then used his/her fingers to reach into the bottle and take more tablets. For sealing, all drugstores used rubber bands to wrap around to plastic bag. Given an easily hydrolyzed nature of aspirin, it could be said that the majority of drugs obtained were of compromised quality.

Table 4 Characteristics of the aspirin sample

Variable	Number (percent)
Source of the medicine	
Thailand	62 (64.6)
Vietnam	21 (21.9)
India	9 (9.4)
Malaysia	3 (3.1)
USA	1 (1.0)
Type of packing	
Blister packed	52 (54.2)
Bottle packed	44 (45.8)

2. Quality Determination

2.1 Analysis of Aspirin

In this study, HPLC and UV Spectroscopy method were used to determine a labeled amount or a content of drug in the uncoated aspirin tablets and an amount of drug dissolved in dissolution testing.

The labeled amount of aspirin and the presented salicylic acid in the tablet were assayed by HPLC method described under the monograph of aspirin and aspirin tablet in USP XXV. A representative HPLC chromatogram of aspirin and salicylic acid solution indicated the peak of aspirin and salicylic acid at retention time of 19.09 and 15.80 minutes, respectively (Figure 10). Peak area of aspirin obtained from HPLC analysis of various concentrations of aspirin RS solution are demonstrated in Table 5. The Beer's law plot between the concentration of aspirin and the peak area revealed very good linearity with correlation coefficient of 0.9997 as shown in Figure 11. The precision of this analytical method was acceptable when the relative standard deviation, RSD (%), of both aspirin was not more than 2.0, and salicylic acid was not more than 4.0. The tailing factor of aspirin was not more than 2.0. The resolution, R, between salicylic acid and aspirin is not less than 2.0 as specified in USP (Table 6).

The UV spectroscopic method used for dissolution testing was modified from the method described under the monograph of aspirin tablet in USP XXV. In case of the UV spectroscopy, absorbances of various concentrations of aspirin RS solution in 0.05 M acetate buffer at the wavelength of 265 nm are shown in Table 7. The concentration of aspirin was plotted against the absorbance. The calibration curve obtained showed very good linearity with correlation coefficient of 0.9997 (Figure 12).

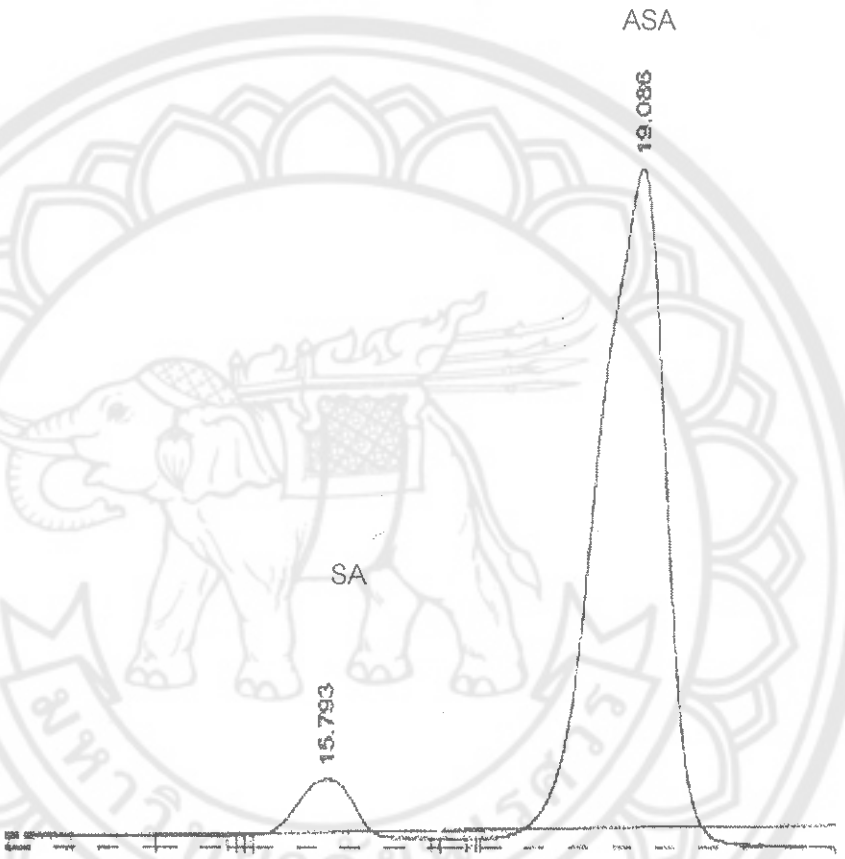

Figure 10. Standard chromatogram of aspirin, ASA, and salicylic acid, SA

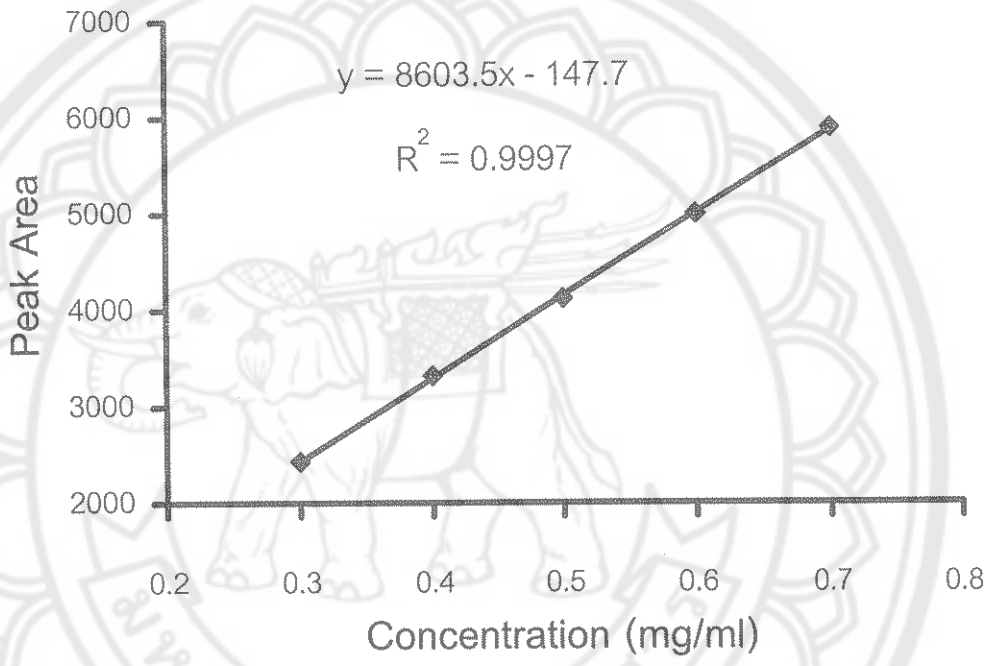

Figure 11. Calibration curve of aspirin RS in solution by HPLC method

Table 6. Precision of HPLC method for aspirin assay

Method requirement	Experiment	USP requirement
Relative standard deviation, RSD, (%) of ASA	1.29	not more than 2.0
Relative standard deviation, RSD, (%) of SA	3.44	not more than 4.0
Tailing factor of ASA	0.88	not more than 2.0
Resolution ,R, between SA and ASA	2.85	not less than 2.0

$$N_{ASA} = \frac{16 t_R^2}{W^2} = 4017.87$$

$$HETP_{ASA} = \frac{L}{N} = 0.0062$$

The results of N (Number of theoretical plates in column) and HETP (Height Equivalent to a Theoretical Plate) showed the column efficiency is very good.

