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A MATHEMATICAL MODEL FOR DRUG RELEASE FROM O/W EMULSIONS: APPLICATION TO CONTROLLED RELEASE MORPHINE EMULSIONS

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ABSTRACT

Stable morphine submicronized emulsions were prepared under optimal experimental conditions. Mean droplet size and zeta potential of the morphine emulsions ranged from 400 to 700 nm and from -50 to -70 mv respectively. In vitro release kinetic analysis indicated that the drug transfer from the oily dispersed droplets into the external aqueous phase was the rate determining step in the overall kinetic process providing the main portion of the drug was localized in the oily phase. A kinetic equation model was proposed and found suitable for the description of morphine release from the emulsion due to conformity of the experimental data to the expected kinetic data as calculated by means of this equation .

INTRODUCTION

Physostigmine which inhibits brain acetylcholinesterase was shown in both clinical and animal studies to cause a significant reversal of the respiratory depressant effect of morphine without affecting the analgesia.[1,2] However, the duration of action of physostigmine is too short and the present authors have already shown that it is possible to prolong the pharmacological activity by incorporating physostigmine into an injectable emulsion delivery system.[3,4] In view of these findings it may be possible to design a dose regime of treatment in human subjects with a combination of morphine and physostigmine (in the same delivery system) which would maintain analgesia without concomitant respiratory depression. Therefore, before such a combined formulation could be investigated, it has been decided to prepare morphine emulsions and to examine how morphine incorporation would affect the physicochemical properties of the emulsion formulation, mainly the stability and drug release kinetics. In addition, an analysis of the in vitro drug release kinetics from these submicronized emulsions as a function of various process parameters such as droplet size, oil phase ratio and initial drug concentration was carried out.

MATERIALS

Soybean oil, crude phospholipids and mannitol were purchased from Sigma Chemicals Co (St. Louis, MO, USA). Morphine base was purchased from Diosynth (Apeldoorn, Holland). The phospholipids were purified according to the method reported by Schubert and Wrethind.[5]

METHODS

1. Emulsion preparation and evaluation

The purified phospholipids and morphine were dissolved in the oil phase containing a stabilizer additive. The non-ionic

emulsifier and mannitol were dissolved in the aqueous phase. Both phases were heated separately to 70°C and dispersed by a magnetic stirrer. Emulsification was completed using a "high speed mixer" (ultraturrax) for 1 min at 85°C. The resulting fine emulsion was cooled rapidly below 20°C. A typical formulation (% w/w) consisted of morphine base 0.5, oily phase 20.0, purified phospholipids 1.0, non-ionic emulsifier 2.0, mannitol 6.0 and double distilled water to 100 g. Each emulsion batch was prepared in triplicate. The mean droplet size and zeta potential measurements were carried out using the methods previously described. [6]

2. In vitro morphine release

Determination of morphine release from various solutions and from the emulsions were carried out in an apparatus composed of two compartments separated by a Nuclepore membrane.[3] The emulsion (1 ml) was placed in the donor compartment and the sink solution (50 ml) in the receptor compartment. Both compartments were immersed in a constant-temperature water bath at 37°C. The drug released from the emulsions diffused through the membrane to the sink solution. Samples were taken at various time intervals from the sink solution the pH of which was varied from 1.5 to 8.0. These buffer solutions were prepared according to NF XIV. The concentration of morphine released was determined spectrophotometrically at 284 nm using a calibration curve based on standard solutions. The Nuclepore membrane was selected after screening various membranes in diffusion studies using morphine solution in order to prevent the membrane from acting as the rate limiting factor in the overall kinetic process. It should be noted that the various emulsions remained stable over the entire kinetic process and no oily droplets crossed the membrane. The effect of pH in the donor compartment and the agitation conditions were also studied.

3. Apparent partition coefficient determinations

A given amount of morphine was dissolved in 2 g of the oily phase either with or without the purified phospholipids. This phase was kept in contact without agitation with 8 g of an aqueous phase having the same composition as in the emulsion but at various pH conditions. At different time intervals over a period of 48 hours, samples were taken from the aqueous phases and morphine concentrations were measured spectrophotometrically as previously described till an equilibrium was established between the phases. The apparent partition coefficient was then calculated according to the equation $P = C_o/C_w$ where C_o and C_w are the equilibrium concentrations of morphine in the oily and aqueous phases respectively.

