Effects of Type of Vehicles on The Dissolution Rate of A poorly Soluble Drug : Nitrofurantoin

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تأثيرات نوع المحاليل (المواد السوارية) على معدل ذوبان الأدوية القليلة الذوبان: نايتروفيورانتين

الخلاصة

تم بحث معدل سرعة تحرير النايتروفيورانتين من معلقات زيتية ومائية محتوية على مواد صيدلانية مختلفة. استخدمت في هذا البحث طريقة ال فلاسك ستيرر. تم تقليص مدة تعرض محاليل النايتروفيورانتين الى الضوء قدر الممكن. لقد اعتبر الوقت اللازم لظهور ٥٠% من الدواء واذابته في المحلول، احتسب ذلك من الرسوم البيانية الفردية لمعدل تحرير الدواء لكل صيغة دوائية، كأداة لمعدل تحرير النايتروفيورانتين. دلّت النتائج بأن تحرير النايتروفيورانتين من المحاليل المائية هو اسرع وبدلالة احصائية مقارنة مع المحاليل (الصيغ) الزيتية المختلفة. نسق معقد لتحرير النايتروفيورانتين قد ظهر من المحاليل الزيتية المختلفة معتمدا على لزوجة المحلول كسبب و \ او على وجود السكروز او كاب او سيل كسبب اخر. الأسباب الممكنة لهذه الأختلافات مع التأكيد على الكاب او سيل او نزعة السكروز لتكوين الفقاعات في المحاليل الزيتية وطول عمر هذه الفقاعات قد نوقشت.

Abstract:

The dissolution rate of nitrofurantoin from different aqueous and oily suspensions containing different pharmaceutical excipients was investigated. Flask-stirrer method was used. The exposure of nitrofurantoin solutions (standard solutions and the solution in the dissolution flask, to light was minimized as far as possible. The time required for 50% of the drug to appear in solution, i.e $t_{50\%}$, calculated from individual dissolution rate curves for each formulation, was used as an index of the dissolution rate of nitrofurantoin. The results showed that significantly rapid release of nitrofurantoin ($P<0.01$) from aqueous vehicles compared with different oily vehicles (formulations). A complex pattern of release of nitrofurantoin was shown from the different oily formulations depending partly on the viscosity of the vehicle and/or partly on the presence of sucrose or Cab-o-sil. Possible reasons for these differences are discussed with particular reference to the Cab-o-sil or globules forming tendencies of sucrose containing oily formulations and the life times of these globules.

Keywords: Nitrofurantoin, Fractionated coconut oil (FCO), Oily formulation, Release rate, Dissolution rate.

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Introduction

For poorly soluble drugs, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. Therefore, the solubility and dissolution behavior of a drug are key determinant of its oral bioavailability. There have been numerous efforts to improve drug dissolution rate. These include, (a) solubilization in surfactant systems; (b) reducing particle size to increase surface area, thus increasing dissolution rate of drug; (c) use of pro-drug and drug derivatization such as a strong electrolyte salt forms that usually have higher dissolution rate; (d) formation of water-soluble complexes; (e) manipulation of solid state of drug substance to improve drug dissolution i.e. decreasing crystallinity of drug substance through formation of solid solutions; (f) use of different vehicles having a physicochemical and may have a physiological effects on the gastric emptying rate (GER) which consequently affect the rate and extent of drug absorption in vivo. It has been found that oil significantly affect the rate and extent of in vivo absorption of ampicillin (1); salicylates (2-4).

Nitrofurantoin, exhibits poor solubility (5). This undesirable physical property may increase the incidence of irritating side effects on the gastrointestinal tract because of a prolonged contact time with the mucosa. The use of oily suspension of nitrofurantoin might provide a layer that can protect the gastric mucosa from the irritant effect of this drug. Furthermore, this type of vehicle might have an effect on the absorption profile of nitrofurantoin by virtue of its physiological effect on GER and intestinal motility (6).

