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RELEASE KINETICS OF ASPIRIN FROM SUPPOSITORIES

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تمت دراسة انطلاق الاسبرين من قواعد اللبوسات الدهنية وكذلك التى تذوب فى الماء باستخدام وسط ذو رقم هيدروجينى قدره ٨ ونظرا لتحلل الاسبرين المنطلق الى حامض السالسيليك وحامض الخليك فانه يؤدى الى زيادة الحموضه فى الشرج ومن ثم الى تاثير مؤلم. وتهدف الدراسة الى تقييم حركية كل من الأسبرين وحامض السالسيليك من القواعد الدهنية والتى تذوب فى الماء وخلال الدراسة تم استخدام خلية انطلاق مكونة من حجرتين يفصل بينهما غشاء سيلوفانى شبه منفذ. وبدراسة انطلاق الأسبرين من لبوسات الأطفال المحتوية على ١٠٠ مجم فقد اظهرت النتائج ارتفاع كمية الأسبرين الكلى المنطلق من وتبسول هـ١٥ (١) عنه فى حالة سبوسيرام (٢) بينما لوحظ أن القاعدة المؤلفة من مزيج من القواعد السابقه بنسبة ٥٠٪ لكل منهما (٣) أظهرت اقل انطلاق للأسبرين ١٨,٦٪ وقد أدى إضافة توين ٨٠ الى (١)و(٢) الى زيادة كمية الأسبرين المنطلق من ٤٠ ال ٦١,٦٪ل (١) ومن ٢٤,٩ الى ٢٥,٢ ل(٢). بينما كانت نسبة الأسبرين المنطلق من القاعدة التى تذوب فى الماء بعد ٥ ساعات هو ٣١,٧٪ وتراوحت نسبة حامض السالسيليك المنتشر بالنسبة الى الأسبرين الكلى مابين ٤٣,٧ الى ٧٢,٦٪ وقد أدت اضافة توين ٨٠ الى تقليل كمية حامض السالسيليك. وقد تم حساب ثابت معدل الديلزه حيث كان أعلى ثابت هو ٠,٣٩٩٢ وأقلها ٠,٠٦٦٩ ساعة$^{-1}$. كما وانه تمت دراسة انطلاق الأسبرين مع تحلله وانتشاره من خلال الغشاء السيلوفانى باستخدام نموذج مقترح لذلك ، وقد تبين وجود علاقة طردية بين ثابت معدل الانطلاق وثابت معدل الديلزه.

The release of aspirin from certain suppository bases, mainly oleaginous and water soluble were studied in-vitro using phosphate buffer of pH 8 as the releasing medium. In this study infantile size suppositories containing 100 mg aspirin were prepared and tested using diffusion cell of two compartments separated by semipermeable cellophane membrane. After five hours, 40.6% aspirin was released from witepsol H15 (I) compared to 24.9% for suppocire AM (II). While a base composed of 50% from each of I, II (III) showed the lowest release (18.6%). Addition of 5% tween 80 to I (IV) and to III (V) enhanced the total aspirin release (61.6% for IV and 25.2% for V). Aspirin release from a water-soluble base (VI) was 31.7% after five hours. Salicylic acid resulted from the hydrolysis of aspirin in the diffusion medium was determined. The salicylic acid (%) diffused to the total aspirin reanged from 43.7% for IV and up to 72.6% for each of III and V. Also, the addition of tween 80 to I decreased the salicylic acid (%) released from 59.6% to 43.7% (IV). The results obtained were compared with a commercial suppository containing 130 mg aspirin. The results showed that the diffusion from IV have the highest rate constant (0.3992 h^{-1}). The release of aspirin from suppository together with its hydrolysis and diffusion through the cellophane membrane was studied using an assembled model. A direct relationship was found between the release rate constants and the dialytic rate constants.