4. Stability studies

Long-term stability studies were conducted at 4°C and 20°C. The chemical and physical changes that might occur in the emulsion during the storage were followed up by visual observations (phase separation, creaming, etc.). The emulsion samples were stored in 10 ml, stoppered, graduated measuring cylinders and the degrees of creaming and of separation of the oily phase were assessed at given time intervals.

RESULTS AND DISCUSSION

In the current study, the experience gained during the previous investigation [3,6] on physostigmine emulsion was exploited. Morphine base was incorporated into a modified emulsion vehicle which remained stable for more than forty weeks storage when prepared under optimal experimental conditions. Mean droplet size and zeta potential of the morphine emulsions ranged from 400 to 700 nm and from -50 to -70 mv respectively. These values indicated that morphine incorporation did not affect the physicochemical properties of the stabilized emulsion. The low values of the mean

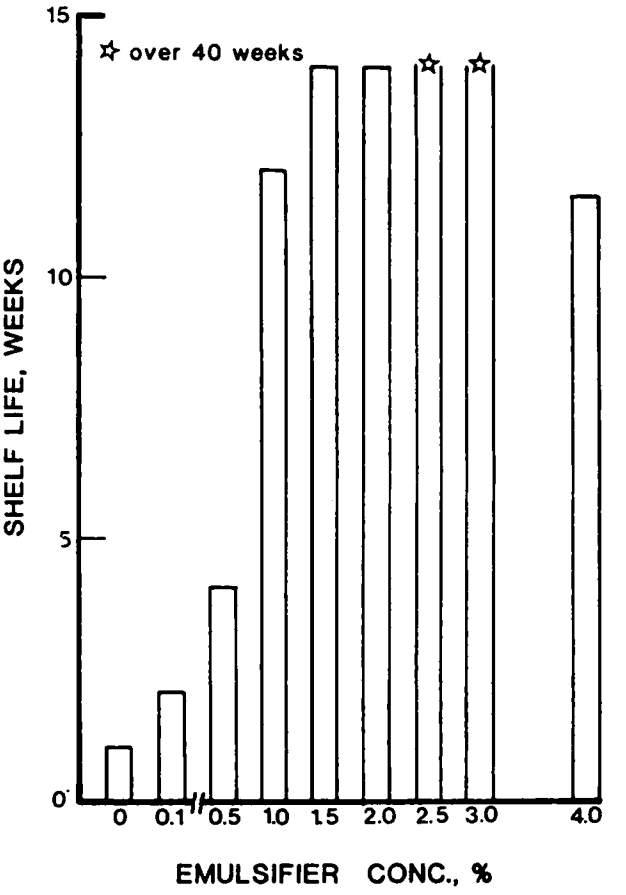

Fig. 1 - EFFECT OF EMULSIFIER CONCENTRATION ON MORPHINE EMULSION STABILITY

droplet size reflected the formation of a close- packed mixed film of both emulsifying agents at the oil-water interface. It should be noted that the resulting zeta potential values were high enough to prevent coalescence of the droplets and preserved the integrity of the emulsions formed. This was also confirmed by the results obtained during the long-term stability studies conducted on the morphine emulsion (Fig. 1).

It can be seen from Fig. 1 that at room temperature, shelf-life of the emulsion was dependent on non-ionic emulsifier concentration and at least 2% of the emulsifier was needed to maintain emulsion stability over 40 weeks storage. Similar behaviour was also observed at 4°C storage. These findings conformed with previous results reported on physostigmine emulsion.[6] It should be emphasized that emulsifier concentration over 3% decreased the shelf-life of the emulsion.

Drug partition analysis between aqueous and oily phases

An accurate analysis of in vitro drug release from emulsions requires first, a knowledge of the distribution of the drug in the various phases of the emulsion delivery system. Usually the aqueous continuous phase contains micelles or "a micellar phase". Therefore, at equilibrium, drug could be distributed or partitioned among the various phases (the oily dispersed droplets, the micelles and the continuous aqueous phase). The extent of partition of the drug between the various phases and the nature of the interdependence of the parameters would influence the release of the drug from the emulsion.