Table 7. UV absorbance of aspirin RS solution 0.05 *M* acetate buffer at the wavelength of 265 nm

Concentration of aspirin (mg/ml)	Absorbance
0.10	0.3947
0.15	0.6133
0.20	0.7724
0.25	0.9954
0.30	1.1590
0.40	1.5450
0.50	1.9458
0.60	2.3215
0.70	2.6856

Correlation coefficient (r^2) = 0.9997

Slope = 3.8180

Intercept = 0.0239

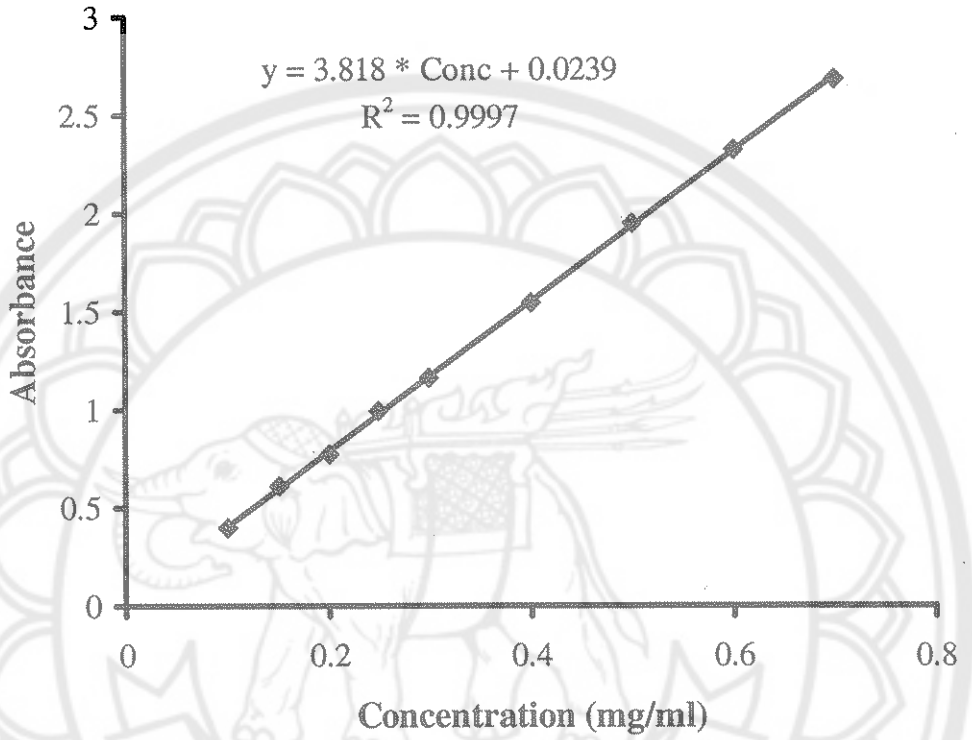

Figure 12. Calibration curve of aspirin in 0.05 M acetate buffer solution by UV spectroscopy at 265 nm

2.2 Studies on the Properties of Uncoated Aspirin Tablets

The uncoated aspirin tablets contained 300 or 325 mg of acetylsalicylic acid per tablet from seven districts of Phnom Penh city were evaluated for their properties including labeled amount or drug content, weight variation, hardness, friability, disintegration time, and dissolution.

The percent labeled amount of aspirin in tablet was assayed by HPLC method as described in section of analysis of aspirin. As specified in USP, aspirin tablets contain the equivalent of not less than 90.0% and not more than 110.0% of the labeled amount of acetylsalicylic acid. The results shown in Table 8 revealed the labeled amount of the aspirin tablets collected from Phnom Penh city were complied with the range specified in USP, 81 of 96 (84.4%) (Table 15). SA amount presented in samples was found less than 0.3% which stated in USP for acceptable amount (Table 14).

Table 9 showed the weight variation of all samples. Different mean weights of tablets due to different tablet formulations were found. These can be approximately classified by three kinds as follow: 325mg, 350mg, and 500mg. The weight variation of each kind tablet weight obtained from all samples almost conformed the USP specification, 95 of 96 (99%) (Table 15). It is well known that the weight variation of tablet may relate to flowability of powders, especially, the starting material powder in a formulation process. In addition, the weight variation of tablet can be affected by the formulation as well as the powder filling process of the tableting machine. According to the data collecting as mentioned above, it was found that the most tablet samples obtained from different tablet preparations. Therefore, the different powder filling process of tablet formulation might affect the weight variation of the tablets to some extents.

Tablet hardness data are presented in Table 10 for all samples. The hardness of the uncoated aspirin tablets are mostly acceptable, 94 of 96 (97.9%) (Table 15) i.e. there were only two samples of 96 samples showed their average weights lower than 4Kg or 39.2 Newtons. It is widely known, in tablet formulation process, the effect of compression force and material properties might affect the tablet hardness. The tablet hardness increased as the compression force increased, and as binder contents increased. In this study, although there are many samples from different sources which believed different

formulations, however, the hardness of samples were mainly found to be acceptable (not quite low).

Friability data of the collected tablets are shown in Table 11. The data correlated well with the hardness. The results exhibited the majority acceptable 63 of 96 samples (65.6%) (Table 15). As expect, the friability of a tablet formulation decreased as the compression force increased. However, in this study the detail of product formulation did not know.

Although USP did not specify a time of the disintegration of the uncoated drug tablet, the disintegration times of samples were determined follow it, and with respected the specified time stated in European pharmacopoeia (Disintegration time < 15 minutes). The results were reported as average of disintegration time of six tablets. The data shown in Table 12 indicated that there were mainly acceptable samples, 80 of 96 samples (83.3%) (Table 15). The tablets disintegrated due to the water penetration into tablet causing tablet disintegration or dissolution. Thus, if a tablet formulation failed disintegration time, it would not also be expected to pass dissolution test. Therefore, the samples which failed disintegration test did not investigate dissolution test, for dissolution.

Table 13 shows the dissolution data of the uncoated aspirin tablets obtained from seven districts in Phnom Penh. The results demonstrated the differences in dissolution characteristics of the tablets between each sample. It was indicated that the dissolution rate of the aspirin tablets are almost low. There are only 6 of 66 samples (9.1%) (Table 15) met USP requirement, which specified that not less than 80% of the labeled amount of acetylsalicylic acid was dissolved in 30 minutes. It is widely recognized that the dissolution problem of the tablet products cause of the particle size property of materials, the material capacity of wettability, and formulation process. The results in this study revealed the dissolution rate of tablet related to their sources. There were strong discrimination of the dissolution behavior among these different formulations. Differences in dissolution rate may be explained by the use of different excipients and differences in the manufacturing process. For example, the use of different binders may influence the

dissolution behavior of the tablets. A correlation of disintegration time with dissolution is likely for all aspirin tablets, i.e. the tablets are readily dissolve as soon as the dosage form break up. The cause of the tablet dissolution problems were not further known due to all tablets were just collected from markets. Aspirin is a poorly soluble drug. Galia, Horton & Dressman [1] found the problematic dissolution of poorly soluble drugs. Investigators suggested reproducible and sufficient release of these compounds could only be guaranteed by careful formulation and high quality manufacturing procedures. Common approaches to improve the release rate of poorly soluble drugs could be done either by increasing the surface area by means of micronization or by adding surfactants to the formulation.

Table 8. Labeled amount of the uncoated aspirin tablets obtained from Phnom Penh city

Formulation	1	2	3	4	5	6	7	8	9	10	11	12
Content (% Labeled amount)	95.51	110.96	96.86	113.45	110.75	97.16	99.07	102.64	102.90	111.84	111.41	110.76
Formulation	13	14	15	16	17	18	19	20	21	22	23	24
Content (% Labeled amount)	101.74	99.06	101.40	99.03	113.14	94.79	98.40	105.37	104.80	101.88	109.08	101.48
Formulation	25	26	27	28	29	30	31	32	33	34	35	36
Content (% Labeled amount)	94.64	102.57	101.43	102.30	94.03	97.50	106.93	102.19	96.20	105.04	101.41	104.47
Formulation	37	38	39	40	41	42	43	44	45	46	47	48
Content (% Labeled amount)	113.13	95.40	110.05	103.18	87.92	99.66	101.00	106.21	107.56	98.64	93.14	97.12
Formulation	49	50	51	52	53	54	55	56	57	58	59	60
Content (% Labeled amount)	101.08	98.98	98.34	96.76	95.71	94.17	93.35	98.78	100.13	94.41	106.14	103.58

Table 8. Cont.

