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# Biopharmaceutic and pharmacokinetic studies following the oral administration of sodium salicylate in oily and aqueous vehicles to rabbit

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**Abstract**

The pharmacokinetic parameters, i.e. peak concentration ($c_{max}$); peak time ($t_{max}$); area under the curve (AUC); elimination rate constant ($k$); absorption rate constant ($k_a$); Drug clearance ($cl_t$), and the volume of distribution ($v_d$) of sodium salicylate administered in fractionated coconut oil (FCO) have been compared with that from an aqueous and glycerin vehicles using a three-way crossover study in 12 rabbits. The results of the study show that all of the pharmacokinetic parameters tested differ significantly when administered in oily rather than aqueous or glycerin vehicles. No statistically significant difference was found between any of the above mentioned parameters when comparison was made between aqueous and glycerin formulations. The results indicate that sodium salicylate is absorbed at a lower rate but to a greater extent from oily formulation. Possible reasons for these differences are discussed and is suggested, therefore, that the oily formulation might be used as a sustained release preparation.


*Keywords:* Gastric emptying rate (GER); Fractionated coconut oil (FCO); Drug clearance ($cl_t$); Volume of distribution ($v_d$); Elimination rate constant ($k$); Absorption rate constant ($k_a$); Area under the curve (AUC)

## 1. Introduction

The rate and extent of absorption of sodium salicylate, aspirin and salicylic acid together with their in vitro dissolution rate studies have been extensively reported and reviewed. Among these studies are the effects of pH (Truitt and Morgan, 1964; Nayak and Benet, 1974) and dissolution rate (Levy, 1961) on the bioavailability of salicylate. The effects of gastric emptying rate on the rate and extent of salicylate absorption were also reported extensively (Sleight, 1960; Lolli and Smith, 1964; Barzegar-Jalali and Richards, 1979; Alhamami and Richards, 1983, 1996; Alhamami, 2002, 2003).

Several reports and studies on salicylates have recently been concentrated on a variety of aspects. For example, the effects of the shape of sodium salicylate particles on the physical properties as well as the in vitro aerosol behaviour of the granules were reported (Watanabe et al., 2003). Therapeutic effects of salicylates or aspirin (Preston et al., 1989); effects of rheumatoid diseases on the pharmacokinetics of acetyl salicylic acid (Juarez Olguin et al., 2004); pharmacokinetics and metabolism of salicylates in rabbits (Short et al., 1991); in broiler chickens (Baert and De Backer, 2002); in broiler chickens and homing pigeons (Baert et al., 2004); in human (Dubovska et al., 1995; Lares-Asseff et al., 1999, 2004; Juarez Olguin et al., 2004) have also been investigated.

All of these reports and studies emphasize on physical properties and in vitro release, bioavailability, therapeutic effects, and pharmacokinetics and metabolism studies of salicylate or aspirin from solid dosage forms (e.g. tablets and capsules) and little were done on the liquid preparations (Barzegar-Jalali and Richards, 1979; Short et al., 1991; Baert and De Backer, 2002, 2003). These latter investigations were done on aqueous preparations. Information on the bioavailability of salicylate administered as a suspension in a non-aqueous vehicles (e.g. oils) have received little attention (Alhamami and Richards, 1983, 1996; Alhamami, 2002, 2003) and the pharmacokinetic studies of salicylates administered in oil-based vehicles and the effects of oils on the different pharmacokinetic parameters is

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virtually non-existent, even though this type of dosage form may, in some circumstances, offer advantages over the use of more conventional ones (Stephens and Su, 1975). In view of this deficiency and because oily vehicles for pharmaceutical formulations have been patented (Stephens and Su, 1975; Lin and Pramoda, 1978) the present work was undertaken in order to investigate the effect of oil on the pharmacokinetic parameters of sodium salicylate administered in fractionated coconut oil (FCO). FCO was compared with two vehicles having no effect on gastric emptying rate (GER) (water and glycerin) (Robert, 1931). The glycerin (which is more viscous than FCO) was used in order to eliminate the effect of viscosity of the oil on GER. FCO was, arbitrarily, used because it consists of medium chain fatty acids and, therefore, easily digested and absorbed. The digested products of fats enhance the bile salts secretion; which when reabsorbed, could be the humoral agent mediates gastric inhibition by fats (Alhamami, 1981).

## 2. Materials and methods

### 2.1. Materials

Sodium salicylate, glycerin and the reagents used in the determination of blood salicylate concentrations, i.e. Analar ferric nitrate and mercuric chloride, were obtained from BDH Chemical Ltd. Leicester, England). Fractionated coconut oil BPC was obtained from Alembic Product Ltd. (Chester, Cheshire, England).