In preliminary kinetic studies, the rate of morphine release or permeation through the membrane from various non-ionic emulsifier concentrations was studied. Neither positive nor negative effect was observed, indicating that the presence of morphine in micelles did not affect the rate of transport of the drug through the membrane to the sink solution. Therefore, morphine partition extent was determined between the lipophilic and hydrophilic phases of the emulsion only.

As expected, decreasing the pH of the aqueous phase favoured the formation of a water soluble protonated morphine salt and decreased the apparent partition coefficient (Fig. 2). Whereas,

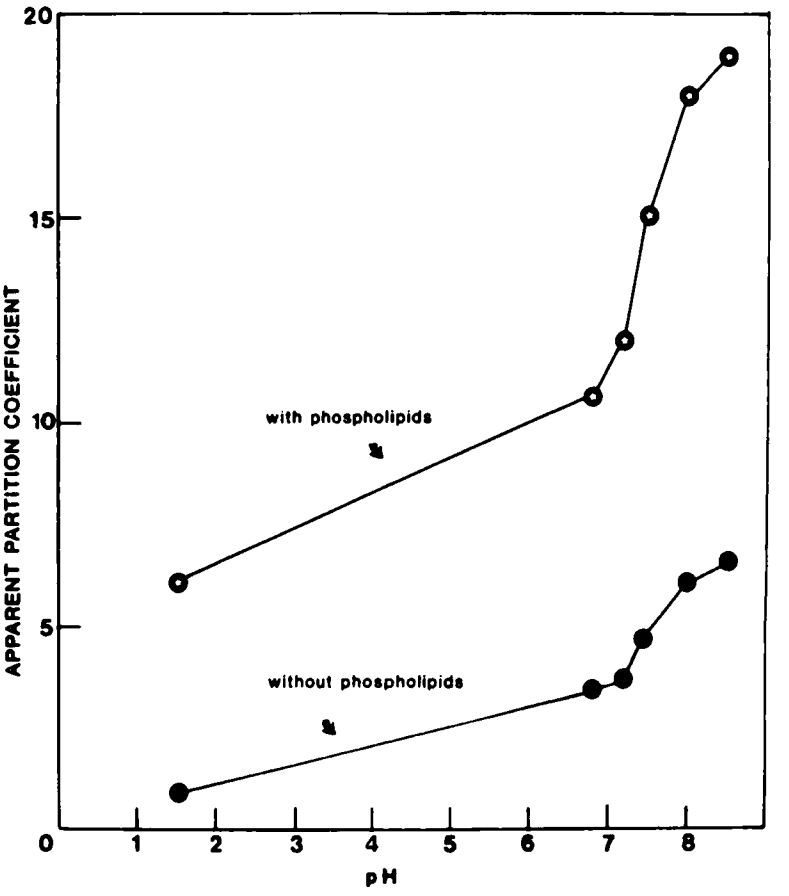

Fig.2-EFFECT OF pH ON MORPHINE PARTITION BETWEEN AQUEOUS AND OILY PHASE

increasing the pH above 7 promoted the formation of the oily soluble morphine base and increased the apparent partition coefficient indicating that the morphine base was more localized in the oily phase than in the aqueous phase similar in composition to the phases of the emulsion. Furthermore, the presence of purified phospholipids in the oily phase augmented the solubility of morphine especially in the alkali pH range and increased significantly the apparent partition coefficient (Fig. 2).