Formulation	61	62	63	64	65	66	67	68	69	70	71	72
Content (% Labeled amount)	100.80	99.70	98.12	94.62	105.03	99.90	96.67	97.90	95.28	96.85	96.34	97.24
Formulation	73	74	75	76	77	78	79	80	81	82	83	84
Content (% Labeled amount)	95.80	105.37	104.15	104.64	96.94	109.44	109.66	111.06	109.70	113.40	111.44	99.12
Formulation	85	86	87	88	89	90	91	92	93	94	95	96
Content (% Labeled amount)	96.70	103.36	105.45	110.44	113.07	99.99	103.06	107.18	105.95	100.54	104.16	94.66

Table 9. Weight variation of the uncoated aspirin tablets obtained from Phnom Penh city

Formulation	1	2	3	4	5	6	7	8	9	10	11	12
Weight variation												
Mean (mg/tablet)	370.25	344.95	502.90	344.66	338.63	342.78	500.06	501.07	501.27	529.81	473.27	502.72
(SD)	(7.29)	(4.53)	(4.11)	(8.10)	(8.29)	(5.29)	(4.68)	(4.28)	(4.18)	(5.43)	(6.37)	(8.15)
Formulation	13	14	15	16	17	18	19	20	21	22	23	24
Weight variation												
Mean (mg/tablet)	340.07	499.78	500.29	500.80	344.47	537.58	499.92	343.14	341.51	323.82	499.94	500.07
(SD)	(6.70)	(5.50)	(5.87)	(7.24)	(6.29)	(8.02)	(4.97)	(5.36)	(5.22)	(8.95)	(6.65)	(3.63)
Formulation	25	26	27	28	29	30	31	32	33	34	35	36
Weight variation												
Mean (mg/tablet)	501.26	501.07	322.41	499.96	470.80	332.14	337.52	323.66	540.69	505.55	506.01	338.94
(SD)	(7.75)	(6.17)	(7.17)	(7.37)	(5.80)	(3.76)	(10:12)	(4.74)	(6.60)	(7.67)	(8.01)	(6.61)
Formulation	37	38	39	40	41	42	43	44	45	46	47	48
Weight variation												
Mean (mg/tablet)	499.57	351.67	503.51	498.72	323.29	436.07	502.41	342.98	344.44	500.82	498.52	334.14
(SD)	(8.70)	(8.33)	(9.17)	(6.93)	(6.56)	(4.05)	(5.99)	(4.05)	(2.95)	(11.59)	(5.74)	(2.24)

Values in parentheses represent standard deviation of 20 determinations

Table 9. Cont.

Formulation	49	50	51	52	53	54	55	56	57	58	59	60
Weight variation												
Mean (mg/tablet)	502.01	333.18	501.45	319.91	501.77	322.38	332.94	501.05	501.95	330.05	341.71	530.98
(SD)	(3.70)	(9.95)	(7.69)	(7.89)	(9.58)	(5.89)	(2.18)	(4.61)	(5.00)	(3.04)	(4.85)	(11.10)
Formulation	61	62	63	64	65	66	67	68	69	70	71	72
Weight variation												
Mean (mg/tablet)	470.15	500.28	504.83	323.40	506.88	504.19	503.33	499.03	330.12	506.80	501.37	329.67
(SD)	(10.20)	(5.45)	(9.99)	(5.45)	(7.68)	(9.91)	(9.79)	(8.35)	(2.99)	(7.39)	(9.38)	(2.07)
Formulation	73	74	75	76	77	78	79	80	81	82	83	84
Weight variation												
Mean (mg/tablet)	501.69	501.48	501.73	501.48	322.16	343.48	343.95	341.08	339.15	346.89	533.13	500.76
(SD)	(8.68)	(8.37)	(6.90)	(4.24)	(7.99)	(5.71)	(3.42)	(6.80)	(9.74)	(4.38)	(6.17)	(5.04)
Formulation	85	86	87	88	89	90	91	92	93	94	95	96
Weight variation												
Mean (mg/tablet)	333.66	501.86	499.54	338.70	535.74	545.95	502.94	342.91	340.34	436.94	502.57	500.61
(SD)	(3.41)	(4.22)	(10.51)	(6.24)	(9.17)	(7.39)	(5.40)	(4.51)	(4.49)	(5.95)	(3.89)	(7.18)

Values in parentheses represent standard deviation of 20 determinations

Table 10. Hardness of the uncoated aspirin tablets obtained from Phnom Penh city

Formulation	1	2	3	4	5	6	7	8	9	10	11	12
Hardness												
Mean (N/tablet)	112.40	91.10	83.40	96.70	98.50	89.10	76.30	71.50	73.80	115.30	131.90	54.70
(SD)	(9.55)	(4.53)	(11.13)	(8.79)	(11.07)	(6.08)	(8.39)	(9.65)	(7.00)	(12.68)	(10.16)	(8.33)
Formulation	13	14	15	16	17	18	19	20	21	22	23	24
Hardness												
Mean (N/tablet)	91.80	37.20	64.70	54.00	100.00	121.10	59.30	76.60	98.60	115.30	55.80	81.30
(SD)	(9.22)	(9.19)	(10.40)	(10.34)	(6.60)	(13.51)	(7.96)	(4.90)	(6.06)	(16.12)	(7.33)	(9.83)
Formulation	25	26	27	28	29	30	31	32	33	34	35	36
Hardness												
Mean (N/tablet)	110.90	53.70	109.30	57.40	143.70	131.30	89.10	99.10	112.80	46.50	58.20	101.10
(SD)	(8.43)	(8.50)	(8.64)	(9.91)	(13.11)	(24.51)	(8.81)	(10.59)	(19.31)	(9.07)	(12.63)	(8.80)
Formulation	37	38	39	40	41	42	43	44	45	46	47	48
Hardness												
Mean (N/tablet)	53.80	85.70	103.00	59.50	111.70	156.20	101.30	86.50	88.30	132.30	103.50	135.40
(SD)	(7.04)	(17.85)	(11.72)	(13.15)	(19.66)	(10.34)	(13.59)	(4.09)	(5.21)	(18.77)	(11.42)	(22.58)

Values in parentheses represent standard deviation of 10 determinations

Table 10. Cont.

Formulation	49	50	51	52	53	54	55	56	57	58	59	60
Hardness												
Mean (N/tablet)	76.60	111.50	55.60	104.80	108.80	94.80	107.30	81.20	67.20	101.40	89.40	118.90
(SD)	(4.74)	(10.66)	(6.67)	(15.48)	(14.01)	(12.40)	(9.19)	(11.75)	(7.94)	(7.07)	(4.09)	(12.10)
Formulation	61	62	63	64	65	66	67	68	69	70	71	72
Hardness												
Mean (N/tablet)	134.20	61.10	54.40	83.50	57.50	118.80	121.20	123.60	110.90	51.60	57.10	104.80
(SD)	(14.09)	(9.80)	(9.74)	(13.18)	(6.15)	(14.32)	(10.90)	(14.28)	(13.19)	(15.67)	(14.06)	(11.02)
Formulation	73	74	75	76	77	78	79	80	81	82	83	84
Hardness												
Mean (N/tablet)	129.10	61.00	50.10	78.30	92.20	94.80	101.60	96.80	101.60	95.90	127.10	48.70
(SD)	(14.53)	(9.02)	(6.01)	(13.21)	(15.65)	(12.65)	(4.86)	(12.86)	(14.73)	(8.60)	(11.24)	(6.70)
Formulation	85	86	87	88	89	90	91	92	93	94	95	96
Hardness												
Mean (N/tablet)	130.90	74.60	31.90	99.50	126.90	130.60	56.60	87.60	82.70	159.80	75.40	126.20
(SD)	(24.00)	(8.81)	(8.17)	(9.34)	(10.56)	(16.26)	(8.36)	(4.14)	(10.29)	(9.07)	(11.35)	(20.02)

Values in parentheses represent standard deviation of 10 determinations

Table 11. Friability of the uncoated aspirin tablets obtained from Phnom Penh city

Formulation	1	2	3	4	5	6	7	8	9	10	11	12
% Friability	1.32	0.70	0.85	0.62	0.84	0.94	1.40	1.33	1.12	0.31	0.21	6.17
Formulation	13	14	15	16	17	18	19	20	21	22	23	24
% Friability	0.84	16.57	3.21	8.71	0.66	0.05	7.29	0.77	0.70	0.09	3.17	0.91
Formulation	25	26	27	28	29	30	31	32	33	34	35	36
% Friability	0.29	4.93	0.00	6.18	0.18	0.06	0.86	0.00	0.00	8.95	7.33	0.71
Formulation	37	38	39	40	41	42	43	44	45	46	47	48
% Friability	11.06	0.25	0.51	1.97	0.00	0.00	0.40	0.92	0.87	0.23	0.31	0.13
Formulation	49	50	51	52	53	54	55	56	57	58	59	60
% Friability	1.10	0.09	11.01	0.01	0.26	0.00	0.19	1.03	2.07	0.12	0.81	0.27
Formulation	61	62	63	64	65	66	67	68	69	70	71	72
% Friability	0.23	3.37	11.52	0.00	4.80	0.28	0.36	0.31	0.25	9.12	6.72	0.13

Table 11. Cont.