INTRODUCTION

Aspirin is an old analgesic and anti-inflammatory drug, and because of its gastrointestinal side effects, the rectal route appears to be an alternative route of administration especially for pediatric use. Aspirin is an acidic drug (pKa, 3.2) and in the alkaline medium of rectum aspirin is easily hydrolyzed. On complete hydrolysis of one mole

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aspirin, one mole of each of salicylic and acetic acids is produced.[1,2]

In this case, the acidity in the rectum appears to increase and irritation of the rectal mucosa occur. Satoh and Horiguchi[3] reported that aspirin induced sever erythrema on the rectal membrane of rabbits 6 hr after intrarectal administration that was regenerated within 24 hr. While the repeated administration of rectal aspirin caused more serious damage. Also, Borg *et al.*[4] reported that, healthy volunteers exhibit rectal pain, tenesmus and blood in the stools as a side effect for aspirin suppository. Although, aspirin act pharmacologically as salicylate, it is superior to salicylic acid as analgesic and anti-inflammatory agent.[5,6] Also, the effect on blood platelets is an important action of intact aspirin.[7] Keeping Hxe released aspirin intact (without hydrolysis) before recHxl absorption takes place will, of course, minimize the increasing acidity and decrease irritation in the rectum, the objective of this work was to study the kinetics of release of intact aspirin and salicylic acid from some selected oleaginous suppository bases as well as water-soluble base.

EXPERIMENTAL

1. Materials and instruments

Aspirin (acetylsalicylic acid, Aldrich), Witepsol H15 (Interpharm), Suppocire AM (Dynamite Nobel), PEG4000 and PEG400 (FLUKA) and tween 80 (E-Merck). Commercial pediatric suppository preparation, Vagaskin, containing 130 mg aspirin (Alexandria pharm. Co Egypt batch no. 15686). All other chemicals were of analytical grade. Water bath shaker (GFL, England) and double beam spectrophotometer (Shimadzu, Japan).

2. Formulation of suppositories

The suppositories were prepared by molding, where, the powdered drug was suspended in the melted base of appropriate consistency. Table 1 shows the formulas of the different suppositories. The suppositories were solidified at room temperature and after removal they were stored refrigerated until examination.

3. *In-vitro* drug release

The drug release from the prepared suppositories was deHxrminHx using two compartment diffusion cell separated by 4.5 cm^2 cellphane membrane (30/32). One suppository was inserted in the donor compartment with 2 ml of phosphate buffer pH8. The receptor compartment contain 150 ml phosphate buffer pH8 maintained at $37° \pm 0.2$ in water bath shaken at 50 shake/min. At predetermined time intervals, aliquots of 10 ml were removed from the receptor compartment for the determination of the released aspirin and salicylic acid.

4. Assay of the released salicylic acid

The free salicylic acid was determined by the measurement of the developed violet colour from the reaction with ferric chloride spectrophotometrically at 250 nm. Briefly, from the outer compartment, 5 ml of the sample were withdrwan followed by sudden cooling (using ice bath) to stop further hydrolysis of aspirin, then the sample was acidified with HCl. One ml of ferric chloride test solution (2% w/v in 0.1 N HCl) was added and the volume was completed to 10 ml with dilute HCl where a violet colour was developed and measured at 250 nm against a blank similarly treated.

5. Assay of the released aspirin

Aspirin was determined as salicylic acid after complete hydrolysis of samples. 5 ml of sample were acidified with HCl and incubated in boiling water-bath for two hours. The total salicylic acid (the free salicylic acid and that resulted from aspirin hydrolysis) was determined as above. For the determination of aspirin the amount of free salicylic acid was subtracted from the total salicylic acid in the same sample.

6. Determination of aspirin hydrolysis

50 mg of aspirin were dissolved in 150 ml of phosphate buffer pH 8, and then incubated in $37° \pm 0.2$ water bath. 5 ml samples were withdrawn and assayed for the remaining aspirin at different time intervals as above.

