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Effects of Oily Vehicles on the Bio-availability of Orally Administered, Sodium Salicylates in Rabbit.

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Effects of Oily Vehicles on The Bioavailability of Orally Administered, Sodium Salicylates in Rabbit.

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ABSTRACT

The bioavailability of sodium salicylate administered in aqueous, glycerin and oily vehicles was compared in rabbits. Glycerin formulation was compared with both aqueous and oily formulations using a two - way crossover test in eight rabbits, in each study. The results indicate that the oily formulation gave a lower rate of absorption and a greater extent of absorption than the other formulations. No significant difference in the rate and extent of absorption was shown between glycerin and aqueous formulations. Possible reasons for the differences are discussed with particular reference to the effects of oils on the gastric emptying rate.

ملخص

تأثير المحاليل الزيتية على التوافر الحيوي لساليسيلات الصوديوم المعطى فحويا للأرنب

تم مقارنة التوافر الحيوي لساليسيلات الصوديوم معطى في سواغات (محاليل. صيغ) مائية، كليسرين وزيتية في الأرنب. وقد تم مقارنة صيغة (محلول) الدواء، الكيسيرني مع كلا الصيغتين، في الزيت والماء، باستعمال الطريقة الاحصائية ـ الاختبارين المتبادلين ـ في ثمان أرانب، لكل دراسة. وقد وضحت النتائج ان المحاليل الزيتية خفضت معدل الامتصاص وعززت مدى الامتصاص مقارنة مع المحلولين الآخرين. لا يوجد فرق ذو دلالة معتدة في معدل ومدى الامتصاص عندما تمت المقارنة بين المحاليل المائية والكيسرين. وقد نوقشت الأسباب المحتملة لهذه الاختلافات مع التركيز بشكل خاص على تأثير الزيت على معدل الافراغ المعوي.

الكلمات المفتاح:
التوافر الحيوي *bioavailability*، معدل الافراغ المعدي *gastric emptying rate*، ساليسيلات الصوديوم *sodium salicylate*.

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Key words: Sodium Salicylate, Gastric Emptying Rate (GER) , Bioavailability.

Introduction

Several factors can influence the absorption of drugs from the gastroitestinal tract . Among these factors are, intragastric pH [1,2], gastric emptying rate [3-9], viscosity of gastric contents [10], dissolution rate [11] and others.

It has been recognized that the bioavailability of drugs may be altered by their administration in oils containing dosage forms or coadministration with fatty meals [12-17] or other drugs [3,4]. Fatty meals and oil are known to delay GER [18-22]. The rate at which the stomach emptying its contents affects significantly the rate and extent of drug absorption. Delay in the gastric emptying rate significantly decreased the rate of absorption of paracetamol and aspirin [3,4,6]. Stimulating gastric emptying, on the other hand, accelerated the absorption of the drugs [3,4,6] and decreased significantly the extent of ampicillin absorption [5]. Alhamami and Richards, 1983 [16] reported that oily vehicle significantly delayed the rate but significantly increased the extent of salicylate absorption. The authors suggested that the significant alteration in the bioavailability of salicylate was due to (i) delaying effect of the oil on GER, (ii) the oil could act as a reservoir that controls the release of salicylate and consequently controls the dissolution rate of the drug.

However, the effect of the oil on the GER might be a physiological effect alone or partly due to the more viscous oily vehicle, compared with aqueous vehicle, which could delay gastric emptying beside the physiological effect. The significance of each of the above effects of the oil on the bioavailability of sodium salicylate, due to delaying effect on GER, was not clearly identified.

The present study was undertaken, therefore, in order to find out and detect the net effect of the oil on the biavailability of sodium salicylate, with

particular attention to the effect of the oil on the rate of gastric emptying. A non-aqueous vehicle glycerin has no effect on GER [23] and is more viscous than oil was used. Glycerin formulation was compared with both oily and aqueous formulations.

Materials and methods

Animals

Adult male New Zealand white rabbits, weighing (3.75- 4. 95) kg and fed with a standard diet, were used. The animals were fasted for 20 hrs. The experiments were initiated at the same time of the day and fasting was continued for the first 9 hrs of the experiments.

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) and the fractionated coconut oil BPC was obtained from Alembic Products Ltd (Chester, Cheshire, England). The acid and saponification values of the oil were checked every two weeks to ensure they remain within the limits that described in the 1998 BP.