Formulation	73	74	75	76	77	78	79	80	81	82	83	84
% Friability	0.35	5.63	14.02	1.11	0.00	0.79	0.84	0.76	0.92	0.99	0.24	4.98
Formulation	85	86	87	88	89	90	91	92	93	94	95	96
% Friability	0.14	1.37	10.31	0.75	0.24	0.13	2.97	0.95	0.96	0.07	1.16	0.38

Table 12. Disintegration time of the uncoated aspirin tablets obtained from Phnom Penh city

Formulation	1	2	3	4	5	6	7	8	9	10	11	12
Disintegration time												
Mean (Sec)	>900	219.50	90.50	453.17	41.00	39.50	76.83	54.00	49.33	167.50	201.00	31.00
(SD)		(146.23)	(35.62)	(284.52)	(5.51)	(12.65)	(26.03)	(14.25)	(11.55)	(52.21)	(205.80)	(11.26)
Formulation	13	14	15	16	17	18	19	20	21	22	23	24
Disintegration time												
Mean (Sec)	189.50	26.17	28.83	26.17	43.17	297.50	24.17	19.00	40.50	>900	34.67	55.17
(SD)	(112.87)	(4.12)	(4.22)	(8.11)	(3.19)	(121.00)	(3.92)	(3.10)	(3.08)		(6.98)	(9.26)
Formulation	25	26	27	28	29	30	31	32	33	34	35	36
Disintegration time												
Mean (Sec)	>900	22.83	>900	30.00	221.00	>900	314.67	>900	318.67	19.33	32.00	693.83
(SD)		(3.37)		(9.27)	(166.02)		(131.40)		(88.51)	(3.88)	(9.42)	(205.79)
Formulation	37	38	39	40	41	42	43	44	45	46	47	48
Disintegration time												
Mean (Sec)	30.67	509.50	191.17	31.00	>900	614.50	89.17	25.67	37.50	302.17	>900	>900
(SD)	(10.01)	(291.36)	(207.68)	(4.73)		(94.07)	(30.96)	(4.37)	(11.73)	(93.78)		

Values in parentheses represent standard deviation of 6 determinations

Table 12. Cont.

Formulation	49	50	51	52	53	54	55	56	57	58	59	60
Disintegration time												
Mean (Sec)	49.17	>900	37.67	>900	91.17	>900	185.67	55.83	43.33	23.17	28.83	188.17
(SD)	(10.21)		(17.22)		(25.20)		(34.71)	(12.01)	(10.80)	(5.56)	(9.41)	(104.57)
Formulation	61	62	63	64	65	66	67	68	69	70	71	72
Disintegration time												
Mean (Sec)	442.33	23.17	28.33	>900	41.00	193.00	349.67	419.00	87.50	30.67	24.67	29.50
(SD)	(376.57)	(4.67)	(8.64)		(10.68)	(106.05)	(129.67)	(185.81)	(35.81)	(15.16)	(2.50)	(17.89)
Formulation	73	74	75	76	77	78	79	80	81	82	83	84
Disintegration time												
Mean (Sec)	372.00	30.33	30.67	37.67	>900	35.17	576.17	202.50	299.33	103.50	156.50	24.50
(SD)	(144.08)	(8.91)	(11.13)	(4.18)		(8.82)	(214.98)	(136.85)	(151.40)	(31.73)	(96.29)	(6.16)
Formulation	85	86	87	88	89	90	91	92	93	94	95	96
Disintegration time												
Mean (Sec)	>900	51.50	23.67	609.00	238.50	251.17	29.33	46.33	70.00	769.33	41.17	>900
(SD)		(12.31)	(6.89)	(307.28)	(63.41)	(71.98)	(6.15)	(18.18)	(26.39)	(85.54)	(2.14)	

Values in parentheses represent standard deviation of 6 determinations

Table 13. Dissolution of the uncoated aspirin tablets obtained from Phnom Penh city

Formulation	1	2	3	4	5	6	7	8	9	10	11	12
% Dissolution												
Mean (6)	49.91	82.96	52.17	50.35	52.13	63.50	45.92	50.68	55.93	57.05	50.33	82.61
(SD)	(5.52)	(5.21)	(6.96)	(4.95)	(6.43)	(9.82)	(8.79)	(7.34)	(6.76)	(5.60)	(12.33)	(1.53)
Formulation	13	14	15	16	17	18	19	20	21	22	23	24
% Dissolution												
Mean (6)	80.29	54.30	52.51	51.30	54.43	46.24	58.62	65.30	49.96	53.40	51.63	65.79
(SD)	(2.19)	(5.05)	(4.13)	(8.12)	(8.86)	(7.38)	(12.16)	(5.51)	(7.82)	(10.04)	(2.21)	(4.37)
Formulation	25	26	27	28	29	30	31	32	33	34	35	36
% Dissolution												
Mean (6)	48.00	63.81	54.15	77.64	68.33	47.76	66.65	60.07	58.10	67.53	44.52	48.54
(SD)	(4.55)	(6.66)	(4.73)	(9.95)	(10.77)	(6.61)	(5.55)	(6.29)	(7.81)	(11.19)	(6.74)	(8.65)
Formulation	37	38	39	40	41	42	43	44	45	46	47	48
% Dissolution												
Mean (6)	84.67	80.72	41.46	42.13	69.19	55.52	57.72	57.01	28.58	53.42	76.89	57.00
(SD)	(0.83)	(4.90)	(6.44)	(13.74)	(5.41)	(7.89)	(9.51)	(3.51)	(15.25)	(4.43)	(2.10)	(11.28)

Values in parentheses represent standard deviation of 6 determinations

Table 13. Cont.

Formulation	49	50	51	52	53	54	55	56	57	58	59	60
% Dissolution												
Mean (6)	54.42	78.87	46.07	50.80	52.60	49.32	85.51	39.73	44.48	47.06	48.03	45.75
(SD)	(11.82)	(2.15)	(5.67)	(8.63)	(7.78)	(5.59)	(1.30)	(5.74)	(5.18)	(5.01)	(6.11)	(5.28)

Formulation	61	62	63	64	65	66
% Dissolution						
Mean (6)	64.93	54.92	72.62	67.23	59.07	56.93
(SD)	(9.04)	(10.84)	(8.03)	(11.22)	(7.97)	(7.10)

Values in parentheses represent standard deviation of 6 determinations

The results of tablet properties by classifying into 7 districts were exhibited in Figure 13-19. The results from city area (Figure 13-16) can compare with the results from out-skirt area (Figure 17-19). There is one of four districts in city area showed none of samples pass dissolution test while two of three districts in out-skirt area showed none of samples pass dissolution test.