The aim of the present work was to study the effects of oil on the in vitro release of nitrofurantoin from oily suspensions in an attempt to detect the possible effect of oil on its dissolution rate which may, consequently, affect the in vivo bioavailability of nitrofurantoin. The effects of the different pharmaceutical additives, which are involved in the oily vehicles patented by Stephens and Su (7) and Lin and Pramoda (8) on the release characteristics of nitrofurantoin were also investigate

Materials And Methods Materials:

Nitrofurantoin was obtained from Sigma Chemical Co., (England). Colloidal silica (Cab-o-sil) and lecithin 90% (refined grade) were obtained from BDH Chemicals (Leicester, England). Fractionated coconut oil (FCO) was obtained from Alembic Products Ltd. (Chester, England). Aluminium mono and distearates were obtained from Witco Chemical Ltd (USA) and hydrogenated castor oil was obtained from Akzo Chemie UK Ltd. Sucrose (Icing sugar) was obtained from the British Sugar Corporation Ltd (UK). Xanthan gum (Keeltrol-food grade) was obtained from Kelco Co. (USA).

Preparation of the suspensions:

Nitrofurantoin was sieved and the 240/300 portion (53.63 µm) was used to prepare 0.1% w/v suspensions in the following 8 vehicles (formulations) which are presented by the letters A-H.

A = Fractionated Coconut oil (FCO)

B = 20% w/v sucrose in FCO

C = 0.25% w/v xanthan gum in distilled water

D = 0.25% w/v xanthan gum + 20% w/v sucrose in distilled water

E = 1% w/v Cab –o sil in FCO

F = 0.5% w/v aluminium stearate (50:50 mixture of mono and distearate + 0.7% w/v lecithin + 0.35% w/v hydrogenated castor oil + 20% w/v sucrose in FCO

G = 20% w/v sucrose + 0.3% w/v Cab-o-sil in FCO

H = 20% w/v sucrose + 1% w/v Cab-o-sil in FCO

Xanthan gum was used in the aqueous vehicles (C and D) to prevent flocculation of nitrofurantoin. A low concentration (0.25%) was used in order to avoid a high viscosity relative to that of the oily suspension (A). These suspensions were placed in flasks, which were covered by aluminium foil to provide protection from light and left overnight at room temperature. On the following morning they were shaken before removal of the required volume into a syringe.

Spectrophotometric Analysis:

The spectrophotometric analysis of all nitrofurantoin samples were performed at 369 nm (Unicam SP 500 spectrophotometer). Standard curves were constructed by serially diluting of an aqueous stock solution of the drug in 0.1 mole/L HCL to obtain concentrations in the range of 0.1 – 1 mg/100 ml. Each sample was analyzed in triplicate.

Determination of apparent partition coefficient and solubility:

Fifty milliliters of solution containing 1 mg of nitrofurantoin in 100 ml of 0.1 mole/L HCL was equilibrated with 50 ml of FCO for 24 hr in a 250 ml glass-stopped conical flask kept at 37^0c in a shaking water bath and agitated at 100 oscillation per minute. The drug concentrations in the HCL were assayed spectrophotometrically at 369 nm. Preliminary studies showed that equilibrium was attained within 5 hr. The experiment was carried out in the dark. The apparent partition coefficient of nitrofurantoin was calculated by means of the following equation:

$$\text{Apparent partition coefficient} = \frac{C_1 - C_2}{C_2} \quad (1)$$

Where C_1 is the original concentration of the drug in the HCL and C_2 is the equilibrium concentration in the HCL.

The solubility studies of nitrofurantoin in both 0.1 mole/L HCL and FCO were carried out as follows. An excess amount of nitrofurantoin was added to 100 ml of the particular solvent and kept at 37^0C for a week with occasional shaking. Samples were taken periodically from the supernatant solution to predict the equilibrium solubility, filtered through a 0.45 Millipore filter and then diluted to an appropriate extent with the particular solvent. The concentration of the drug (solubility) was assayed spectrophotometrically and calculated from the previously made calibration curves in the HCL and FCO at 369 nm and 363 nm, respectively. Equilibrium solubility was attained in 3 days in all cases. The experiment was carried out in the dark.