RESULTS

The drug release from a suppository is the first step in the path of the bio-absorption of drug from rectum. The fluid present in the rectum plays an important role in dissolving drugs and acts as a medium for their absorption. In the present study, certain oleginous suppository bases and a water-soluble base were selected to study the kinetics of aspirin release from suppository as well as its hydrolysis in the rectal pH. Table 1 shows the composition of the tested suppository containing aspirin. Table 2, represents the effect of the different suppository bases on the release of aspirin and its hydrolysis after 5 hours. For total aspirin release, it was noticed that, the release of drug from witepsol H15 (B1,40.6%) is better than from suppocire (B2, 24.9%). A combination between witepsol H15 and suppocire 1:1 (B3,18.6%) does not improve the release of aspirin from witepsol or from suppocire. In the case of polyethylene glycol base (B6), the water-soluble base, aspirin released (31.7%) was more than that released from B2 and less than that of B1. The effect of the addition of 5% tween 80 on the release of aspirin from witepsol H15 (B4) or the mixture of witepsol and suppocire (B5) was studied. It was found that, tween 80 greatly increased the total aspirin released from the two tested suppository bases to be 61.6% for B4 and 25.2% for B5.

As the pH of the rectum is slightly alkaline, so, it will affect the integrity of the released aspirin molecules leading to its rapid hydrolysis. Fig. 1, present a histogram for aspirin diffusion from the different suppository bases. The figure shows that, B4 showed the best aspirin diffusion (34.64% of dose), However, B2 gave the lowest amount of aspirin released (3.98%). Fig. 2, shows the diffusion of salicylic acid resulted from the hydrolysis of the released aspirin in the internal compartment, together with that resulted from the hydrolysis of the diffused aspirin. The highest amount of salicylic acid diffused was for B4 (26.9%) followed by B1 (24.2%) then B6, B5, B2 and B3. From Table 2, it was noticed for B1, B2 and B3 as the rate of release increase the rate of aspirin hydrolysis decrease. However, the addition of tween 80 decreased the hydrolysis of aspirin in case of B4 and almost did not affect it in case of B5. Although the rate of release of aspirin from the polyethlene glycol base (B6) was less than that of B1, their rates of hydrolysis were comparable.

The release from a commercial aspirin suppository preparation containing 130 mg aspirin was studied. The results were found comparable to B6. The percentage of aspirin hydrolyzed relative to the total aspirin release (R) was calculated and listed in Table 2. It was noticed that, although B4 gave the higher percent of salicylic acid to the tested dose, it gives the lowest percent of salicylic acid to the total aspirin released (43.7%), that was due to the increased amount of aspirin release from that base. Apart from B4, R lies from 58.7% of B6 to 72.6% for each of B3 and B5.These results of R means that, the majority of the released aspirin is degraded. According to the experimental procedure the release of drug was tested through dialysis technique that was used before in many literatures with little differences in the shape of sets used.[8,9] The following equation was used for the caluclation of the apparent dialytic rate constant.[8]

$$Log\ [V_o A_t - (V_o+V_i)A_o] - -[(V_o+V_i)/(2.3V_oV_i)]kt + \log(V_o/A_t) \qquad \text{Eq. (1)}$$

$$k = -slope \times 2.3V_oV_i / (V_o+V_i) \qquad \text{Eq. (2)}$$

Where
k = apparent dialytic rate constant
V_o= volume of the test medium outside.
V_i= volume of the test medium inside.
A_o= amount of drug dialyzed.
A_t= the total amount of drug in the test sample.

Table 2 depicts the calculated dialytic rate constants according to equation 1 and 2. Data showed that the drug release was fastest from suppository prepared with B4 while it was slowest in case of B3. Although the dialytic rate constant (k) reflects the speed of total aspirin diffuses through the cellophane membrane, it seems a factor of three different rate constants. a) The actual release rate constant from the suppository. b) The diffusion rate constant of

Table 1: Composition (w/w) of the tested suppository containing aspirin.