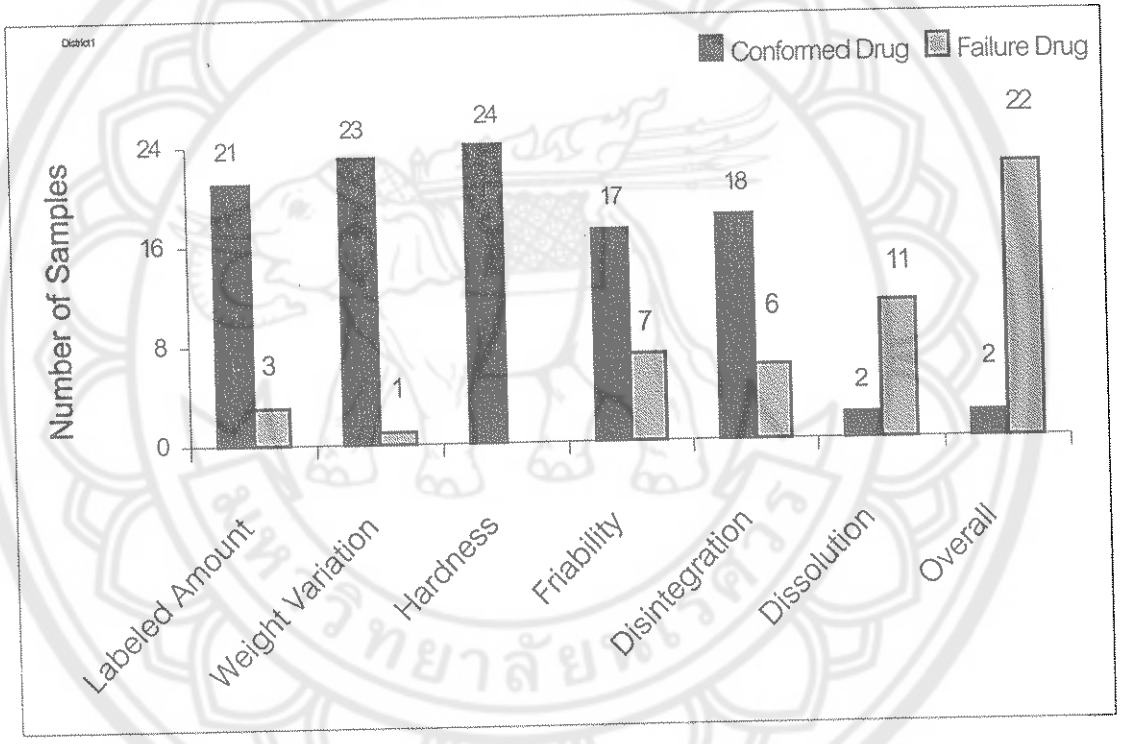

Figure 13. Properties of the uncoated aspirin tablets obtained from district 1

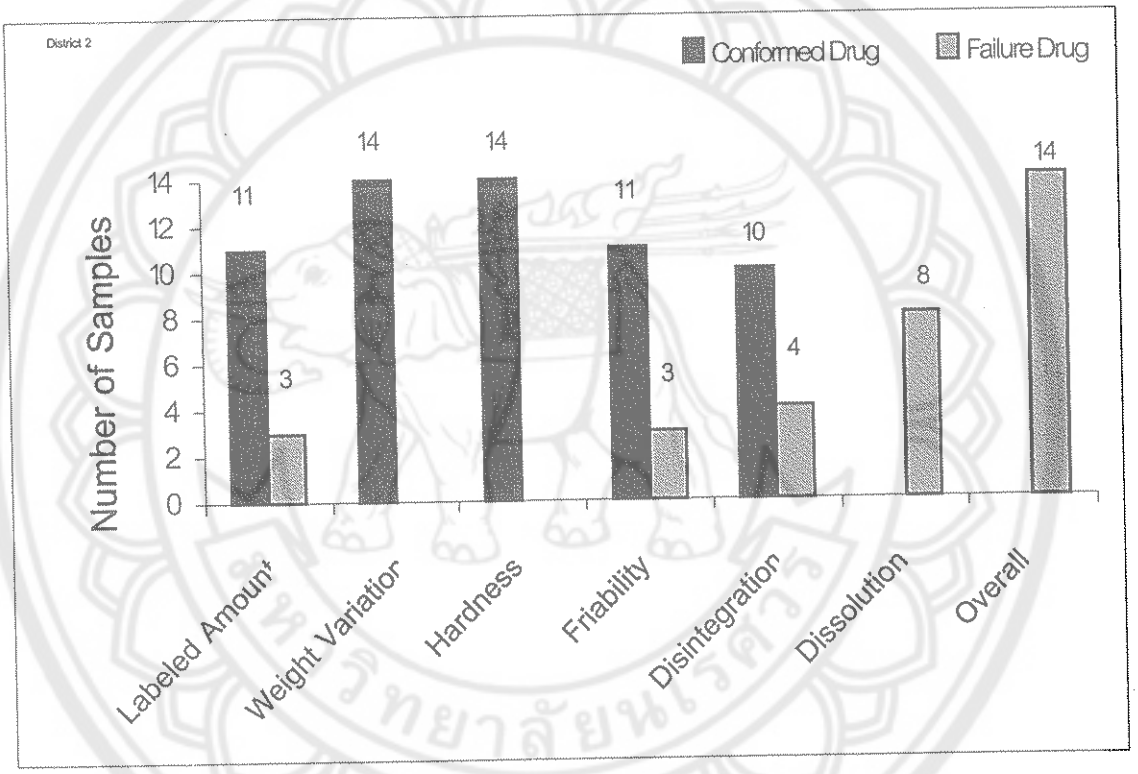

Figure 14. Properties of the uncoated aspirin tablets obtained from district 2

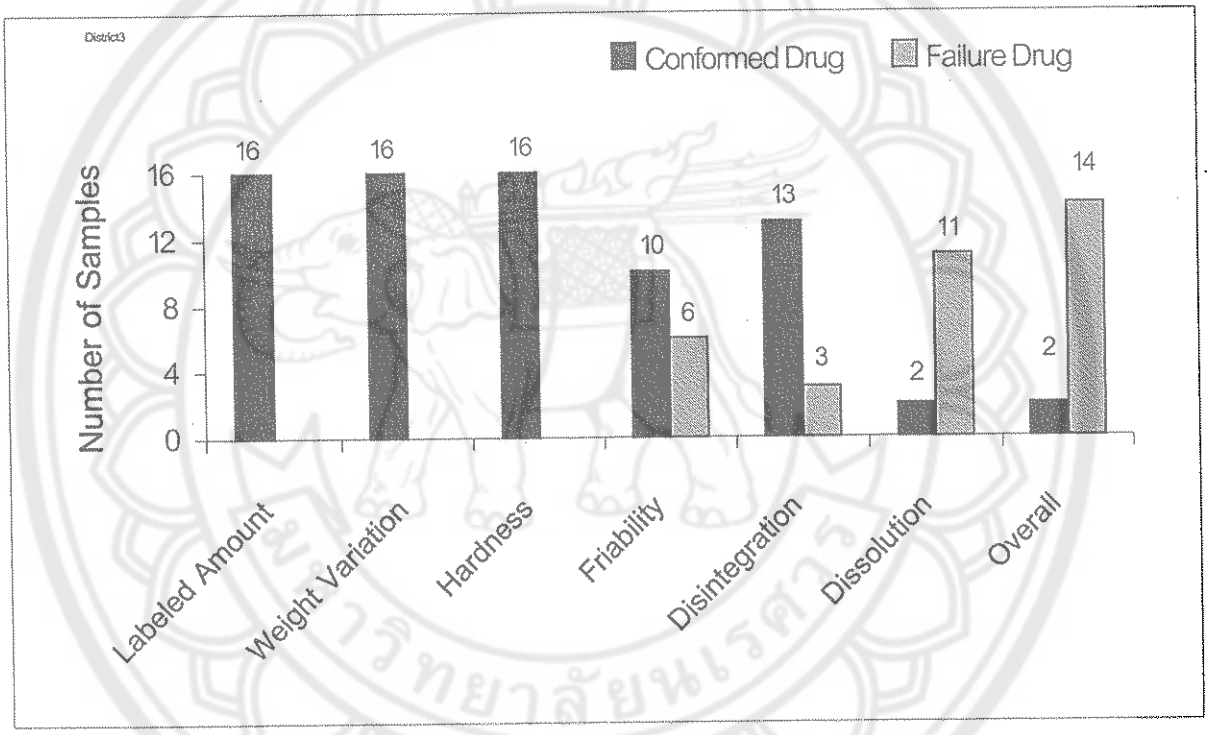

Figure 15. Properties of the uncoated aspirin tablets obtained from district 3

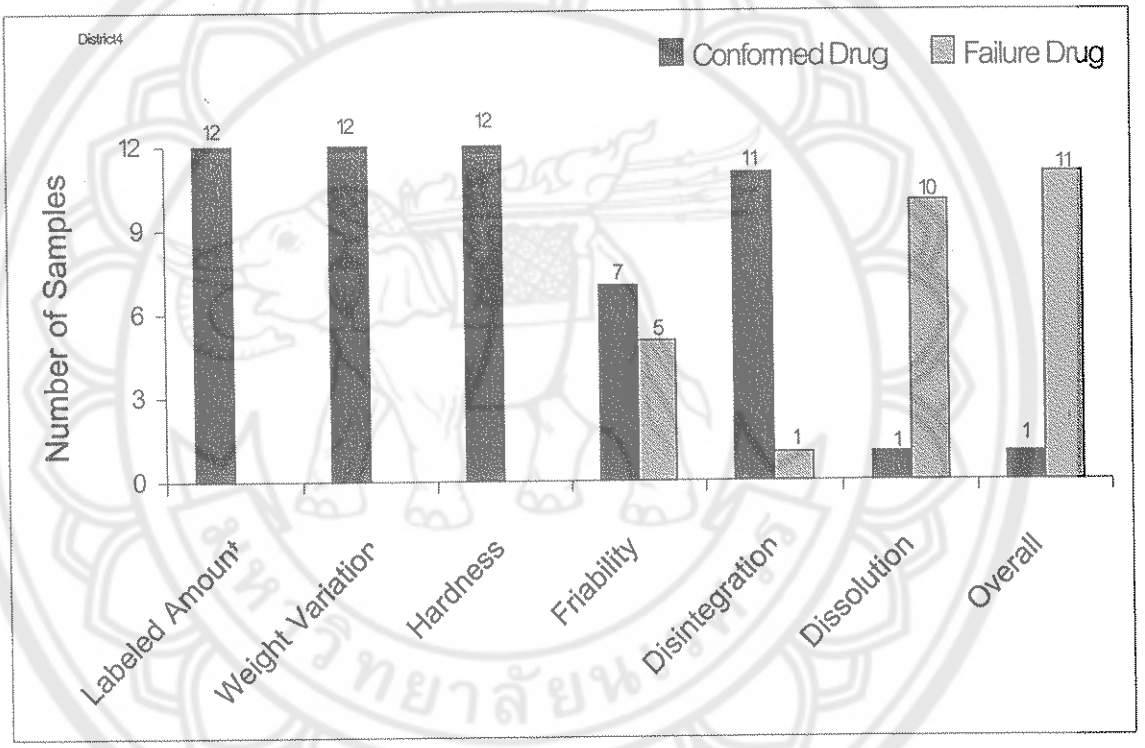

Figure 16. Properties of the uncoated aspirin tablets obtained from district 4

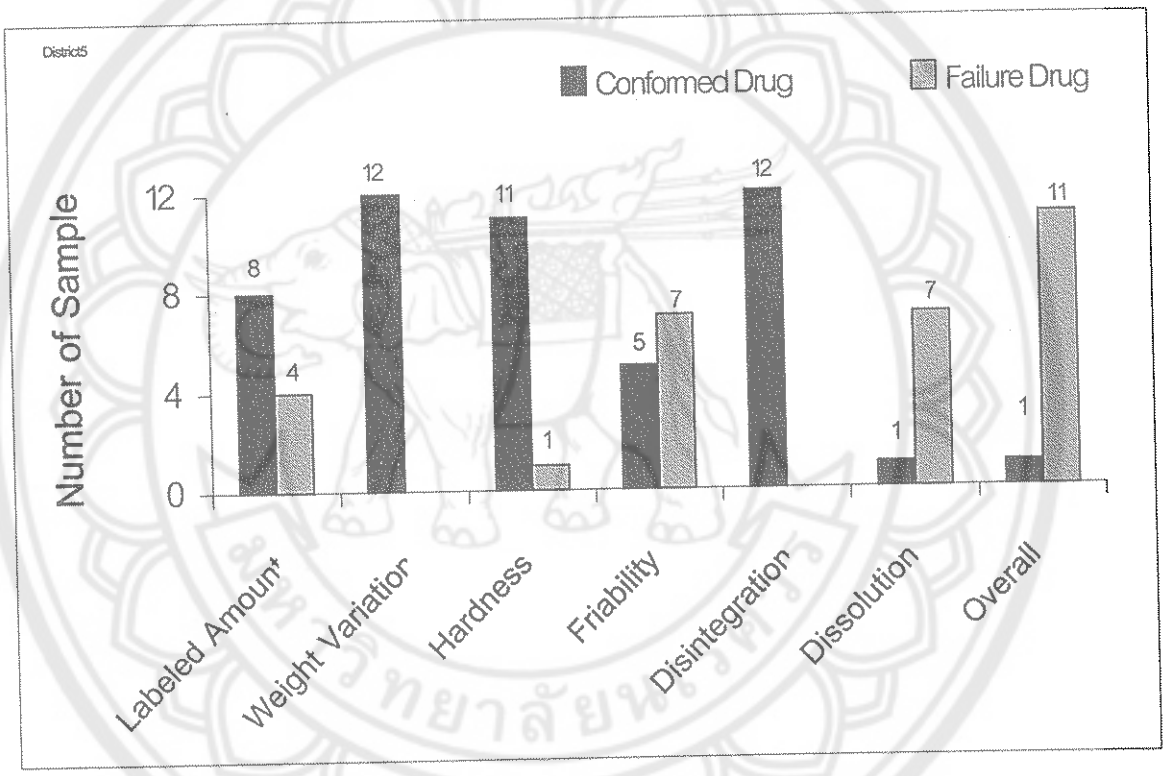

Figure 17. Properties of the uncoated aspirin tablets obtained from district 5

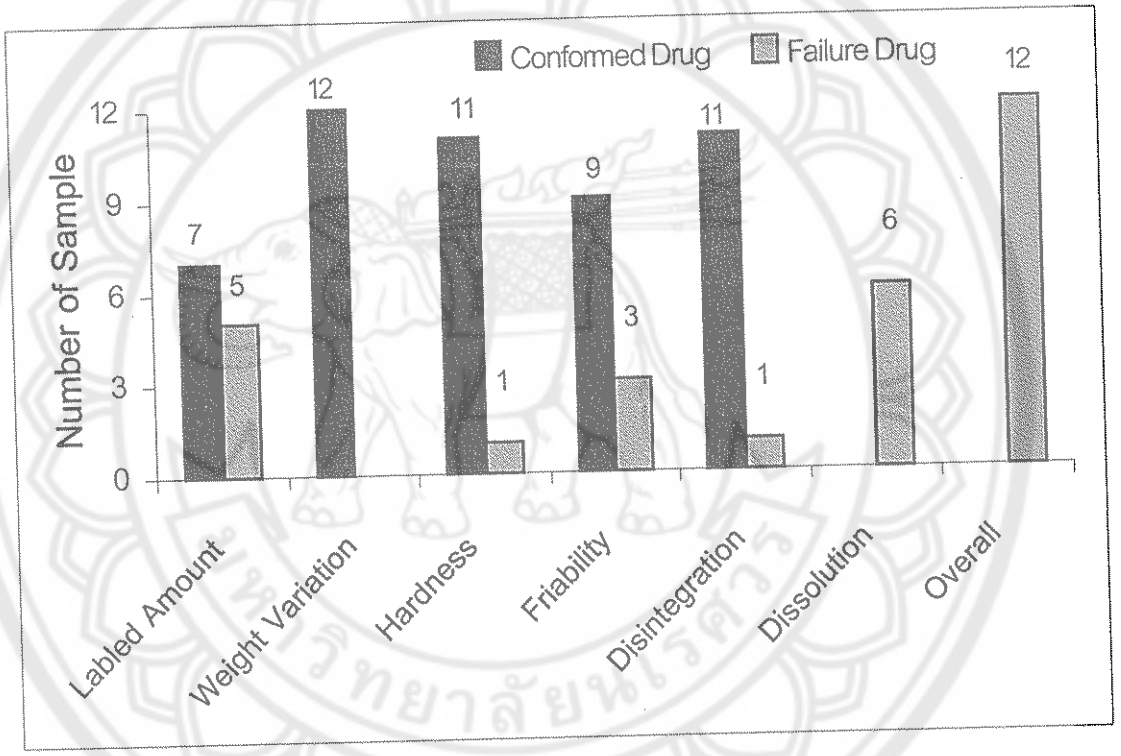