Preparation of dosage forms

Dosage forms (formulations) containing 4% w/v of sodium salicylate in distilled water, fractionated coconut oil 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.

Bioavailability studies.

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 hr. Before removal from the rabbit, the catheter was flushed out with 1/3 of the dose volume of the appropriate vehicle. The dose was based on the work of Lessel and Cliffe [24].

study 1

Bioavailability studies of sodium salicylate administered in two non aqueous vehicles were compared . Fractionated coconut oil and glycerin vehicles were used. Preliminary rheological work indicated that oily vehicle is much less viscous than glycerin. A two way crossover design, as recommended by Wanger [25] and involving 8 rabbits, was used in this study . The design is described in Table 1 fo oily and glycerin formulations.

Table 1: *Experimental design.*

Group	Subjects per group (number of rabbits)	Time periods 1	2
1	1 - 4	G	O
2	5 - 8	O	G

G = glycerin formulation, O = Oily formulation

study 2

The same experimental design was used as described in study 1 (Table1) above. The comparative bioavailability studies of sodium salicylate was made in this study, instead, between glycerin (G) and aqueous (A) formulations. Blood samples, in both studies (1 and 2), were taken from the marginal ear vein immediately before administration of the drug and at specified times during the 24 hrs post administration period. The samples placed in heparinized tubes and stored in a refrigerator until the next day, when the total salicylate content of each sample was determined using Trinder's method [26].

Results

Blood salicylate concentrations versus time curves were plotted for each set of experimental data. The values of the three commonly used bioavailability parameters, i.e .area under the blood concentration versus time curve (AUC0-24), Peak time (PT) and peak concentration (PC)were derived from these individual plots. The AUCs for the 0 to 24 hr post administration period were calculated by the trapezoidal method [27]. Mean blood concentrations at specified times post administration of the dosage forms are given in Tables 2 and 3 for studies 1 and 2 respectively.

Table 2

Mean blood concentrations (mg/100ml) in rabbits following oral administration as a single dose (120 mg/kg body weigh) of sodium salicylate in two formulations (Oily and Glycerin).Each value is the average of 8 experiments.

Formulation	Time (hr)								
	0.5	1	2	3	4	5	6	9	24
Oily	19.6	23.3	24.1	24.6	22.8	21.7	20.5	18.7	11.6
(S.D.) ±	(5.1)	(4.5)	(3.5)	(3.7)	(3.9)	(3.6)	(3.3)	(4.1)	(3.4)
Glycerin	25.5	28.6	24.9	22.2	19.2	16.8	15.9	11.8	3.2
(S.D.) ±	(4.2)	(5.9)	(5.5)	(4.8)	(3.3)	(3.9)	(4.2)	(3.6)	(3.1)

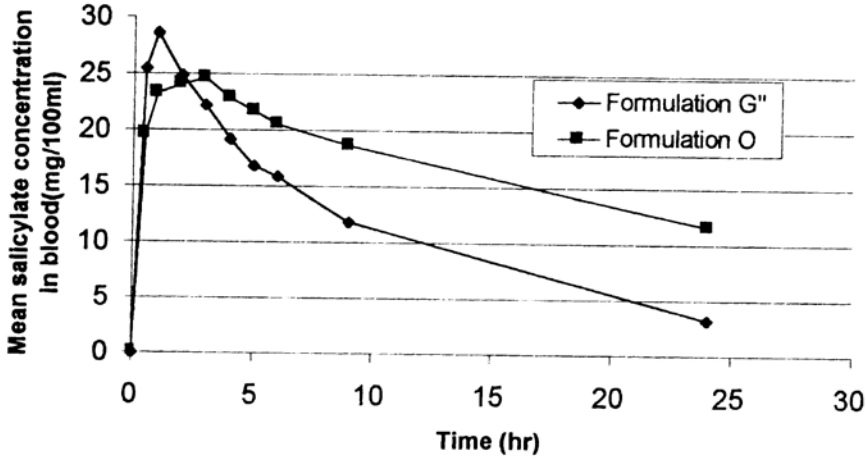
Table 3

Mean blood concentrations (mg/100 ml) in rabbits following oral administration as a single dose (120 mg/kg body weight) of sodium salicylate in two formulations (Aqueous and Glycerin). Each value is the average of 8 experiments.