Ingrediens	Base number					
	B1	B2	B3	B4	B5	B6
Aspirin	1.0	1.0	1.0	1.0	1.0	1.0
Witepsol H15	9.0	--	4.5	--	8.5	4.25
Suppocire AM	--	9.0	4.5	--	--	4.25
PEG 4000	--	--	--	6.7	--	--
PG 400	--	--	--	1.3	--	--
Propylene glycol	--	--	--	1.0	--	--
Tween 80	--	--	--	--	0.5	0.5

Table 2: Effect of suppository base on the release of aspirin and its hydrolysis affer 5 hours.

Suppository bases	k[a]	% Asp.[b]	% SA[c]	R[d]
B1	0.1453	40.6	24.2	59.6
B2	0.1078	24.9	15.9	63.9
B3	0.0669	18.6	13.5	72.6
B4	0.3992	61.6	26.9	43.7
B5	0.0927	25.2	18.3	72.6
B6	0.1682	31.7	18.6	58.7
Commercial	0.1380	30.8	18.7	60.7

a Dialytic rate constant as calculated from equation1.
b Percent of total aspirin released after five hours from the test dose.
c Percent salicylic acid released after five hours from the tested dose.
d Percent of aspirin hydrolyzed relative to the total aspirin release.

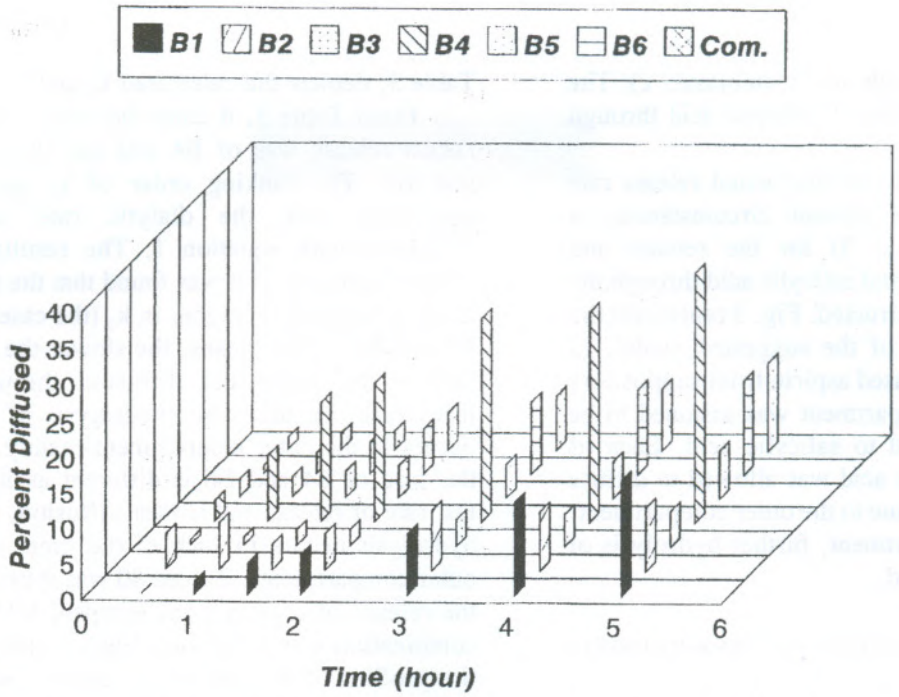

Fig. 1: Diffusion of aspirin from the tested suppository bases.