### 2.2. Preparation of dosage forms

Dosage forms (formulations) containing 4% (w/v) of sodium salicylate in distilled water, FCO and glycerin were prepared. All types of dosage forms were stored overnight. On the following morning the oily suspension was shaken vigorously immediately before use. The portion corresponding to a mesh size of 125–150 μm of sodium salicylate, obtained by sieving the Analar material, was used in the preparation of the dosage forms. The acid and saponification values of the oil were checked every 2 weeks to ensure they remain within the limits described in the 2003 BP.

### 2.3. Bioavailability studies

These were carried out using the method described previously (Alhamami and Richards, 1983) except that the experimental design based on three-way crossover study, as recommended by Wagner (1979) and involving 12 rabbits, was used in the study. This design is described in Table 1. Adult male New Zealand white rabbits, weighing 3.5–4.6 kg and fed with a standard diet, were used. Our investigations were performed after approval by our local ethical committee at Kufa University and in accordance with "Interdisciplinary Principles and Guidelines of the Use of Animals in Research". Doses of 120 mg/kg body weight of sodium salicylate were administered as either of the above mentioned dosage forms by means of a catheter and syringe directly into the stomachs of rabbits that had been fasted for 20 h. Before removal from the rabbits, the catheter was flushed

Table 1
Experimental design

| Group | Rabbit/group | Treatment in period | | |
|---|---|---|---|---|
| | | I | II | III |
| 1 | 1–4 | A | O | G |
| 2 | 5–8 | O | G | A |
| 3 | 9–12 | G | A | O |

The formulation used contained sodium salicylate 4% (w/v) in: A—distilled water, O—fractionated coconut oil (FCO), and G—glycerin.

out with one-third the dose volume of the appropriate vehicle. Fasting was continued for the first 9 h of each experiment. The experiments were initiated at the same time of day in order to eliminate the effect of circadian variation.

Blood samples were then taken from the marginal ear vein immediately before administration of the drug and at specified times during the 24 h post-administration period (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 9, and 24 h). The samples were placed in heparinized tubes and stored in a refrigerator until the next day, when the total salicylate content of each sample was determined using Trindef's method (Trinder, 1954), which was carried out as follow.

About 0.7 $cm^3$ of blood was placed in a cylindrical centrifuge tube and 3.5 $cm^3$ of Trinder's colour reagent were added. The tube was shaken during the addition and shaking was continued for a few seconds to ensure that the precipitated protein was finely dispersed. After centrifugation at 2000 × $g$ for 5 min the supernatant was withdrawn gently using a Pasteur pipette and its absorbance was determined at 540 nm in a Unicam SP 500 spectrophotometer against a blank solution containing 0.7 $cm^3$ of water and 3.5 $cm^3$ of Trinder's reagent.

The AUCs from the 0 to 24 h post-administration period were calculated by trapezoidal method and the $(AUCs)_{0-\infty}$ were calculated using Eq. (1)

$$(AUC)_{0-\infty} = (AUC)_{0-24} + Cp^{(last)}/k \quad (1)$$

where $Cp^{(last)}$ is the salicylate concentration in the blood at the last sampling time, and $k$ is the elimination rate constant. Drug clearance ($Cl_T$) and volume of distribution ($V_d$) were calculated using Eqs. (2) and (3), respectively

$$Cl_T = FD_0/(AUC)_{0-\infty} \quad (2)$$

$$V_d = Cl_T/k \quad (3)$$

$F$ is the fraction absorbed and was, arbitrarily, used as 1, since it ($F$) was used for all formulations for the same drug. $D_0$ is the oral dose.

The elimination half-life ($t_{1/2}$) and the first order elimination rate constant ($k$) were calculated using Eqs. (4) and (5), respectively.

$$t_{1/2} = 0.693\ V_d/Cl_T \quad (4)$$

$$K = 0.693/t_{1/2} \quad (5)$$

Analyses of variance were carried out on the experimental data followed by the application of the multiple range test (Wagner, 1979). The results are shown in Table 2.