Figure 18. Properties of the uncoated aspirin tablets obtained from district 6

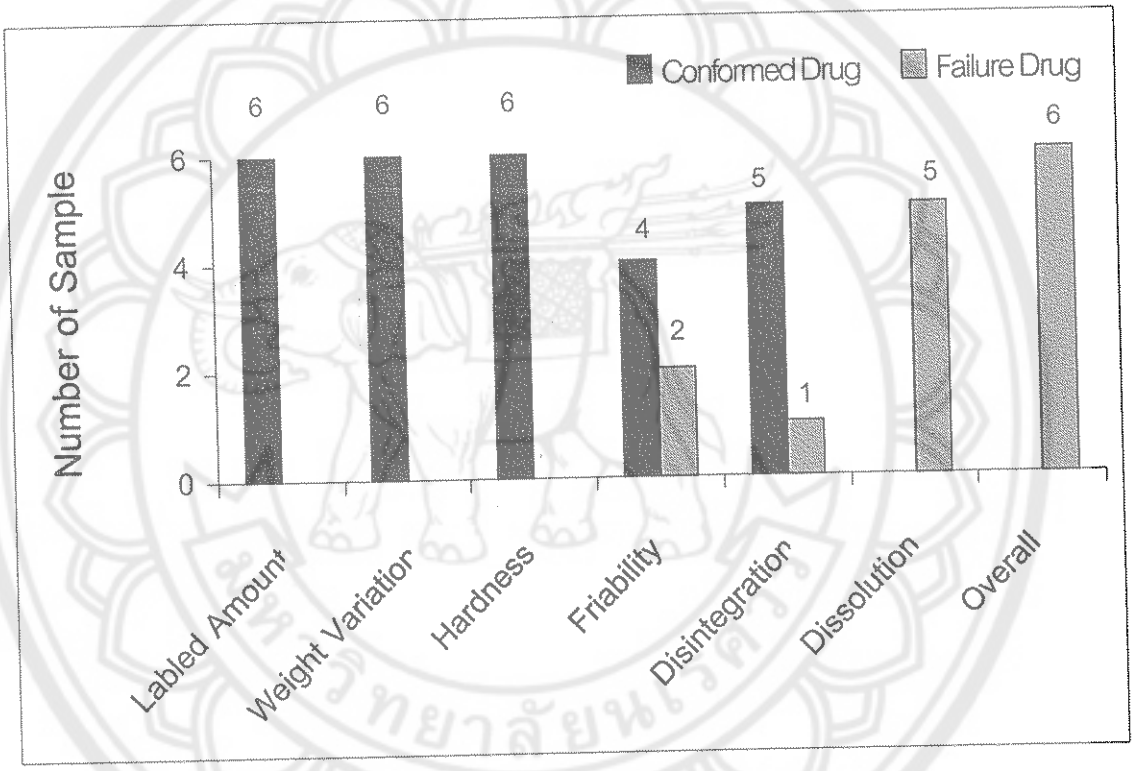

Figure 19. Properties of the uncoated aspirin tablets obtained from district 7

The results of the quality of the uncoated aspirin tablets which were collected from city areas and out-skirt areas are represented in Figure 20. The samples from city areas (7.6%) showed a higher percentage of sample passed criteria than that of those from out-skirt areas (3.3%). The quality of drugs in out-skirt areas is worse than in city areas.

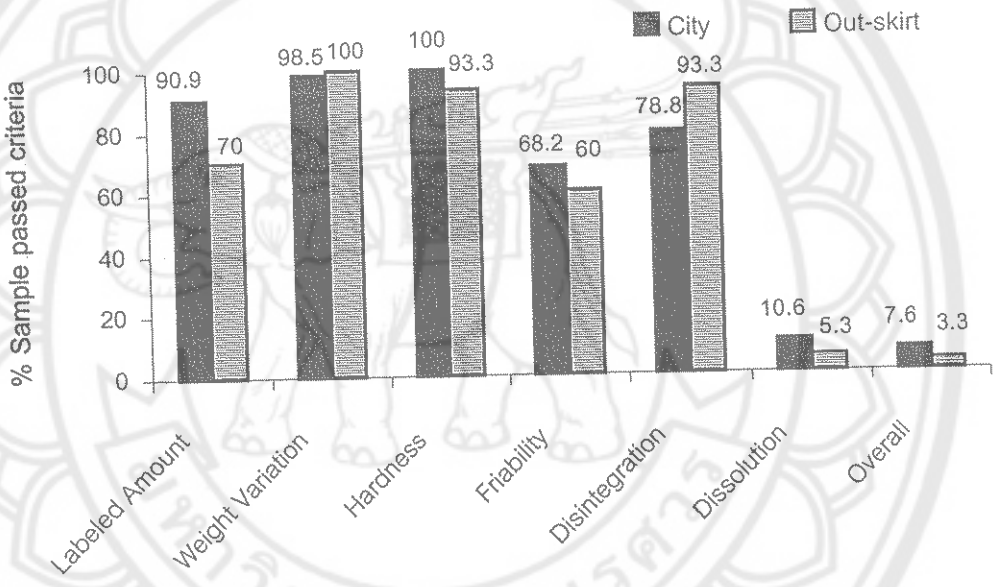

Figure 20. Quality of aspirin tablets by location of the drugstores