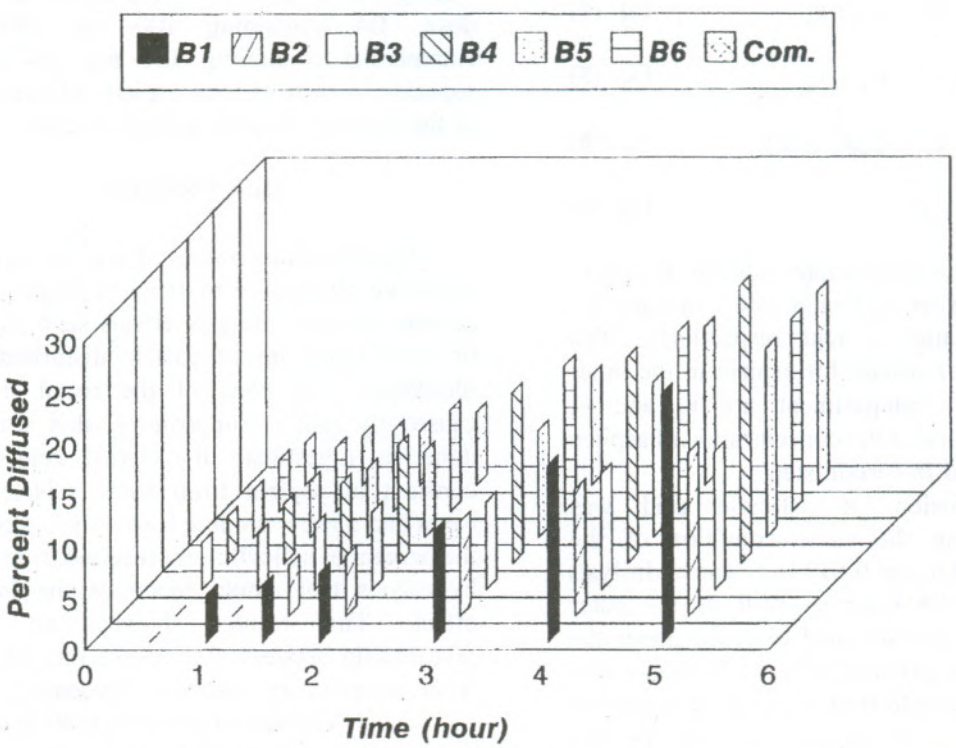

Fig. 2: Diffusion of salicylic acid from the tested suppository bases.

intact aspirin through the membrane. c) The diffusion rate constant of salicylic acid through the membrane.

In order to compute the actual release rate constant under the present circumstances, a specific model (Fig. 3) for the release and diffusion of aspirin and salicylic acid through the membrane was constructed. Fig. 3 represents the schematic diagram of the suggested model. In this model, the released aspirin from suppository in the internal compartment was assumed to be partially hydrolyzed to salicylic acid. Each of aspirin and salicylic acid was allowed to diffuse through the membrane to the outer compartment. In the outer compartment, further hydrolysis of aspirin was occurred.

The following differential equations were used to solve the model;

$$dc(1)/dt = C_4 \times k_2 - C_1 \times k_3 \quad \text{Eq. (3)}$$

$$dc(2)/dt = C_1 \times k_3 + C_3 \times k_4 \quad \text{Eq. (4)}$$

$$dc(3)/dt = C_4 \times k_5 - C_3 \times k_4 \quad \text{Eq. (5)}$$

$$dc(4)/dt = C_5 \times k_1 - C_4(k_2 + k_5) \quad \text{Eq. (6)}$$

$$dc(5)/dt = -C_5 \times k_1 \quad \text{Eq. (7)}$$

Where , k_1 is the release rate constant, k_2 and k_4 are the first order diffusion rate constants for aspirin and salicylic acid respectively. The hydrolysis rate constant for aspirin in the inner and the outer compartment are k_5 and k_3 respectively. C (x) is the concentration of aspirin or salicylic acid in certain step.

The diffusion of salicylic acid was calculated using the same condition of the experiment and it was 0.619 hr^{-1}. The hydrolysis of aspirin in the inner as well as the outer compartments was assumed to occur under the effect of buffer pH and to be at the same rate constant. The pseudo-first order rate constant for the hydrolysis of aspirin in the present conditions of pH was determined and was found to be 0.0914 hr^{-1}. The differential equations of the proposed model were analyzed using non-linear computer program MULTI (Runge).[10]

Table 3, depicts the calculated k_1 and k_2.