Drug release kinetic evaluation from emulsion

The pH of the solution in the donor compartment did not influence the transfer rate of morphine which was mainly affected by the pH of the sink solution. It appears that as a result of free diffusion of the buffer ions between the compartments, the pH of the overall kinetic process is mainly determined by the pH of the receptor compartment due to its large capacity (50 mL). Increasing the pH of the sink solution in the receptor compartment decreased the permeation rate of morphine through the Nuclepore membrane. In any case, under sink conditions, the permeation of morphine through the membrane was rapid and the entire process was completed in 1 hour as shown in Fig. 3. The kinetic results presented in Fig. 3 indicated that the in vitro release of morphine from the emulsion was prolonged compared with that from any buffer aqueous solution. Furthermore, the reduction in release rate of morphine from the emulsion with increasing pH of the sink solution was attributed to the difference in solubility of morphine in the various pH sink solutions which affected the partition rate of morphine between the oily dispersed droplets and the continuous aqueous phase in the donor compartment confirming the previous results reported in Fig. 2. The increase of the permeation rate of morphine from the donor compartment to the receptor compartment will be compensated by an increase in the release of morphine from the internal oil phase to the external aqueous phase until a new equilibrium is reached as observed in Fig. 3.

The increase in oily phase volume ratio of the emulsion reduced significantly the morphine release (Fig. 4). This was attributed to the retention capacity of the dispersed oily droplets, the larger amount of which was able to sustain the morphine release over longer periods of time. Since diffusion through the membrane was shown to be the fastest step, these results indicated that the drug transfer from the oily dispersed

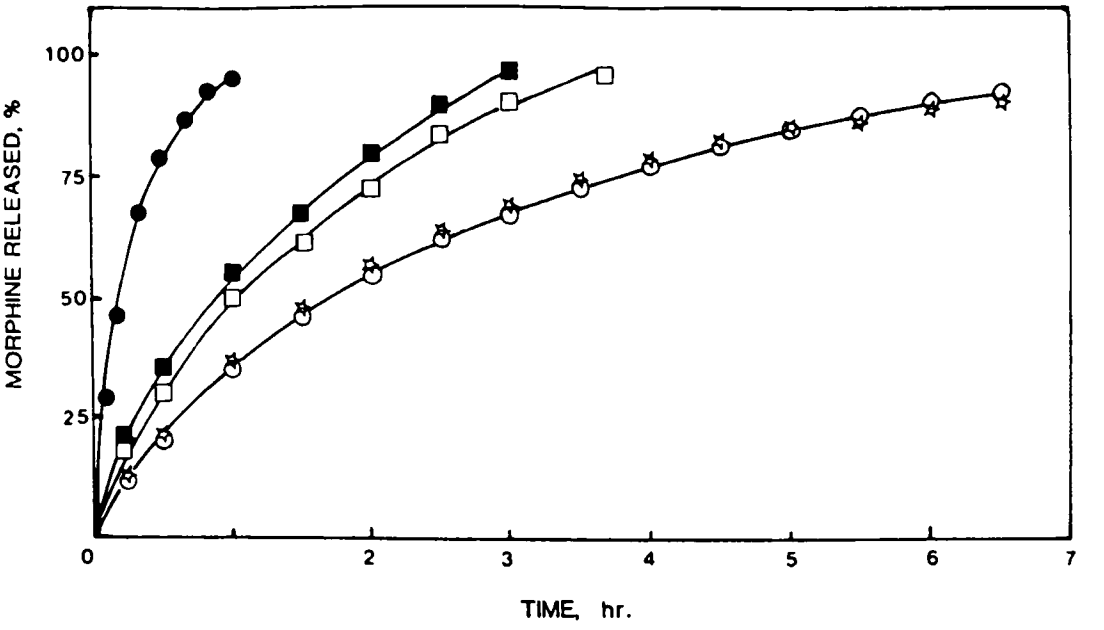

Fig.3-MORPHINE RELEASE PROFILE FROM BUFFER SOL.(●); AND 20% OILY PHASE EMULSIONS INTO PERFECT SINKS OF DIFFERENT pH BUFFERS: 1.5(■); 5.0(□);7.4(○);8.0(☆)

droplets into the external aqueous phase was then the rate-determining step in the overall kinetic process provided the major part of the drug was localized in the oily phase. This was also confirmed by other observations which showed that morphine release rate was decreased with increasing mean droplet size as a result of decreased contact area between the internal and external phases of the emulsion (Fig. 5). Similar kinetic behaviour was observed by other authors.[7]

Drug release kinetic model

The current kinetic model proposed is based on previous reports which examined either the release of a drug from a delivery form enclosed in a small membrane-enveloped compartment[8]