Figure 21 shows the qualities of aspirin tablets which were packed in bottles and blisters. Only aspirin tablets packed in bottles (13.6%) reached standard requirements whereas none of aspirin tablets packed in blisters. This result contradicted to normal belief that the tablet kept in blisters should be better than that kept in bottles.

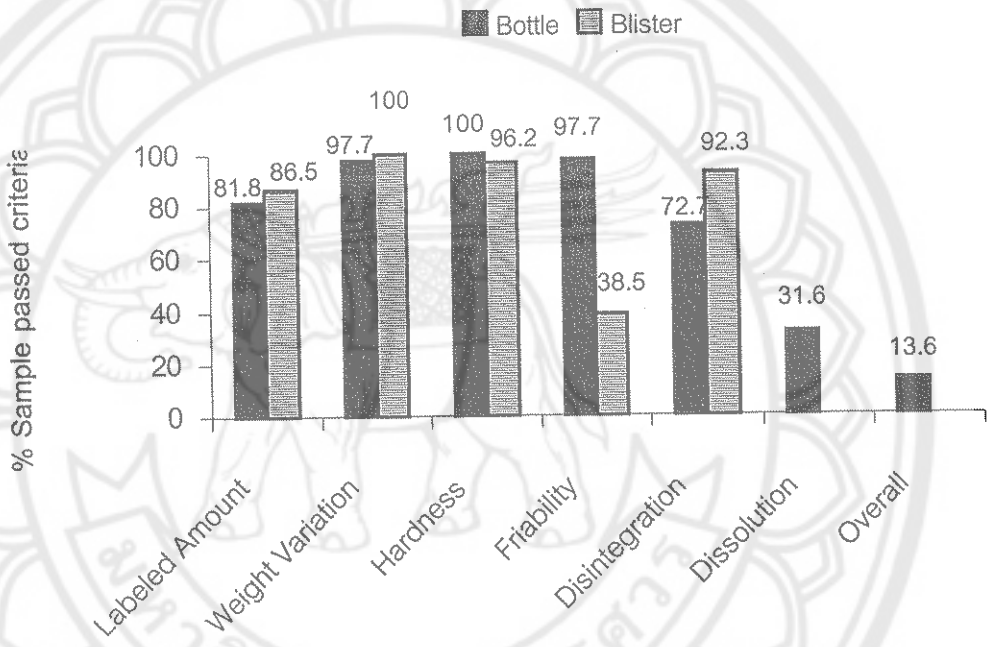

Figure 21. Quality of aspirin tablets by package type

Figure 22 shows the quality of aspirin tablets collected from legal and illegal drugstores. Only aspirin tablets collected from legal drugstores (7.9%) met standard criteria. These results shows that all illegal drugstores strongly affected the quality of drugs in storage.