From Table 3, it could be noticed that the fastest release was of B4 and the slowest one was B3. The ranking order of k_1 appear in agreement with the dialytic rate constant calculated with equation 1. The results of k_2 seems surprising as it was found that the smaller k_1 of certain base is higher in k_2 (the case of B2, B3 and B4). That means, the slower the release rate is the faster the diffusion through the membrane. In this case, hydrolysis of aspirin occurs in the outer compartment mainly. While the case of B4 and B6 is different as it shows fast rate of release and slower diffusion, and so, hydrolysis occurs in each of the inner and the outer compartments. Tween 80 was found fasten the release of aspirin from witepsol H15 or its combination with suppocire. Figs. 4 and 5 show the profiles of the release of aspirin, salicylic acid and the remaining (unreleased) aspirin for B4 and the choosed commercial preparation. Taking into consideration the difference in the dose, B4 containing 100 mg while the commercial containing 130 mg. B4 appears superior in each of total aspirin release as well as the percent of intact aspirin release.

DISCUSSION

Rectal administration of aspirin may be an attractive alternative to the oral doses for the patients to avoid the side effects such as nausea or even more severe gastric disturbance and ulceration.[11] In view of the rectal irritation caused by aspirin suppository, this work was done to investigate the actual release rate constant of aspirin from some selected fatty bases and a water-soluble base. Also, computing the percent of salicylic acid resulted from aspirin hydrolysis that would increases the irritation effect. The results showed an inverse relationship between the release rate of aspirin from suppository and the percentage of its hydrolysis. The presence of tween 80 in the fatty suppository base fastens aspirin release especially with witepsol H15. That effect may be attributed to its effect on the solubility of aspirin. In the case of the polyethylene glycol

Table 3: First order rate constants for the release and diffusion of aspirin from the tests suppositories.

Suppository bases	k_1 (hr^{-1})	k_2 (hr^{-1})
B1	0.7188	0.0742
B2	0.0255	27.722
B3	0.0137	27.729
B4	2.8539	0.1656
B5	0.0209	27.719
B6	2.0089	0.0522
Commercial	2.0705	0.0408

K_1: The release rate constant of aspirin from the base.
K_2: The diffusion rate constant of aspirin through the membrane.