Dissolution studies:

Flask – stirrer method was used based on the apparatus described and used by Berzegar-Jalali and Richards (9). A 2 L wide-mouth, round-bottomed flask, with a lid comprising of four side necks and one central neck, was placed in a water-bath maintained at 37 ± 0.1^0C. A 2 bladed, 8.1 cm diameter glass stirrer was placed through the central neck and located in a standard position relative to the bottom of the flask, i.e 5 cm from the bottom of the flask, and connected to an electric motor (Citenco Ltd.), which rotated the stirrer in a counter-clockwise direction at a speed of 60 ± 2 rpm. A suitable thermometer ($0\text{-}50^0$C) and a plastic cannula for sampling were placed at a constant height, angle and position into the dissolution medium through the side necks. The other side neck was used to introduce the dissolution medium (1480 ml of 0.1 mole/L HCL solution) and sample suspension. A diagram of the apparatus is shown in Fig.1.

Fig 1

While the stirrer was in motion 10 ml of an overnight aged suspensions were injected through the side neck from a 10 ml graduated syringe. The latter was washed out with 10 ml of 0.1 mole/L HCL and the washings were also added to the flask. Using 10 ml of a 0.1% w/v nitrofurantoin suspension in 1490 ml of dissolution medium provided sink conditions for the drug, because its solubility in 0.1 mole/L HCL at 37^0C is 15.59 mg/100 ml (see the results section).

Exposure of the nitrofurantoin solution, i.e the standard solutions and the solution in the dissolution flask, to light was minimized as far as possible by wrapping the containers with aluminium foil or with black plastic film. Samples of the dissolution medium were obtained at various times (Table1). The absorbance of each solution at 369 nm was determined using 0.1 mole/L HCL as the reference solution.

Results

The solubilities of nitrofurantoin in 0.1 mole/L HCl and FCO are 15.59(±3.2) and 4.47 (±1.7) mg/100 ml, respectively. The partition coefficient of the drug between the oil and HCL is 0.48(±.0.18). The results presented are mean values of three determinations with S.D in parenthesis. Table 1 shows the mean percentages of nitrofurantoin dissolved at different times in the flask-stirrer method for each formulation. Plots of these percentages against sampling times, to give the dissolution rate curves for each formulation, is given in Fig 2.

Table 1

Fig 2

The time required for 50% of nitrofurantoin to appear in solution ($t_{50\%}$) was calculated from the individual dissolution rate curves for each formulation were used as indices for estimation of the dissolution rate. The $t_{50\%}$ values are given in Table 2, which also contains the apparent viscosities of the different formulations (10).

Table 2

Analysis of variance and Duncan`s test were carried out(11) to distinguish the significance or otherwise of the differences between the mean $t_{50\%}$ values. The results are summarized below:

Mean values of $t_{50\%}$ in rank order

1% level	D	C	A	B	G	E	H	F
5% level	D	C	A	B	G	E	H	F

Any two means not underlined by the same line are significantly different ($p< 0.05$ or $p< 0.01$) and any two means underlined by the same line are not significantly different.

A cumulative correction to account for the previously removed samples was not made when determining the percentage of drug released, since corrected and uncorrected values are approximately equal after 7 samples are removed. Equation 2, which was described by Bates et al (12), was used to calculate the corrected values.

$$C_n = C_{n,meas.} + \frac{5}{1500} \sum_{s=1}^{n-1} (C_{s,meas.}) \quad (2)$$

Where $C_{n,\,meas.}$ denotes the spectrophotometrically measured concentration (expressed as % in this case), C_n is the concentration (% in this case) of the n^{th} sampling expected in the dissolution medium if the previous samples had not been removed and $\sum_{s=1}^{n-1} (C_{s,meas.})$ is the sum of concentrations (% in this case) measured spectrophotometrically from sample 1 to (n-1) sample.

Table 1: Percentage nitrofurantoin dissolved at various times from different formulations using the flask-stirrer method. Each value is represented as mean ± SD from three experiments.