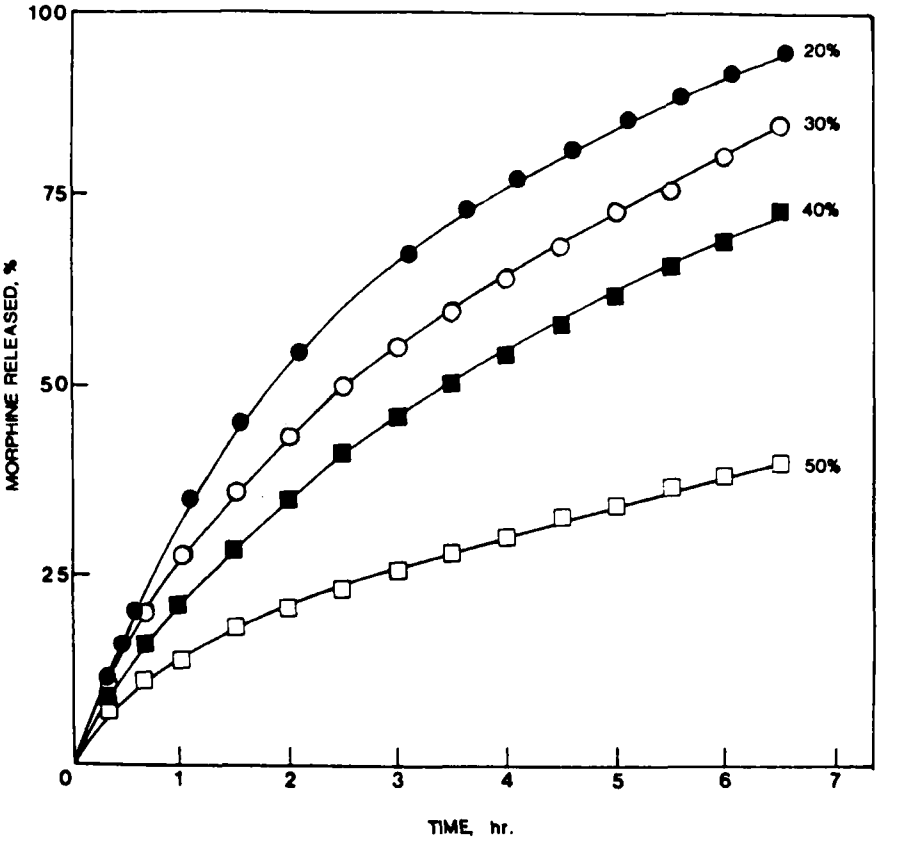

Fig.4-EFFECT OF THE OILY PHASE VOLUME RATIO ON MORPHINE RELEASE PROFILE FROM EMULSIONS

or the release of a drug from a two phase system to a perfect sink.[9] In the former model the initial concentration of the drug in the donor compartment is zero and in the latter model the external aqueous phase is in direct contact with the sink solution. Both models could not meet the initial conditions of the present model. Therefore, the mathematical drug release model applied for the first time to drug release evaluation from an emulsion is presented schematically in Fig. 6. This kinetic model deals with biphasic systems in which drug may be dissolved or partitioned between the lipophilic and hydrophilic phases of the