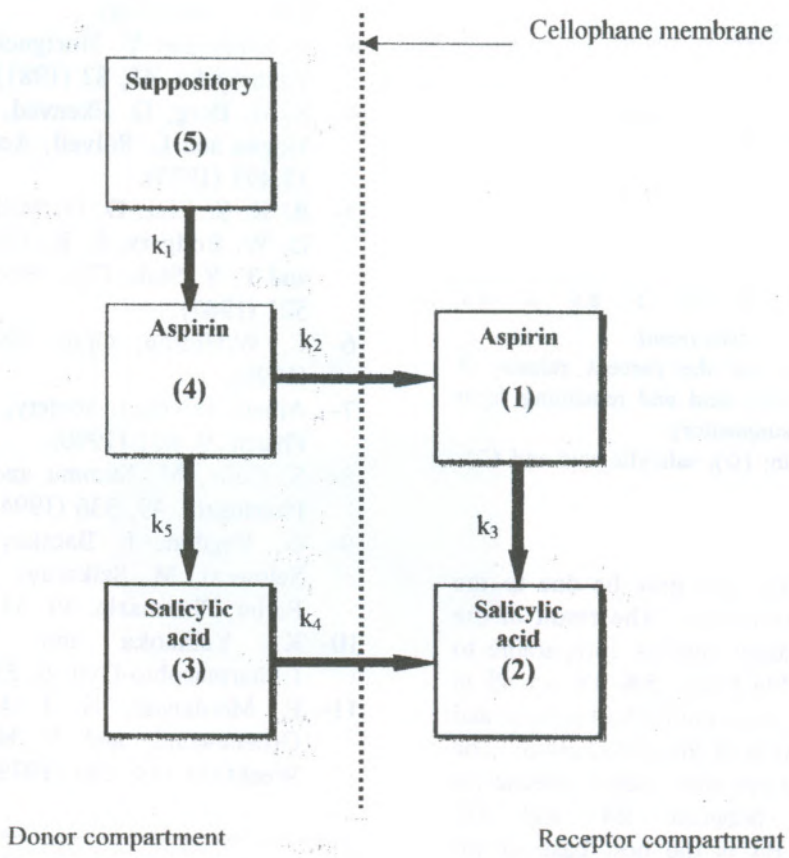

Fig. 3: Schematic diagram for the release and diffusion of aspirin and salicylic acid from suppositories.

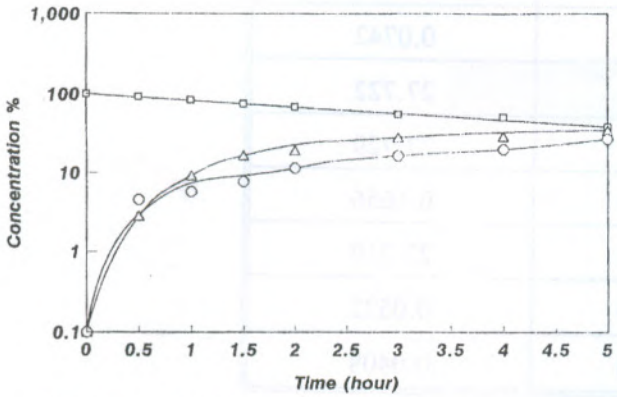

Fig. 4: Semilog plot for the percent release of aspirin, salicylic acid and remaining from B4.
Key: (△), aspirin; (○), salicylic acid and (□), remaining

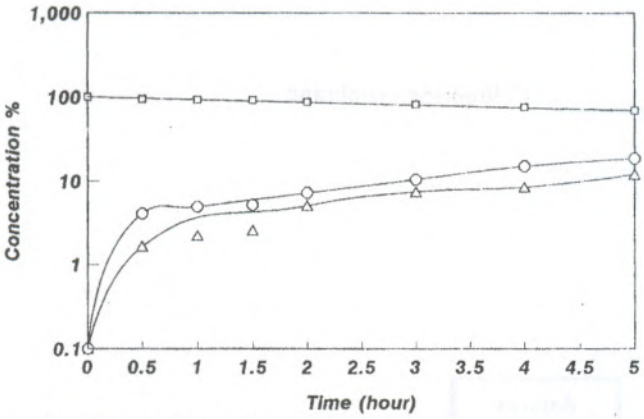

Fig. 5: Semilog plot for the percent release of aspirin, salicylic acid and remaining from commercial suppository.
Key: (△), aspirin; (○), salicylic acid and (□), remaining

base, the fast release rate may be due to the drug's solubility in the base. The result of the commercial preparation appears comparable to B6 (the water-soluble base). 5% Tween 80 in witepsol H15 (B4) gives the highest release and the lowest degradation of the tested group. The increasing dose did not show better release (in the comparison between B4 and the commercial). So, B4 is the best base of the tested group and superior to the commercial. The use of dialytic rate constant in this case of aspirin, will of course, give an idea about the release rate, but the presence of specific model including the hydrolysis product will be more helpful in studing drug release from suppositories. As conclusion, The first step to minimize the rectal irritation of aspirin suppository is by decreasing its hydrolysis in the rectum. Thus, it is not enough to study the total amount of drug released for easily hydrolyzed drugs, such as aspirin, but knowing the release rate and the percentage of drug hydrolyzed are important. That is to minimiz the irritation effect resulted from the drug and or its hydrolysis product to the rectal mucosa.

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