Time (min)	Formulation A	B	C	D	E	F	G	H
5	20.0±1.9	21.8±5.8	79.8±0.8	80.3±1.6	11.9±3.5	5.6±1.7	12.6±2.7	11.0±3.8
10	40.5±2.1	38.7±4.7	84.2±0.5	86.2±2.5	20.5±3.5	10.4±2.4	25.9±3.7	19.3±5.1
20	68.1±2.2	51.5±3.7	86.9±0.6	88.4±3.1	31.5±5.1	16.0±4.2	46.0±3.5	29.0±6.9
30	77.1±1.8	65.4±3.3	88.6±1.3	90.1±1.8	38.5±4.8	26.5±6.6	57.2±4.6	40.0±7.8
45	82.7±2.1	74.8±3.5	90.3±3.8	90.3±3.8	49.3±3.0	39.4±7.9	66.5±4.5	46.8±5.1
60	84.2±1.4	84.1±6.7	90.1±2.6	90.1±2.6	57.2±3.1	51.2±3.4	73.9±5.5	55.9±5.4

Table 2: Apparent viscosities and $t_{50\%}$ values for different nitrofurantoin Formulations.

Formulation	$t_{50\%}$ (min)[a]	η_{app} (mN s m^{-2})[b]
A	12.3±2.3	17.5
B	17.2±4.5	51
C	2.4±1.1	33[c]
D	2.5±1.3	38[c]
E	47.3±4.1	58
F	59.9±5.1	120
G	23.5±3.9	83
H	48.4±6.4	131

a. Each value is represented as mean ± SD from three experiments.
b. η_{app}, apparent viscosity, (Alhamami et.al.,) (10).
c. Alhamami, (5).

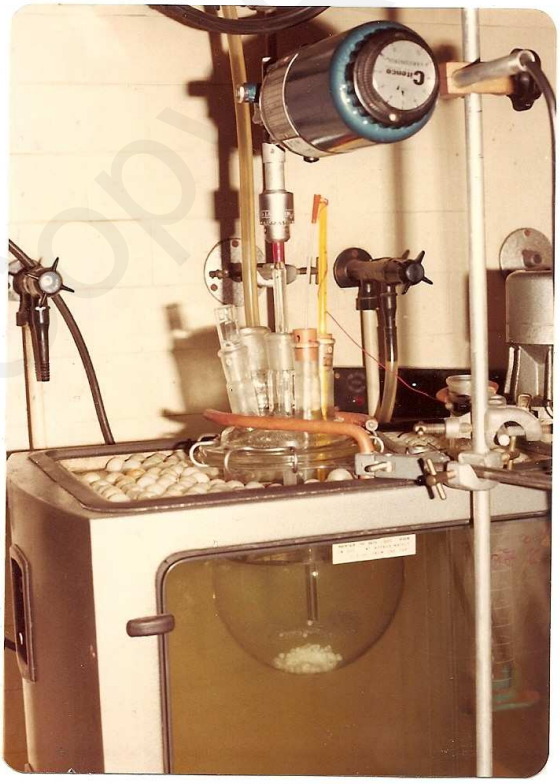

Fig. (1): Flask-stirrer apparatus used for the dissolution studies on different nitrofurantoin suspentions