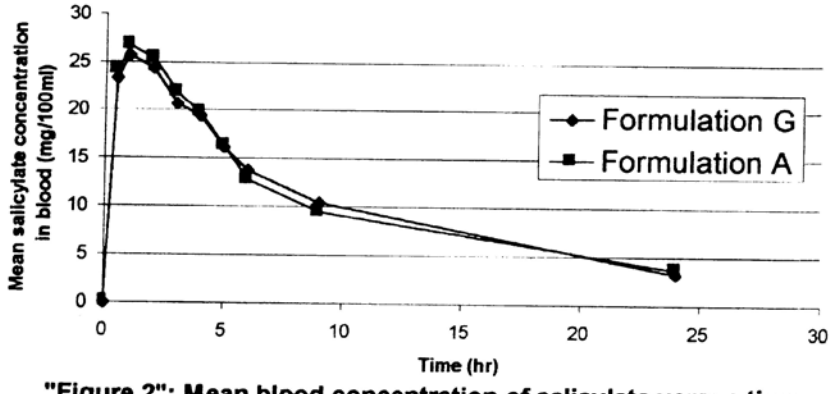
Formulation	Time (hr)								
	0.5	1	2	3	4	5	6	9	24
Glycerin	23.3	25.7	24.3	20.7	19.4	16.1	13.7	10.4	3.3
(S.D.) ±	(5.3)	(4.9)	(5.1)	(4.1)	(3.7)	(4.8)	(4.5)	(4.0)	(4.4)
Aqueous	24.2	26.7	25.4	21.9	19.7	16.2	12.8	9.4	3.7
(S.D.) ±	(5.6)	(4.8)	(4.1)	(5.1)	(4.7)	(3.2)	(4.9)	(4.2)	(4.0)

Plots of the mean salicylate concentration versus time for the three formulations are given in Figs. 1 and 2 for studies 1 and 2 respectively. The val-

ues of the three bioavailability parameters together with the results of an analysis of variance are given in Tables 4 and 5 for studies 1 and 2 respectively.



" Figure 1":Mean blood concentration of salicylate versus time after oral administration of sodium salicylate in Glycerin (G) and Oily (O) formulations to eight rabbits



"Figure 2": Mean blood concentration of salicylate versus time after oral administration of sodium salicylate in glycerin(G) and aqueous (A) formulations to 8 rabbits.

Discussion

The results given in table 4 (study 1) indicate that a statistically significant delay occurred ($p< 0.05$) in the attainment of the peak blood concentration following oral administration of the oily formulation when compared

Table 4

Bioavailability parameters obtained following oral administration of oily(O)and glycerin (G) formulations of sodium salicylate to rabbits.

Rabbit No.	Peak Conc. (mg/100ml)		Peak Time (hr)		AUC_{0-24} (mg.hr/100ml)	
	O	G	O	G	O	G
1	27.8	24.9	1	2	422.0	334.7
2	22.3	29.4	4	0.5	448.7	206.3
3	28.9	30.5	3	1	426.8	321.2
4	30.5	35.9	2	1	397.	258.8
5	21.7	35.8	2	2	391.0	360.7
6	23.2	26.5	4	0.5	422.8	242.7
7	24.4	23.7	2	0.5	452.2	235.3
8	23.4	19.6	3	1	391.6	266.7
Mean	25.3	28.3	2.6	1.1	419	281.7
	No significant difference		*Significant difference*		*Significant difference*	
	($p > 0.05$)		*($p < 0.05$)*		*($p < 0.05$)*	

with that of the glycerin formulation. This difference in PT values is interpreted as an indicaton that the rate of bioavailability of salicylate from oily formulation is reduced in comparison with that from glycerin formulation. However, although the difference between the mean PC values shown in Tables 4 and 6 is not statistically significant the trend towards a lower value for the oily formulation is in keeping with such interpretation (Fig 1).

Possible explanation for these findings may be ascribed mainly to the fact that oils delay GER [18-22] while glycerin has no effect on GER [23]. This explanation is supported when considering study 2. In this study, glycerin and aqueous formulations were compared. Both vehicles having no effect on

GER. The results indicated that there was no statistically significant difference ($p > 0.05$) in the rate of absorption (Tables 5 and 6).

Table 5

Bioavailability parameters obtained following oral administration of glycerin (G) and aqueous (A) formulations of sodium salicylate to rabbits.

