Pakistan Journal of Pharmaceutical Sciences
Vol. 16, No.2, July 2003, pp.17-28

EVALUATION OF HYDROPHOBIC MATERIALS AS MATRICES FOR CONTROLLED-RELEASE DRUG DELIVERY

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ABSTRACT

The present study was undertaken to evaluate the effect of different insoluble and erodable wax-lipid based materials and their content level on the release profile of drug from matrix systems. Matrix tablets of theophylline were prepared using carnauba wax, bees wax, stearic acid, cetyl alcohol, cetostearyl alcohol and glyceryl monostearate as rate-retarding agents by direct compression process. The release of theophylline from these hydrophobic matrices was studied over 8-hours in buffer media of pH 6.8. Statistically significant difference was found among the drug release profile from different matrices. The release kinetics was found to be governed by the type and content of hydrophobic materials in the matrix. At lower level of wax matrices (25%), a potential burst release was observed with all the materials being studied. Bees wax could not exert any sustaining action while an extensive burst release was found with carnauba wax at this hydrophobic load. Increasing the concentration of fat-wax materials significantly decreased the burst effect of drug from the matrix. At higher hydrophobic level (50% of the matrix), the rate and extent of drug release was significantly reduced due to increased tortuosity and reduced porosity of the matrix. Cetostearyl alcohol imparted the strongest retardation of drug release irrespective of fat-wax level. Numerical fits indicate that the Higuchi square root of time model was the most appropriate one for describing the release profile of theophylline from hydrophobic matrices. The release mechanism was also explored and explained with biexponential equation. Application of this model indicates that Fickian or case I kinetics is the predominant mechanism of drug release from these wax-lipid matrices. The mean dissolution time (MDT) was calculated for all the formulations and the highest MDT value was obtained with cetostearyl matrix. The greater sustaining activity of cetostearyl alcohol can be attributed to some level of swelling and erosion within this matrix at lower fat-wax level which is also supported by release exponent values and Fickian fraction release against time profile of this agent. The results generated in this study showed that proper selection of these hydrophobic materials based on their physico-chemical properties is important in designing wax matrix tablets with desired dissolution profile.

INTRODUCTION

In the last several decades, many different types of controlled release dosage forms have been developed to improve clinical efficacy of drug and patient compliance (Merkus, 1986; Jantzen, 1996). Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing sustained-release dosage forms because it makes such manufacturing easy (Cardinal, 1984). Insoluble-erodable polymers and waxes are commonly utilized as matrix forming components and are extensively used for sustaining the release of drugs (Johnson, 1974;

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Goodhart *et al*., 1974; Dakkuri *et al*., 1978 a and b; Shora, 1980). The use of wax seems to have a particular advantage due to wax's chemical inertness against other materials (Miyagawa, 1996). The release mechanism of the embedded drug is diffusion-and/ or erosion-controlled type (Dredan, 1998). However, the release is more effectively controlled by the addition of hydrophilic additives. It has been reported that, a zero-order release can be obtained by incorporation of additives such as povidone into the wax matrix (Dakkuri *et al*., 1978b).

Wide arrays of wax-lipid based hydrophobic materials are available for sustaining drug action and have extensively been reported. The objective of the present study is to evaluate the comparative efficiency of different wax-lipid matrices in controlling the release of active ingredient. Carnauba wax, bees wax, glyceryl monostearate (GMS), stearic acid, cetyl alcohol and cetostearyl alcohol have been used as the hydrophobic matrices and their release-modulating ability were studied in terms of *in-vitro* dissolution testing. The matrices being used possess different physico-chemical property and imparted a diversified impact on the rate and extent of drug release. The effect of wax-lipid loading in the matrix was also investigated. Theophylline, a proven candidate to be formulated in sustained release dosage form, was chosen as the model drug. The kinetics and mechanism of Theophylline release from the matrix systems has been explored and explained with the help of exponential model.