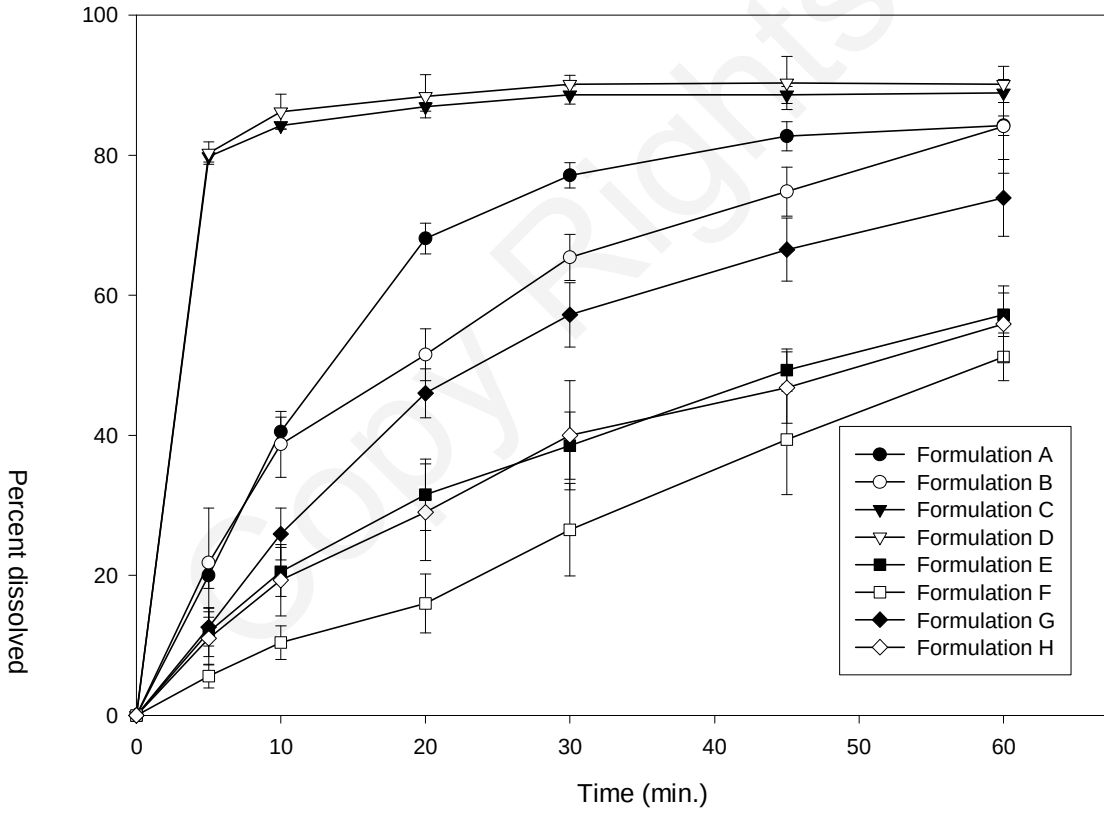

Figure 2: Percentage of nitrofurantoin dissolved vs time for different oily and aqueous suspensions.

Discission

The Results obtained by analysis of variance show that the two suspensions in aqueous vehicles C and D produced rapid release of the drug and gave very close $t_{50\%}$ values. Both vehicles contained 0.25% w/v xanthan gum but D also contained 20% w/v sucrose. The presence of sucrose therefore appeared to have little effect on the release of nitrofurantoin from the aqueous suspensions. This is to be expected because the agitation of the dissolution medium will cause rapid dispersion and dilution of the dissolved sucrose.

The release of nitrofurantoin from the oily formulations was often poorly reproducible and this poor reproducibility was probably associated with the behaviors of the vehicles when they were placed in the dissolution medium. In addition, the variety of behaviors shown by the different vehicles was considered to be a major factor that contributed to the significant differences that were detected in the $t_{50\%}$ values from some of the vehicles.

In general the main difference in behaviors depended on the presence or absence of sucrose in the formulations. Thus, the formulations that did not contain sucrose, i.e. A (FCO only) and E (1% Cab-o-sil in FCO), tended to form oily layers on the surface of the dissolution medium. Under the influence of the agitation of the aqueous medium droplets of oil could be seen to become detached from the oily layer and then coalesce with it, particularly in the case of A. The higher viscosity of the layer formed by E reduced the tendency to form these droplets and was probably responsible for the significant increase in the $t_{50\%}$ value for this formulation over that of A, $p < 0.01$. The release of nitrofurantoin from the simple suspension in FCO (A) was fairly rapid as would be expected from the low oil : 0.1 mole/L HCL partition coefficient of this drug. Because of the low reproducibility of the results, the mean $t_{50\%}$ value for this simple oily suspension did not differ statistically from the mean values for the aqueous suspensions C and D, $P > 0.05$.

