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# INFLUENCE OF CERTAIN ADDITIVES ON THE DIFFUSION RATE OF ASPIRIN, SALICYLAMIDE AND PHENACETIN THROUGH THE RAT"S ILEUM

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## ABSTRACT

The diffusion rate of aspirin, salicylamide and phenacetin through the rat's ileum was found to be concentration dependent. The presence of glucoseamine hydrochloride decreased the amount diffused from each drug. The higher diffusion rate of aspirin was happened in presence of 0.01% w/v Myrj 59, followed by Brij 58 and then cetrimide. While that of salicylamide increased in presence of 0.01% w/v Tween 80. The more convenient increase in the diffusion rate of phenacetin produced in presence of 0.01% w/v Tween 20 and 0.3% w/v sodium lauryl sulfate. The other tested surfactants either reduced the amounts of drugs diffused or produced insignificant effect. With regard to the effect of aliphatic acids-drugs solid dispersions, tartaric acid increased the diffusion rate of aspirin; citric,tartaric and succinic acids as well as PEG 4000 increased the diffusion rate of salicylamide while, succinic acid increased the diffusion rate of phenacetin through the rat's ileum.





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## INTRODUCTION

The intensity of the pharmacologic response elicited by many drugs is probably directly related to the concentration of the drug in the immediate vicinity of the receptor site in the body[1]. Since it is not possible to measure this concentration directly, it is often assumed that an apparent distribution equilibrium is established between the drug in plasma and receptor compartment. Once this equilibrium has been attained, measurement of the drug concentration in plasma is assumed to provide an indirect measure of the concentration of the drug at the receptor site. Therefore the determination of the drug in the plasma at time intervals may allow one to follow the time course of the pharmacologic activity. Drugs must be in solution in fluids of gastrointestinal tract before they can be absorbed into the blood.

Schanker et al.[2] stated that the pH of the fluids in the rat stomach is varied. Accordingly, if the contents of the stomach are made alkaline, the absorption of weakly acidic drugs should be depressed and that of weakly basic drugs enhanced.

A number of weakly acidic and basic drugs are poorly absorbed from the gastrointestinal tract, even though they exist in the unionized form in some regions of the tract. Poor absorption results from the fact that the gastro-intestinal absorption of drugs is influenced not only by the degree of ionization but also by the lipid solubility of the unionized form. A good correlation to Lipid solubility of a drug is provided by its oil/water partition coefficient. Sckanker [3] had been studied the correlation between the partition coefficient of barbiturates and the

corresponding amount absorbed. He found that a direct relationship between the partition coefficient and the amount absorbed.

The present study aimed to, study the effect of certain additives such as ionic and non-ionic surfactants, on the diffusion rate of aspirin , salicylamide and phenacetin through the rat's ileum. The effect of aliphatic acids and water soluble carriers such as polyethylene glycols 4000 and 6000 and urea when they were fused or physically admixed with each of the three drugs was also studied.

## EXPERIMENTAL

### Materials and Methods:

#### Materials :

Aspirin , salicylamide[a]; phenacetin, tartaric acid and succinic acid[b]; Tween, 20, 40, 60 and 80, citric acid[c]; Myrjs 52, 59[d]; Brijs 35 and 58[e]; sodium lauryl sulfate, urea, PEGs 4000 and 6000, potassium chloride[f]; calcium chloride, sodium hydroxide, benzalkonium chloride, cetrimide[g], glucoseamine hydrochloride, sodium hydroxide.[h] All chemicals are of pure grade.

#### Animals :

Adults male Hooded Wistar rats, 240-280 g.

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a) CID company, Egypt.
b) M & B
c) Merck
d) Hekel International, Duss eldoff, W. Germany.
e) Atlas, Chemie, Essan, W. Germany.
f) BDH
g) El-Nasr Pharmaceutical Co. Egypt.
h) Prolabo.

Solutions :

1) 1 mg/ml aspirin solutions were prepared in Ringer's solutions at pH 4 in presence of 0.01% w/v of either Tween 20, 40, 60 or 80; Myrj 52 or 59; Brij 35 or 58, benzalkonium chloride, cetrimide, 0.3% w/v sodium lauryl sulfate or 0.2% w/v glucoseamine hydrochloride.