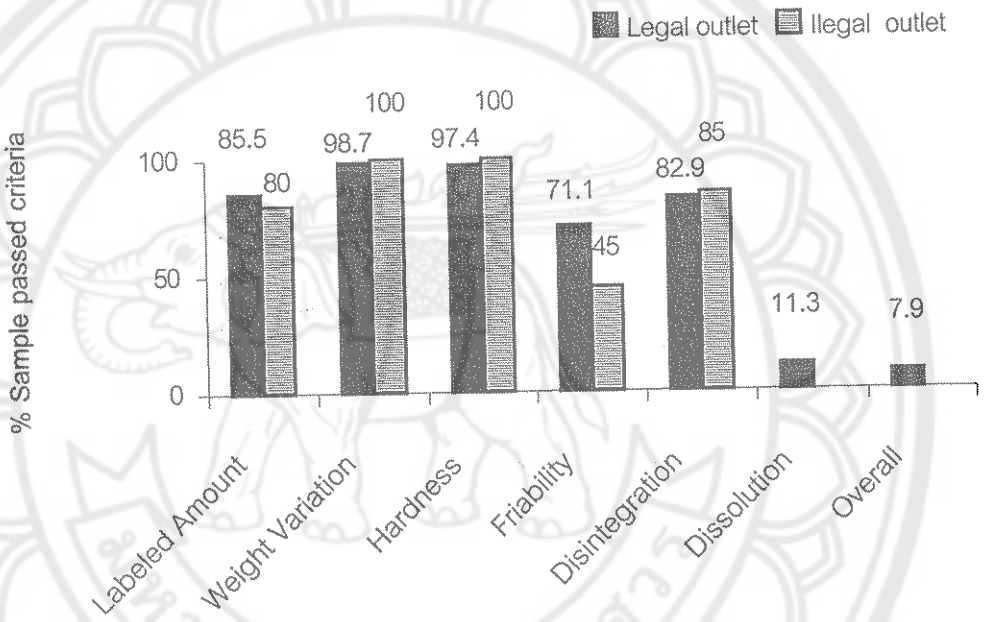

Figure 22. Quality of aspirin tablets by type of the drugstores

Table 14. The presented salicylic acid of the collected samples

Formulation	1	2	3	4	5	6	7
	(11)	(25)	(29)	(43)	(46)	(47)	(50)
% SA	0.11	0.13	0.12	0.04	0.07	0.10	0.07
Formulation	8	9	10	11	12	13	14
	(53)	(61)	(66)	(67)	(68)	(73)	(96)
% SA	0.05	0.09	0.03	0.09	0.07	0.07	0.06

Numbers in parenthesis represent the code number of sample, which presented SA

The results of quality determination of aspirin tablets are shown in Table 15. Overall, only six (6.3%) of the total samples passed all six criteria. Dissolution test appeared to be the most critical step in determining aspirin quality.

Eighty one samples passed the percent labeled amount test. Among those that failed (15, 15.6%), all but one failed in the upper direction, i.e., the tablets were found to contain more than 110% of the active ingredient claimed on the label.

Table 15. Sample that passed the quality determination criteria

Properties	Passed Drug	Failed Drug	% Passed Drug
Labeled Amount	81	15	84.4%
Weight Variation	95	1	99.0%
Hardness	94	2	97.9%
Friability	63	33	65.6%
Disintegration	80	16	83.3%
Dissolution (n = 66)	6	60	9.1%
Overall test	6	90	6.3%

3. Factors Relating to the Quality of Aspirin Tablets

Four factors were hypothesized to be related to the quality of aspirin tablets. They were type of the drugstores, location of the drugstores, type of packaging, and source of the drugs as shown in Table 16.

The results indicated that all of the quality samples were from legal drugstores. In addition, the majority of them were in the city area. However, no statistical difference was found for these two factors.

The factors that were statistically related to the quality of the sample were type of packaging. All the drugs that passed the six criteria were packed in bottles. Source of the medications was also significantly related to their quality. Among six samples that passed the test were from Vietnam.

Table 16. Factors relating to the quality of aspirin tablets

Hypothesized variable	Number of sample		Statistics[1]
	Passed	Failed	
Type of the drugstores			Chi-square 1.634[ns]
Legal	6	70	
Illegal	0	20	
Location of the drugstores			Chi-square 0.634[ns]
City	5	61	
Out-skirt	1	29	
Type of packaging			Chi-square 7.564*
Blister	0	52	
Bottle	6	38	
Source of the drugs			Chi-square 22.857*
Thailand	0	62	
Vietnam	6	15	
India	0	9	
Malaysia	0	3	
USA	0	1	

Note: [1] For Chi-square test of 2 by 2 tables, the significance was assessed by Fisher's Exact.

[ns] $p > 0.05$

* $0.001 < p < 0.005$

Discussion

Before the discussion, we would like to point out three limitations of this study. The readers should take these imperfections into account when applying the results to other situations. First, this study was conducted only in Phnom Penh city. Therefore, generalizability of the findings to other parts of the country is limited.
Second, the nature of our survey hindered us to observe the appropriateness of lighting and moisture level in the stores. This precluded two important variables that could be used to determine the quality of aspirin samples. In addition, we were not able to ascertain whether the responsible person, such as pharmacists in Legal A-type drugstores, stepped out for a moment, or was completely absent. Further study using other techniques such as in-depth interview and observation, which allowed the researcher more time in the store, is warranted to better understand these factors. Last, our study could demonstrate that any sample which failed outside the United States Pharmacopoeia range was clearly substandard. However, whether this was intentionally fraudulent product, incompetently made, or caused by inappropriate storage cannot be determined from the data alone.

Beginning with the condition of the drugstores and their personnel, we found that much needs to be improved. Even though most of the drugstores had appropriate cabinets in which the drugs were kept, none of them were found to arrange the items appropriately. That is, we found all the drugs kept together without categorization according to pharmacological properties. This practice potentially led to mistakes in drug dispensing. In addition, from 54 Legal A-type drugstores surveyed, only nine had registered pharmacists on duty. This is a violation to regulation that this type of drugstores needs to have a pharmacist on duty throughout the business hours. In legal B and C, likewise, we found mostly normal sellers on duty. This rises a flag for Cambodian authority to monitor the availability of drugstore personnel to be in accordance with the regulations.

With regard to the personnel services, the majority of the sellers did not ask any question or give any advice when dispensing the medication. Aspirin is a drug with special precautions of which consumers should be informed. There are many factors

leading to this practice. Among them is lack of knowledge regarding the indication and adverse reactions of the drug. We hypothesized that this could be a major determinant contributing to such practice since most of the sellers in our study were non-professionals who had not received adequate training. On the contrary, all pharmacists and a nurse in this study were found to ask question and give advice accompanying their dispensing.

The average price for 100 uncoated tablets of aspirin in this study was found to be approximately 4,000 Riels. Compared with the figure reported by Ministry of Health in 1998 that people spent on average 39,300 Riels for one episode of illness, this finding confirmed the belief that self-care by buying medications from drugstores is cheaper than any other modes of treatment.

Quality determination analyses revealed that dissolution test is the criteria which most samples failed according to the United States Pharmacopoeia XXV standard. Dissolution test is an important indicator of bioavailability of the drugs in human body. Therefore, the study indicated an alarming fact that the aspirin that people purchased may not be beneficial for their ailments. In addition, we found that 14 of 15 samples that failed the percent label amount test in upper direction, i.e. the tablets contained more active ingredient than that claimed in the label. Fortunately, aspirin has a wide therapeutic level so the danger of ingesting too much aspirin may not be as serious. However, this finding can be used as an example for the authorities to exert more caution when it comes to drugs with narrow therapeutic level.

We found two factors that significantly correlated with the quality of aspirin sample. The first factor was sources of the medication. It was found that six samples that passed the standard criteria came from Vietnam. Special caution, then, should be placed on imported drugs from other countries. Unfortunately we could not collect any sample that was locally produced. Therefore, a comparison could not be made.

Packaging was another factor correlated with the quality of the sample; that is, those packed in bottles were significantly better than those packed in blister packs. This finding is somewhat contradict to lay beliefs that blister packages should better preserve

the items than bottles. However, there are many types of blister packs with different permeability. Considering that the blistered samples were in only two brand names, it can be assumed that the quality of blister packages utilized by this particular manufacturer was compromised.

The location and type of drugstore were not statistically correlated with quality of medication in this study. However, a trend emerged. That is, samples from legal drugstores and city area were more likely to meet the standard than the samples from illegal drugstores and out-skirt area. Since there was no statistical difference in the sources of medication among type and location of the store, the only factor that could lead to this trend in quality difference was the storage condition.

Interestingly, hydrolysis of aspirin did not occur for all samples. The hydrolysis samples is aspirin tablets which presented salicylic acid greater than 0.3%, expectedly. This finding is in the opposite direction to the theory that the drugs should be decomposed in bad condition in storage time. Further studies into this issue is highly warranted.