In the case of sucrose containing formulations, i.e. B (20% sucrose in FCO), G (0.3% Cab-o-sil + 20% sucrose in FCO, H (1% Cab-o-sin + 20% sucrose in FCO and F (which corresponded to Stephens and Su`s patent (7), the oily vehicle tended to form a relatively large pear-shaped globules, in which the sucrose and other solid ingredients sedimented inside the globules leaving a clear oily layer at the top of the globule. The sizes of these globules ranged from approximately 1-10 mm and their overall densities caused them to fall to the bottom of the dissolution flask (Fig. 1). As the sucrose was removed from the globules by dissolution into the aqueous phase they gradually disappeared and the oil then formed a layer on the surface of the aqueous phase. The lifetimes of these globules therefore appeared to depend on the dissolution rate of sucrose, which in turn will depend on the viscosity of the oily liquid inside the globules. Thus, the lifetimes of the globules formed by B (20% sucrose in FCO) was only of the order of 5 minutes so that an oily layer was formed on the surface of the dissolution

medium in a relatively short time. The viscosity of this layer was presumably similar to that of FCO alone and the release of nitrofurantoin from formulation B would therefore be expected to be not too much slower than from a suspension in FCO alone (A). In fact, the $t_{50\%}$ value for B was about 5 min longer than that for A and the two values were not statistically different, P> 0.05.

The lifetimes of the globules produced by the remaining sucrose containing formulations fell into the order G < H < F. Formulations G and H also contain Cab-o-sil in 0.3% and 1% concentrations, respectively. The resultant higher viscosities will delay the loss of sucrose from the globules and the release of nitrofurantoin not only from the globules but also from the oily layer that is eventually produced on the surface of the dissolution medium. In fact, the globule forming tendencies of these two formulations caused by their sucrose contents do not seem to be as important as the effect produced by including 1% Cab-o-sil, because formulation E and H gave very similar $t_{50\%}$ values (Table 2).

These two formulations both contain 1% Cab-o-sil but only H contains 20% sucrose. Although the apparent viscosities of these two vehicles are markedly different (Table 2), it is likely that the viscosities of the oily layers produced by both of them will be similar when the sucrose has been removed from H. The increase in viscosity of an oily layer produced by 0.3% Cab-o-sil does not appear to be sufficient to lead to a significant decrease in the release rate of nitrofurantoin because the $t_{50\%}$value of formulation G did not differ significantly from that of B, P> 0.05).

Finally, although the apparent viscosity of formulation F, which corresponds to the patent of Stephens and Su (7), was less than that of H (Table 2) the lifetime of the globules was greater in F. This increase in globule`s lifetime appears to be responsible for the higher mean $t_{50\%}$ value for F compared to H, and the difference between these values was significant, P <0.05.

One final point concerning the aqueous suspensions of nitrofurantoin (C and D) is that the maximum amount of drug released appeared to be about 90% and this value remained constant over the last few sampling times. This may suggest that some nitrofurantoin remains in the oily vehicle but the low oil: 0.1 mole/L HCL partition coefficient does not support this suggestion. The decomposition of nitrofurantoin under the influence of light offers an alternative explanation. Such decomposition was confirmed by preliminary studies and although the dissolution experiments were carried out in the dark as far as possible, exposure to light could not be avoided completely. Thus, some decomposition of dissolved nitrofurantoin is likely to occur and may reduce the rate of apparent dissolution of the drug particularly in the latter stages when the concentration of nitrofurantoin in solution is high and when the rate of dissolution is decreasing.

Conclusion

Sucrose and Cab-o-sil are beneficial in the formulation of oily preparations. Although sucrose increased the viscosity of oily formulations, but it is unlikely to do so in vivo, because of rapid dissolution in the dissolution medium. These viscosity increasing agents could be beneficial to prepare a stable suspensions that provide a good flow properties, is highly resistant to settling and caking of suspended materials and is useful for preparing ready-to-use pharmaceutical suspensions of water-degradable physiologically active agents. Although nitrofurantoin was released at a slower rate from oily formulations, which may indicate a slower absorption in vivo, yet it could be used as a sustained release preparations. Extrapolation this study in vivo is recommended.

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