Table 2
Mean values of the pharmacokinetic parameters following oral administration of sodium salicylate in different formulations as a single dose in a three-way crossover design

| Parameter | Formulation[a] | | |
|---|---|---|---|
| | A[b] | G[b] | O[c] |
| $C_{max}$ (mg/100 cm$^3$) | 29.63 ± 3.74 | 31.34 ± 4.02 | 20.33 ± 3.75 |
| $T_{max}$ (h) | 1.21 ± 0.51 | 1.32 ± 0.61 | 2.93 ± 1.33 |
| $AUC_{0-24}$ (mg h/100 cm$^3$) | 196.34 ± 44.64 | 205.13 ± 65.33 | 306.0 ± 46.24 |
| $AUC_{0-\infty}$ (mg h/100 cm$^3$) | 202.64 ± 50.94 | 212.06 ± 72.39 | 563.28 ± 76.07 |
| $K$ (h$^{-1}$) | 0.15 ± 0.06 | 0.18 ± 0.05 | 0.04 ± 0.02 |
| $K_a$ (h$^{-1}$) | 2.75 ± 1.53 | 2.39 ± 1.13 | 1.14 ± 0.66 |
| $Cl_T$ (L h$^{-1}$) | 0.26 ± 0.07 | 0.259 ± 0.10 | 0.11 ± 0.05 |
| $V_d$ (L) | 1.86 ± 0.69 | 1.46 ± 0.37 | 2.63 ± 0.64 |

Each value is represented as mean ± S.D. from 12 experiments.
[a] See Table 1 for formulation (vehicle) codes.
[b] No statistical significant difference between formulations A and G for all parameters ($P > 0.05$).
[c] A statistically significant difference between formulation O and both formulations A and G for all parameters ($P < 0.05$).

## 3. Results

Blood salicylate concentrations versus time curves were plotted for each set of experimental data. The pharmacokinetic parameters, peak concentration ($C_{max}$), the time at which the peak was reached ($T_{max}$), area under the curve $(AUC)_{0-24}$ and $(AUC)_{0-\infty}$, first order elimination rate constant ($K$), first order absorption rate constant ($K_a$),drug clearance ($Cl_T$), and the volume of distribution ($V_d$) were derived from these individual plots. The mean values of these parameters are given in Table 2. The mean concentrations of salicylate in the blood samples taken from the 12 rabbits at various times after oral administration of the three formulations of sodium salicylate are given in Table 3. Plots of the mean salicylate concentration versus time for the three formulations are shown in Fig. 1.

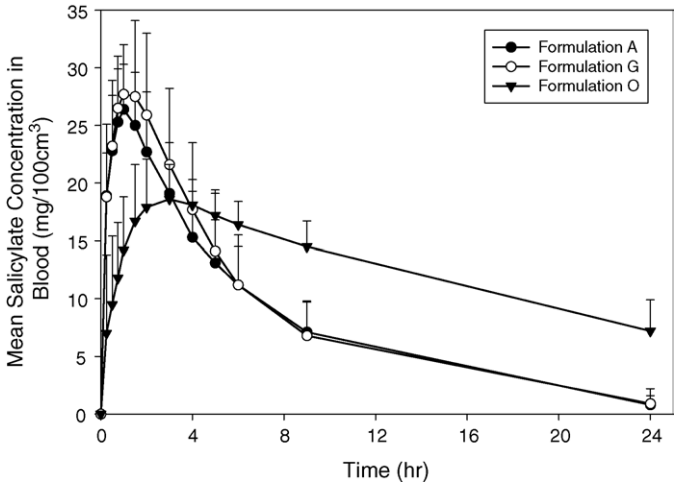


Fig. 1. Mean blood concentration of salicylate vs. time after oral administration of sodium salicylate in aqueous (A), Glycerin (G) and Oily (O) formulation to 12 rabbits.

Table 3
Mean salicylate blood concentration (mg/100 cm$^3$) during different sampling times following oral administration of sodium salicylate (120 mg/kg body weight) as a single dose in different formulations to 12 rabbits

| Formulation | Time (h) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.25 | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 5 | 6 | 9 | 24 |
| Aqueous (A) | 18.9 ± 6.2 | 22.8 ± 6.1 | 25.3 ± 4.6 | 26.4 ± 3.9 | 25.0 ± 4.6 | 22.7 ± 5.2 | 19.1 ± 4.4 | 15.3 ± 4.0 | 13.1 ± 3.7 | 11.2 ± 3.3 | 7.1 ± 2.6 | 0.8 ± 0.8 |
| Glycerin (G) | 18.8 ± 3.8 | 23.3 ± 4.4 | 26.5 ± 4.5 | 27.7 ± 4.3 | 27.5 ± 6.6 | 25.9 ± 7.1 | 21.6 ± 6.6 | 17.7 ± 5.8 | 14.1 ± 5.3 | 11.2 ± 4.3 | 6.8 ± 3.0 | 0.9 ± 1.3 |
| Oily (O) | 7.0 ± 6.8 | 9.5 ± 5.9 | 11.8 ± 4.8 | 14.2 ± 4.6 | 16.7 ± 4.9 | 17.9 ± 4.2 | 18.6 ± 3.0 | 18.1 ± 2.2 | 17.2 ± 1.9 | 16.4 ± 2.0 | 14.5 ± 2.2 | 7.2 ± 2.7 |

Each value is represented as mean ± S.D. from 12 experiments.