2) Aspirin solid dispersions were prepared with each of : citric, tartaric and succinic acids, urea , PEGs 4000 and 6000 at the eutectic ratios. The solid dispersions prepared were finely powdered and an accurate weight of the fused mixture corresponding to 25 mg was dissolved in 25 ml Ringer's solution at pH4 so as to prepare 1 mg/ml aspirin in each carrier.

3) The same procedures were adopted to prepare 1 mg/ml solutions of salicylamide in Ringer's solution adjusted at pH5.

4) 0.5 mg/ml phenacetin solutions were prepared also in presence of the above mentioned adjuvants at pH6.

Procedures :

The rats were fasted for period of 20-24 h and water was allowed ad Libitum. The rats were killed by a blow on the head. The abdominal region was exposed by means of a midline incision. The entire small intestine was removed immediately and the lumen was washed with Ringer's solution. The distal portion was discarded to prevent the inclusion of the enterance of the bile duct in the test segment. The method adopted in this study included the isolation of small equal segments from the rat intestine, filling the sac with a small volume of the tried drugs solutions (1 ml/5 cm). Both ends of each segment were tied off, and the segment

was immersed in a measuring cylinder containing 25 ml Ringer's solution free from the drug. The measuring cylinder and its contents were immersed in a water-bath at 37°C and its contents were oxygenated during the experimental time. 1 ml samples from the organ bath were withdrawn at 10 min time intervals, diluted and assayed spectrophotometrically at 232, 236 and 245 nm for aspirin, salicylamide and phenacetin respectively, against a blank prepared similarly but free from the drug. Each experiment was done 4 times and the average amount of the drug transferred through the rat's intestine into the organ bath was plotted versus time.

## RESULTS AND DISCUSSION

The effect of different concentrations (0.1, 0.2, 0.4 and 0.8 mg/ml) of each of aspirin salicylamide and phenacetin on their diffusion rate through the rat's ileum was investigated. From the data obtained it can be deduced that as the concentration of the investigated drugs increased the drug diffusion was correspondingly increased. This indicated that each of the three drugs were mainly passively diffused through the rat intestine. The presence of 0.2% w/v glucoseamine hydrochloride decreased the diffusion rate of aspirin, salicylamide and phenacetin through the rat's ileum (Table 1). The results indicated that these drugs are not only passively transported through the rat's ileum, but also actively transported in a lesser extent. This may be attributed to that glucose molecules decrease the diffusion rate of these drugs (as it was previously reported for salicylamide[4]). With regard to the effect of 0.01% w/v of different Tweens on the diffusion rate of each drug through the rat's ileum, the data obtained illustrate that all the tried Tweens slightly decreased

Table 1 : Effect of glucoseamine hydrochloride on the diffusion rate of aspirin, salicylamide and phenacetin through the rat's ileum at 37°C.

| Time (min) | Amount of drug diffused (mcg/ml) | | | | | |
|---|---|---|---|---|---|---|
| | Control | Aspirin | Control | Salicyla-mide | Control | Phenacetin |
| 10 | 33.92 | 27.68 | 17.21 | 15.60 | 11.07 | 8.57 |
| 20 | 40.18 | 39.28 | 22.11 | 16.78 | 17.14 | 15.36 |
| 30 | 47.32 | 45.32 | 25.70 | 18.93 | 23.21 | 18.21 |
| 40 | 54.46 | 52.13 | 30.71 | 21.42 | 26.78 | 23.57 |
| 50 | 59.82 | 55.16 | 31.28 | 22.86 | 30.00 | 24.28 |
| 60 | 70.53 | 63.27 | 35.71 | 25.10 | 32.85 | 28.57 |
| AUC | 2710 | 2512 | 1449 | 1081 | 1246 | 1043 |

the diffusion rate of aspirin except Tween 40 which exhibited a slight increase in the diffusion rate. The area under diffusion rate curves were calculated according to the obtained data and tabulated in Table (2A). In case of salicylamide, it was found that Tween 80 increased its diffusion rate, while, the other tested Tweens produced insignificant effect.

The effect of Tweens on the diffusion rate of phenacetin can be arranged as follow : Tween 20 > Tween 60 > Control > Tween 80 > Tween > 40 (Table 2A). This influence may be due to some effects of polysorbates

Table 2 : Area under the diffusion rate curves (10→60 min) of Aspirin, salicylamide and phenacetin through rat's ileum in presence of different surfactants.