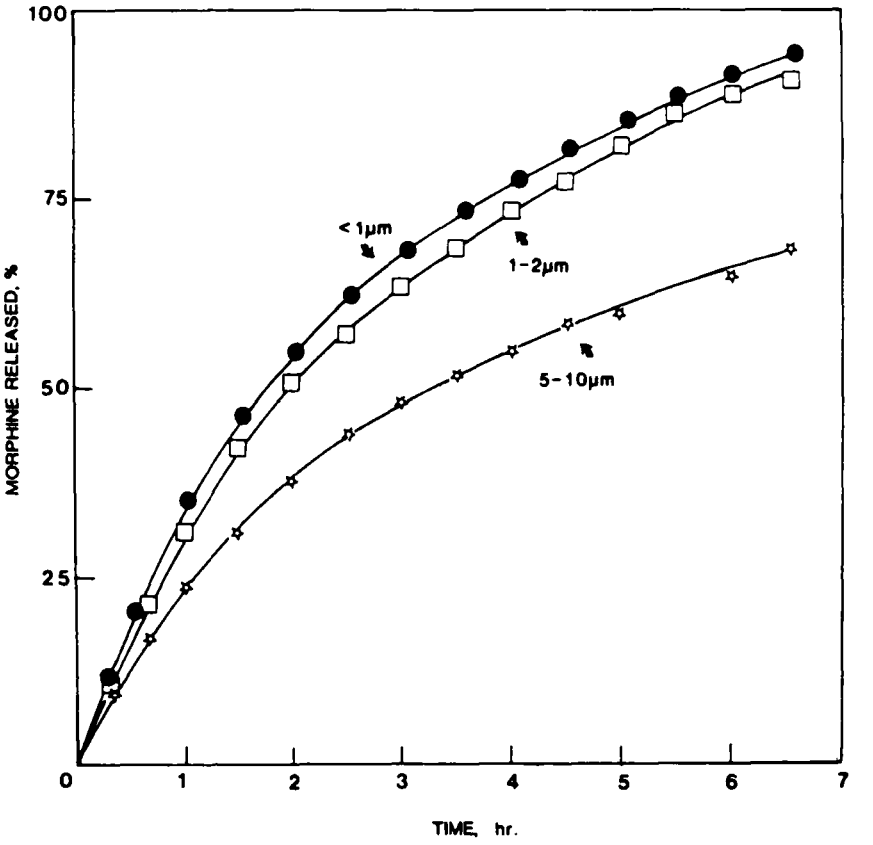

Fig.5- EFFECT OF DROPLET SIZE RANGE ON MORPHINE RELEASE PROFILE FROM EMULSION

emulsion but separated from the sink solution by a membrane which is not the rate-limiting step in the overall process. Drug diffusion through the membrane obeys first Fick's law.

The following assumptions were made: the drug is the only diffusing compound, the dispersed tiny droplets do not disintegrate or coalesce during the entire process and drug partition between the internal and external phase in the emulsion is a first-order single-step phenomenon.

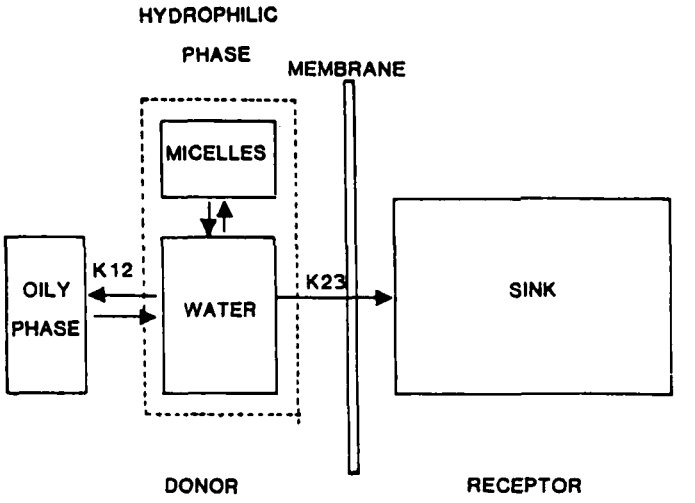

Fig.6-SCHEMATIC REPRESENTATION OF DRUG RELEASE THROUGH MEMBRANE FROM AN EMULSION

The drug is exchanged between three model compartments: (a) the oily dispersed droplets; (b) the aqueous phase; and (c) the sink solution where sampling is performed.

Drug dissolved in external aqueous phase easily diffuses through the membrane to the sink solution. Drug diffusion through the membrane obeys first Fick's law. Eventually the aqueous phase becomes diluted and this drug loss is almost compensated by transfer of morphine from the internal oily phase to the hydrophilic phase, so that a steep concentration gradient is maintained between the external aqueous phase and the sink solution. This implies that the major part of the released drug is supplied by direct delivery from the internal dispersed oily phase; the latter process therefore controlled the overall kinetic pattern. It was observed that two main processes took place: "net outward partition" (i.e. net drug transfer from the internal to

the external phase) and diffusion of the drug from the external phase to the sink solution through the membrane. In principle, they are consecutive processes, except initially where parallel processes prevailed as a result of drug diffusion originated from the initial amount of drug already dissolved in the external aqueous phase of the emulsion at initial equilibrium.