Tables 1 and 2 and Fig. 1 show that a statistically significant reduction in ($k_a$) and a significant delay occurred in the attainment of the peak blood concentration ($T_{max}$) and significantly a lower value of the mean peak concentration ($C_{max}$) ($P < 0.05$), following oral administration of the oily formulation (O) when compared with both glycerin (G) and aqueous (A) formulations. AUC is significantly increased when sodium salicylate was administered in oily formulation compared with both formulations (G) and (A) ($P < 0.05$). No significant difference was found regarding all parameters between formulations (G) and (A).

These results indicate that sodium salicylate is absorbed both at a lower rate and to a greater extent following oral administration of the oily formulation (O) when compared with the glycerin (G) or aqueous (A) formulations. The rate of elimination is also significantly reduced from the oily formulation, since the $K$ and $Cl_T$ were significantly lower from this formulation compared with that obtained from formulations (G) or (A), ($P < 0.05$).

## 4. Discussion

A higher rate of absorption from the aqueous vehicle (A) is expected because a greater initial concentration of salicylate is more likely to be produced in the aqueous gastrointestinal fluids when this formulation is administered. The use of water soluble salts of weak acids to enhance absorption rate is well known and the particle size of any solid particles of parent acid precipitated by the low gastric pH is considered to be sufficiently small to provide relatively rapid rates of subsequent dissolution.

Absorption of a drug from a solution in a lipid vehicle is considered to involve liberation of the drug from the vehicle into the aqueous luminal fluid followed by transport across the gastrointestinal epithelium and the transfer from the vehicle to the aqueous phase may become the rate determining process in the bioavailability pathway. Thus, it is likely that the oil used in the present study provides a reservoir for the uptake of salicylic acid (formed by hydrolysis of the sodium salts by the gastric acid) and so reduces the amount of drug initially available for absorption by controlling its release to the gastrointestinal fluids. Such ease of partitions of salicylic acid in the FCO is indicated by the relatively high apparent partition coefficient (38.6) (Alhamami and Richards, 1983) of sodium salicylate between the oil and 0.1 mol/L hydrochloric acid solution at 37 °C. This explanation seems to be the likely one in the light of the results of studies on the in vivo and in vitro release of water soluble drugs from their suppositories in non-aqueous vehicles such as suppository bases and liquid paraffin (Schoonen et al., 1976).

The rate of absorption of salicylate will also be affected by the fact that oil delays the emptying rate of the stomach (Hunt and Knox, 1968; Borgstrom and Arborelius, 1975; Alhamami, 1981; Salim and Alhamami, 2003) and consequently decreases the rate of appearance of the drug in the small intestine. This latter site is regarded normally as the optimum site of absorption for most drugs even if the drugs are readily absorbed from the stomach, such as aspirin and related drugs (Levy, 1961), and even if the drug is ionized in the intestine and nonionized in the stomach (Benet, 1973). This explanation seems to be a more likely one, and viscosity of the FCO, 17 mN s m$^{-2}$ at shear rate of 100 s$^{-1}$ and at temperature 37 °C (Alhamami and Richards, 1996), seems to play no role for the results obtained in this study. This conclusion is supported by the fact that formulation G showed no significant difference ($P > 0.05$) in the rate of absorption ($K_a$, $T_{max}$ and $C_{max}$) when compared with aqueous formulation (A) and significantly differed ($P < 0.05$) when compared with oily formulation (O) (Table 2); although G is more viscous than A but having no effect on GER (Robert, 1931), as water does. Further evidence for the above conclusion was reported by Alhamami (2003), who found that a significant reduction ($P < 0.05$) in the absorption rate of sodium salicylate when administered in aqueous vehicle (A) pretreated with probanthelin (P) (a drug which delays GER) (formulation or treatment AP) compared with the aqueous vehicle alone (formulation A). Furthermore, this treatment (AP) (aqueous formulation pretreated with probanthelin) showed no significant difference ($P > 0.05$) in the absorption rate when compared with oily formulation (O) (Alhamami, 2003). If delaying in GER reduces the rate of salicylate absorption, it follows that acceleration in GER should enhance the absorption rate. In fact, a number of reports recognized that acceleration of gastric emptying can increase the rate of aspirin absorption (Sleight, 1960; Lolli and Smith, 1964) and increase the toxicity and shorten the onset of action of sodium salicylate. These findings are in good agreement with the results obtained in this study. It is suggested, therefore, that the delay in GER brought about by oil is more likely explanation for the present results.