(A)

| Surfactant | A U C of : | | |
|---|---|---|---|
| | Aspirin | Salicylamide | Phenacetin |
| Tween 20 | 2299 | 1207 | 898 |
| " 40 | 2564 | 1036 | 580 |
| " 60 | 2089 | 1159 | 706 |
| " 80 | 2272 | 1547 | 621 |
| Control | 2384 | 1130 | 667 |

(B)

| | | | |
|---|---|---|---|
| Myrj 52 | 2281 | 1331 | 741 |
| " 59 | 3963 | 1166 | 821 |
| Brij 35 | 2273 | 1002 | 796 |
| " 58 | 2882 | 1286 | 740 |
| Control | 1882 | 1359 | 894 |

(C)

| | | | |
|---|---|---|---|
| Sod. l.sulfate | 2889 | 1571 | 1081 |
| Benzalkonium Cl. | 2598 | 1389 | 943 |
| Cetrimide | 3642 | 1598 | 927 |
| Control | 2710 | 1653 | 930 |

(Tweens) on the permeability characteristics of the membrane.

The effect of 0.01% w/v Myrj 52 and 59; Brij 35 and 58 on the diffusion rate of each of the three drugs through the rat's ileum was investigated. These surfactants enhanced the diffusion rate of aspirin in the order of Myrj 59 Brij 58 Myrj 52 Brij 35 control. This enhancing effect may be due to an interaction or say affinity between the surfactants and the cellular surface of the rat's ileum, permitting more diffusion of the drug molecules (Table 2B). While, the same surfactants retarded the diffusion rate of salicylamide and phenacetin. The degree of retardation varied according to the type of surfactant and may be attributed to certain changes in the permeability properties of the membrane in presence of these surfactants.

Table (2c) illustrates the effect of benzalkonium chloride, cetrimide and sodium lauryl sulfate on the diffusion rate of aspirin through the rat's ileum as represented by the area under curve. Aspirin diffusion enoromously increased in presence of cetrimide, while, sodium lauryl sulfate produced a minor increase in its diffusion rate. Benzalkonium chloride has insignificant effect. These ionic surfactants, generally , decreased the diffusion rate of salicylamide. With regard to phenacetin, 0.3% w/v sodium lauryl sulfate increased its diffusion rate, while both benzalkonium chloride and cetrimide produced insignificant effect.

The diffusion rate of aspirin, salicylamide and phenacetin solid dispersions with aliphatic acids across the rat's ileum was studied. The area under curves of the obtained data were calculated and serveyed in table 3. From the results, it was found that all

Table 3 : Area under the diffusion rate curves (10 → 60 min.) of aspirin, salicylamide and phenacetin solid dispersions through the rat's ileum at 37°C.

| The Carrier | AUC of : | | |
|---|---|---|---|
| | Aspirin | Salicylamide | Phenacetin |
| Citric acid | 2491 | 2823 | 709 |
| Tartaric " | 3152 | 2311 | 803 |
| Succinic " | 2625 | 2134 | 907 |
| Control | 2176 | 1127 | 777 |
| Urea | 3000 | 1112 | 659 |
| PEG 4000 | 2010 | 1318 | 836 |
| PEG 6000 | 1705 | 1186 | 893 |
| Control | 1696 | 1282 | 818 |

the tested acids when fused with either aspirin or salicylamide, markedly increased the diffusion rate, while that of phenacetin increased only in presence of succinic acid followed by tartaric acid, but decreased with citric acid. The effect of water soluble carriers such as urea, PEG 4000 and PEG 6000 when they were fused separately with each of the three drugs at their eutectic composition was investigated. The data revealed that urea highly increased the diffusion rate of aspirin while decreased that of both salicylamide and phenacetin.

PEG 4000 also increased the diffusion rate of both aspirin and salicylamide. A slight increase in the diffusion rate of phenacetin was affected by solid dispersion with either PEG 4000 or 6000, while a decrease in the diffusion rate of salicylamide-PEG 6000 solid dispersion was noticed.

The enhancement of diffusion rate produced in some cases for any of the tested drugs when it was fused with a water soluble carrier may be due to the higher solubilizing effect of the carrier towards the drug and to the increase in the effective surface area of the medicament in these dispersions. While the cases in which the diffusion rate of the drug did not increased or retarded may be attributed to the nature and properties of both the carrier and the drug and the presence or absence of surfactant may all influence the diffusion process of any drug.



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