Rabbit No.	Peak Concn. (mg/100 ml)		Peak Time (hr)		AUC_{0-24} (mg.hr/100ml)	
	G	A	G	A	G	A
1	27.2	31.9	1	0.5	335.9	251.2
2	27.5	30.9	2	2	251.1	313.4
3	24.8	27.0	1	2	220.9	284.9
4	25.5	28.9	1	1	233.5	259.0
5	30.9	30.9	1	1	291.2	284.9
6	26.5	29.9	2	2	252.2	248.3
7	30.0	24.3	1	1	315.9	231.6
8	22.0	29.5	0.5	0.5	248.1	163.4
Mean	26.9	29.1	1.2	1.3	256.1	254.6
	No significant		*No significant*		*No significant*	

Table 6

Mean values of peak time (PT), peak concentrations (PC) and the area under the curve(AUC_{0-24}) after oral administration of sodium salicylate in different formulations in a two way cross-over design in 8 rabbits.

Mean values	Formulation			
	O	G	G	A
PT (hr)	2.6	1.1	1.2	1.3
PC (mg/100ml)	25.3	28.3	26.9	29.1
Auc_{0-24} (mg.hr/100ml)	419.0	281.7	256.1	254.6

- *Any two means not underscored by the same line are significantly different ($p<0.05$).*
- *Any two means underscored by the same line are not significantly different ($p>0.05$).*

Delay in the GER 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 [28] and even if the drug is ionized in the intestine and non-ionized in the stomach [29]. It has been recognized that acceleration of gastric emptying can increase the rate of aspirin absorption [30,31] Propantheline delayed gastric emptying and markedly slowed the absorption of paracetamol in 6 convalescent hospital patients. Conversely, the absorption of paracetamol in 5 healthy volunteers was accelerated by metoclopramide, a drug which stimulates gastric emptying [3,4, 6] .Peak plasma concentration of paracetamol occurred late and was lower in patients with delay gastric emptying because of the fatty meals [32]. Oily formulation reduced significantly the rate of salicylate absorption when compared with aqueous formulation [16]. All of these findings are in agreement with the present results.

AUC0-24 values obtained using the 3 formulations differed depending on the type of vehicle used, Tables 4 and 5. AUCs obtained in study 2 (aqueous and glycerin formulations) are not statistically significantly different, Tables 5 and 6. Both vehicles have no effect on GER. AUCs obtained, when comparison was made between oily and glycerin formulations (study 1), indicated that there is a statistically significant increase in the extent of salicylate absorption from oily formulation, (Tables 4 and 6). Alhamami and Richards (1983) [16] reported that oily formulation gave a lower rate of absorption and a greater extent of absorption of salicylate than aqueous formulation. This indicates that the delaying effect of the oil on GER plays a significant role in the estimation of the rate and extent of absorption of salicylates.

Although salicylates are absorbed mainly from the small intestine under normal condition, appreciable gastric absorption of aspirin and salicylate has been reported [2,33]. 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 dissolution to occur before transfer into the intestine.

If delay in GER significantly incrased the extent of absorption, it follows, therefore, that acceleration in GER should lead to reduction in the extent of absorption of drugs. In fact, this is the case with the work reported by Ali and Farouk (1980) [5]. They found that acceleration in the GER caused by Sudanese diet reduced the extent of ampicillin absorption. Consequently, one would expect that the drug is maximally absorbed if sufficient time is given for drug to be absorbed (long residence time at the site of absorption). The present study is in good agreement with these findings. However, the delaying effect of the oil on the rate of stomach emptying could be (i) physiological effect, (ii) viscosity of the oily vehicle or (iii) both effects.

This study suggested that the delaying effect of the oil on GER predominates and masks the effect of the viscosity. The viscosity of the vehicles used plays no significant role in the results obtained. This suggestion is supported by the fact that there was no significant difference in the rate and extend of salicylate absorption when comparison was made between glycerin and aqueous formulations, study 2 (Tables 5 and 6) in spite of the fact that glycerin is much more viscous than water but both vehicles have no effect on GER. Further evidence was shown when considering study 1. A statistically significant delay in the rate and increase in the extent of salicylate absorption were shown when administrated in oily formulation compared with the glycerin formulation, Tables 4 and 6, bearing in mind that glycerin is more viscous than oil but without effect on GER [23]. In a recent study, probantheline (a drug which delays GER) administrated 15 minutes prior to administration of vehicles having no effect on GER (glycerin and distilled water) and compared with oily vehicle (delays GER). There was no signifi-

cant difference ($p > 0.05$) in the rate and extent of salicylate absorption between these three formulations of sodium salicylate (unpublished data).