The rate of drug exchange is determined by the microconstants k_{12} and k_{23} where k_{12} is the first-order partition rate constant between the internal oily phase and external aqueous phase in the donor compartment and k_{23} is the first-order permeation rate constant of the drug through the membrane.

The kinetics of the drug release and the diffusion are represented by the following set of equations:

$$\frac{dC_a}{dt} = -\frac{k_{12}}{V_a}\left[C_a(t) - C_b(t)\right] \qquad (1)$$

Under sink conditions

$$\frac{dC_c}{dt} = \frac{k_{23}}{V_c} C_b(t) \qquad (2)$$

Mass balance $$M_\infty = V_a C_a(t) + V_b C_b(t) + V_c C_c(t) \qquad (3)$$

Where M stands for mass and C for the concentration and V for volume, the subscript referring to a particular compartment.
Upon Laplace transformation with respect to time of C, the drug concentrations in the different compartments:

$$S\,C_a(s) - C_a(t=0) = \frac{k_{12}}{V_a} C_b(s) - \frac{k_{12}}{V_a} C_a(s) \qquad (4)$$

$$S\,C_c(s) - C_c(t=0) = \frac{k_{23}}{V_c}\,C_b(s) \qquad (5)$$

$$\frac{M_\infty}{S} = V_a\,C_a(s) + V_b\,C_b(s) + V_c\,C_c(s) \qquad (6)$$

Where the Laplace transforms, F(s) of the function F(t) is:

$$L[\,F(t)\,] = F(s)$$

and

$$L\left[\frac{d\,F(t)}{dt}\right] = S\,F(s) - F(t=0)$$

The general solution for $C_c(s)$ is:

$$C_c(s) = \frac{1}{V_c} \cdot \frac{\frac{k_{23}}{V_b} M_{bo}\,S + \frac{k_{12}\,k_{23}}{V_a\,V_b} M_\infty}{S\left[S^2 + \left(\frac{k_{12}}{V_a} + \frac{k_{12}}{V_b} + \frac{k_{23}}{V_b}\right) S + \frac{k_{12}\,k_{23}}{V_a\,V_b}\right]} \qquad (7)$$

or

$$M_c(s) = \frac{AS + B}{S\,(S+\alpha)\,(S+\beta)} \qquad (8)$$

where

$$A = \frac{k_{23}}{V_b} \cdot M_{bo} \quad \text{and} \quad B = \frac{k_{12}\,k_{23}}{V_a\,V_b} \cdot M_\infty$$

$$\alpha + \beta = \frac{k_{12}}{V_a} + \frac{k_{12}}{V_b} + \frac{k_{23}}{V_b} \quad \text{and} \quad \alpha \cdot \beta = \frac{k_{12} \cdot k_{23}}{V_a \cdot V_b}$$

The final solution for C_c with respect to time is obtained by taking the inverse Laplace transform of equation (8)

$$\text{Inverse Laplace of } M_c(s) = \frac{B}{\alpha\beta} - \frac{A\alpha - B}{\alpha(\alpha-\beta)} e^{-\alpha t} + \frac{A\beta - B}{\beta(\alpha-\beta)} e^{-\beta t} \quad (9)$$

$$M_c(t) = M_\infty - \frac{\frac{k_{23}M_{bo}}{V_b}\alpha - \frac{k_{12}k_{23}M_\infty}{V_a V_b}}{\alpha(\alpha-\beta)} e^{-\alpha t} + \frac{\frac{k_{23}M_{bo}}{V_b}\beta - \frac{k_{12}k_{23}M_\infty}{V_a V_b}}{\beta(\alpha-\beta)} e^{-\beta t} \quad (10)$$

The kinetics of drug release from the emulsion and membrane diffusion were therefore represented by a set of rate equations which were combined after substitutions, rearrangements and Laplace transformations in a unique and comprehensive equation (10).