The results show that the extent of salicylate absorption is greater from the oily vehicle compared with that from the glycerin (G) and aqueous (A) vehicles, as indicated from their relative AUC values in Table 2. Although salicylates are absorbed mainly from the small intestine under normal conditions, appreciable gastric absorption of aspirin and salicylates has been reported (Truitt and Morgan, 1964; Nayak and Benet, 1974). Therefore, an increase in gastric residence time might lead to an increase in the contribution that such absorption makes to the overall extent of absorption. In addition, the slower release of drug from the stomach may improve the efficiency of absorption from the intestine or allow a longer period for drug dissolution to occur before transfer into the intestine. It is suggested, therefore, that the increase in extent of absorption of salicylate, that is obtained when sodium salicylate is administered in an oily vehicle rather than as aqueous or glycerin vehicles, may be ascribed to the reduction in stomach emptying rate that is caused by the oil. This reduction in GER is due to physiological effect of FCO and not due to its viscosity. This result is supported by the findings reported by Alhamami and Richards, (1983,1996) and Alhamami (2003), who found that the extent of salicylate absorption was significantly increased ($P < 0.05$) when administered in oily vehicles rather than aqueous ones.

The results obtained in this study suggest that oil can also affect the rate at which salicylate is eliminated. Table 2 shows that a statistically significant reduction in $K$ and $CL_T$ ($P < 0.05$) and a significant increase in $V_d$ ($P < 0.05$) following oral administration of sodium salicylate in oily vehicle compared with that obtained from formulation A or G. This leads to a longer half-life ($t_{1/2}$) Eq. (4). No statistical significant difference was found in terms of $K$, $Cl_T$, and $V_d$ when comparison was made between

formulations A and G. This is another explanation for the significant increase in the $AUC_{0-\infty}$ following oral administration of oily formulation and suggests, therefore, that oil can be used as sustained release preparation.

The delay in the rate of elimination of salicylate caused by the oil can be explained as follow: Dubovska et al. (1995) confirmed the linearity of salicylate in a broad dose range (moderate and high doses). Therefore, the first order elimination rate constant ($K$) is concentration dependent. The higher the peak blood concentration following oral administration of formulation A or G (Fig. 1) is, the higher $K$ would be. Thus, the lower $C_{max}$ following the administration of oily formulation leads to a lower $K$ and this difference is statistically significant ($P < 0.05$). Furthermore, the rapid attainment of the peak concentration, i.e. shorter $T_{max}$, in case of formulation A and G leads to a shorter absorption phase and consequently incomplete distribution phase of salicylate during the absorption phase. In other words, the blood concentration peaks before the distribution equilibrium has been taken place, which leads to a small volume of distribution ($V_d$) and an enhancement in $Cl_T$. The small $V_d$ and higher $Cl_T$ will shorten biological half-life ($t_{1/2}$) and increasing $K$ as shown in Eqs. (4) and (5).

The significant reduction in $V_d$ and the significant increased in $Cl_T$ ($P < 0.05$) (Table 2) following oral administration of aqueous and glycerin formulations of sodium salicylate, compared with the oily formulation, support such interpretation, i.e. shorter $t_{1/2}$ from formulation A and G, and oil delays the elimination of salicylate.

In conclusion, although a significant reduction in the rate of salicylate absorption was found following oral administration of oily formulation when compared with formulation A or G, the extent of absorption is significantly increased. It is suggested that this increase in the extent of salicylate absorption can be attributed largely to the effect of the oil on total gut transit time, particularly the residence time in the stomach. It is also suggested that slower $K$, larger $V_d$, and decreased $Cl_T$ secondary to the delaying in GER could play a role in the results obtained in this study. Furthermore, the reduction in the rate of salicylate absorption after administration of oily formulation can be explained due partly to the action of the oil as a reservoir that controls the release of salicylic acid and partly to the delay in the GER.

If oil does provide a means of reducing the rate of salicylate absorption whilst enhancing the extent of absorption, then such a formulation may be of value, as a sustained release preparation, in the treatment of chronic rheumatism with anti-inflammatory agents by allowing a reduction in either the dose or its frequency of administration. Furthermore, the oil might provide a layer that can protect the gastric mucosa from the irritant effect of the anti-inflammatory agents. Thus, the study illustrates the need to extrapolate this work for other non-steroidal anti-inflammatory drugs, e.g Indomethacin, Diclofenac or Ibuprofen.

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