If oil do provide a means of reducing the rate of salicylate absorption whilst enhancing the extent of absorption, thus such formulation may be of value 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.

References

1. Christiansen, J., Rehfeld J.F. and stadil F. (1976). Scand .J. Gastroent.11, 673-676.
2. Truitt, E.B. and Morgan A.M. (1964).J. Pharm. Sci., 53, 129-134.
3. Nimmo, J.(1973). Postgrad. Med.J., 49(suppl.), 25-28.
4. Nimmo,J.,Heading ,R.C.,Tothill, p. and prescott, L.F.(1973). British Med.J.,1,587-589.
5. Ali, H.M. and Farouk ,A.M. (1980). Int. J. Pharm .,6, 301 - 306.
6. Aronson,J.K. (1992) .Medicine International , Brodie, M. J., chap.Ed., Medicine group (Journal) Ltd. Pub., London, 101, 4221-4228.
7. Perucca, E. (1992). Ibid .101,4229.
8. Waller, D. and Renwick, A. (1994) in principles of Medical Pharmacology, Bailliere Tindal Pub., London, Chapter 2.
9. Shargel , L. and Andrew, B.C.YU.(1999) " Applied Biopharmaceutics and Pharmacokinetics,4 th ed., Appleton and Lange, stamford, connecticut, chpter 5, p114-115.,
10. Martimarvola, Jussipirjola and Ansahuikari, (1979) Int. J. Pharm. 3,I3-22.
11. Levy, G.,(1976).J. Invest. Dermatol. 67,667-668.
12. Crounse,R.G., (1961). J.Invest. Dermatol., 37, 529-533.
13. Carrigan, P.J. and Bates, T.R. (1973) . j. Pharm. Sci., 62,1476-1279.
14. Bloedow, D.C. and Hayton, W.L. (1976) Ibid 65, 328-334.
15. Chakrabarti, S. and Belpaire, F.M. (1978).J. Pharm. Pharmacol., 30, 330- 331.
16. Alhamami, O.M.O. and Richards, J.H. (1983) Pharm. Acta. Helv., 58, 237-240.
17. Alhamami, O.M.O and Richards, J.H. (1996). Pharm Acta. Helv. 71, 297-303.
18. Card, W.I.(1941) Amer.J. Digest. Dis. , 8,47-53.
19. Quigley, J.P., Werle, J.,ligon, E.W.Jr., Read,M.R.,Radzow,K.M.and Meschan,I. (1941).Amer.J. Physiol., 134, 132-140.
20. Hunt , J.N. and Knox, M.T. (1968). J. Physiol. 194, 327-336.
21. Borgstrom, S. and Arborelius, H. Jr. (1975). Scand. J. Gastronet., 10,599-601.
22. Yamahira, Y., Noguchi, T., Takenaka, H. and Maeda, T, (1978) J. Pharm. Dyn. 1, 160-167.
23. Robert, W.M. (1931). Quart. J. Med., 24, 133-152.
24. Lessel, B. and Cliffe, E. (1964). Nature , 203, 304-305.
25. Wagner, J.G.(1971) Biopharmaceutics and relevant pharmacokinetics", Drug Intell. Pub., Illinois, Chapter 5.

26. Trinder, P. (1954). Biochem.J., 57, 301-303.
27. Notari, R.E.(1980) " Biopharmaceutics and clinical Pharmacokinetics, an introduction", 3rd .ed., Marcel Dekker Inc., New York, P. 86-87.
28. Levy, G. (1961) .J.Pharm .Sci. 50, 388-392.
29. Benet, L.Z. (1973). Biopharmaceutics as Basis for the Design of Drug products in "Drug Design " vol. Iv, Ariens, E.J., Ed., Academic Press, London, Chapter 1, P.26.
30. Lolli, G. and Smith, R. (1964). New Engl. J. Med., 235, 80-84.
31. Sleight, p. (1960). 1,305-307.
32. Heading,R.C. Nimmo,J., Prescott, L.F. and Tothill, P. (1973). Br.J. Pharmc . 47, 415-421.
33. Nayak, R.K. and Benet, L.Z. (1974). J. Pharmacoki. Biopharm., 2, 417-431.