For the purpose of confirming the applicability of equation 10 to describe the release profile of morphine from the emulsion the following terms which appear in equation 10 were determined directly and are presented in Table 1. It should be noted that k_{23} was calculated using the equation $Q = W_o(1-e^{k_{23}t})$ which characterized morphine permeation through the Nuclepore membrane under non steady-state conditions from aqueous morphine solutions. Q and W_o were the diffusing and initial amount of morphine respectively.

The values of the different parameters in Table 1 correspond to the kinetic experiment carried out to determine the release profile of morphine from the emulsion having 20% oily phase volume ratio as shown in Fig. 4.

Table 1: DETERMINATION OF THE FOLLOWING TERMS APPEARING IN EQUATION 10 FOR THE CALCULATION OF k_{12}

Volume of oily internal phase = V_a	= 0.2 ml
Volume of aqueous external phase = V_b	= 0.8 ml
Initial drug amount in the aqueous external phase	$M_{bo} = \frac{M_\infty \times 20.5}{100}$
Total amount of drug in the mulsion M_∞	= 100%
First order permeation constant of morphine through the Nuclepore membrane k_{23}	= 0.05 min^{-1}

In the present study, M_∞ , the total amount of morphine was varied from 0.2 to 0.8 g in 100 g of emulsion.

All the values were inserted in equation 10 and the values of k_{12} the first order partition rate constant were calculated for the various kinetic data observed in the release profile of morphine from 20% emulsion as reported in Fig. 4. Ten different release kinetic points, i.e. percent of morphine release and their corresponding time values were inserted also in equation 10 and the values of k_{12}, the first-order transfer rate constant from the internal to the external phase were calculated by means of an IBM PC computer. The ten values of k_{12} obtained were identical and equal to 0.0012 min^{-1} indicating that equation 10 described accurately the release profile of morphine from the emulsion having 20% oily phase volume ratio.

In a second step, the values of the kinetic constants k_{12} and k_{13} were introduced in equation 10 with the other appropriate

Table 2: COMPARISON OF PREDICTED RELEASE KINETIC DATA CALCULATED BY MEANS OF EQUATION 10 TO OBSERVED KINETIC DATA AS A FUNCTION OF OILY VOLUME RATIO VARIATIONS, CONSTANTS: $K_{12} = 0.0012 min^{-1}$, $K_{23} = 0.050 min^{-1}$

Time min	Va=0.3, Vb=0.7ml M_{bo} =14.0% of M_∞		Va=0.4, Vb=0.6ml M_{bo} = 9.1% of M_∞		Va=0.5, Vb=0.5ml M_{bo} = 5.7% of M_∞	
	P	O	P	O	P	O
15	11.7	11.5	8.7	9.0	5.4	5.6
30	18.7	18.4	13.9	13.2	9.1	9.1
60	28.5	27.9	21.6	21.5	15.4	14.7
90	36.5	36.2	28.2	28.5	21.0	19.9
120	43.5	43.5	34.2	35.0	26.5	25.5
180	55.3	55.0	44.8	47.6	36.1	35.3
240	64.6	64.4	53.7	54.1	44.5	43.6
300	72.0	73.0	61.2	62.0	51.8	50.6
400	81.0	82.1	71.0	71.9	61.9	60.2
500	87.2	89.0	78.4	79.5	69.8	68.0

P = Predicted O = Observed

M_{bo} was measured using the procedures described in the section METHODS, paragraph 3.

parameter values corresponding to the different release profiles of morphine from the emulsion as a function of the oily phase volume ratio as shown in Fig. 4. The expected amount of morphine released was calculated by means of equation 10 and compared with the observed amount released as reported in Table 2. It can be seen from Table 2 that both kinetic data were similar indi-

cating the goodness of fit and the high level of suitability of the experimental data to the proposed kinetic model. Similar results and kinetic behaviour were observed when instead of oily phase volume ratio, mean droplet size and pH were varied.

CONCLUSION

This kinetic model which took into consideration most of the factors encountered in such a complex situation was found suitable for the description of morphine release from the emulsion.

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