MATERIALS AND METHODS

Materials:

Theophylline was a kind gift from Square Pharmaceuticals Bangladesh Limited. Stearic acid, cetyl alcohol and cetostearyl alcohol was from BDH, UK while carnauba wax and bees wax was procured from Koster Keunen Inc. USA. Glycerol monostearate was procured from JAM, Germany. Aerosil (Silicon di oxide) and Magnesium Stearate were from Hanau Chemicals Limited, Japan. All other ingredients were of analytical grade.

Preparation of Matrix Tablets:

For tablet preparation, method of dry blending of the active ingredients with hydrophobic materials, filler, lubricant and flow promoter followed by direct compression was adopted. The formulations of the tablets with their codes are listed in Table 1 and 2. In all cases the amount of the active ingredient is 100 mg and the total weight of the tablet is 406 mg. Ludipress is used as the neutral filler composed of lactose, kollidon CL and kollidon 30. Properly weighed matrix-forming agents, ludipress, magnesium stearate, aerosil and the active ingredient were blended in a laboratory mixture for 10 minutes. Particular attention has been given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixture were then compressed using a Perkin-Elmer laboratory hydraulic press equipped with a 13 mm flat faced punch and die set. The compression force and compression time were 5 ton and 30 seconds respectively. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study.

Dissolution Studies

In vitro drug release studies from the prepared matrix tablets were conducted using a six station USP XXII type 1 apparatus at 37 ± 0.5°C and 50 rpm speed. The dissolution studies were carried out in duplicate for 8 hours in phosphate buffer of pH 6.8 under sink condition. At every 1-hour interval samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for theophylline by an UV spectrophotometer (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of appropriate

calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Statistics:

To compare the means of all release data and to assess statistical significance between them, either one-way analysis of variance (ANOVA) or an unpaired two-tailed t-test was carried out at 5% significance level.

Table 1
Formulation of wax-lipid matrix tablets at 25% wax-lipid level (in mg)

Ingredients	**TBW-1**	**TCW-1**	**TGMS-1**	**TSA-1**	**TCA-1**	**TCSA-1**
Theophylline	100	100	100	100	100	100
Bees wax	100	-	-	-	-	-
Carnauba wax	-	100	-	-	-	
GMS	-	-	100	-	-	-
Stearic acid	-	-	-	100	-	-
Cetyl alcohol	-	-	-	-	100	-
Cetostearyl alcohol	-	-	-	-	-	100
Ludipress	200	200	200	200	200	200
Mg-stearate	2	2	2	2	2	2
Aerosil	4	4	4	4	4	4
Total wt	406	406	406	406	406	406

Table 2
Formulation of wax-lipid matrix tablets at 50% wax-lipid level (in mg)

Ingredients	**TBW-2**	**TCW-2**	**TGMS-2**	**TSA-2**	**TCA-2**	**TCSA-2**
Theophylline	100	100	100	100	100	100
Bees wax	200	-	-	-	-	-
Carnauba wax	-	200	-	-	-	
GMS	-	-	200	-	-	-
Stearic acid	-	-	-	200	-	-
Cetyl alcohol	-	-	-	-	200	-
Cetostearyl alcohol	-	-	-	-	-	200
Ludipress	100	100	100	100	100	100
Mg-stearate	2	2	2	2	2	2
Aerosil	4	4	4	4	4	4
Total wt	406	406	406	406	406	406

Table 3
Drug release parameters from Biexponential Equation

For 25% wax-lipid loading				For 50% wax-lipid loading			
Formulations	**n**	**K**	**R^2**	**Formulations**	**N**	**K**	**R^2**
DGMS-1	0.4508	0.3333	0.9952	DBW-2	0.4657	0.3891	0.9879
DSA-1	0.4831	0.3687	0.9975	DCW-2	0.4859	0.1732	0.9871
DCA-1	0.4608	0.2415	0.9893	DGMS-2	0.4785	0.1630	0.9862
DCSA-1	0.6211	0.1760	0.9909	DSA-2	0.4322	0.1854	0.9845
				DCA-2	0.4991	0.1496	0.9842
				DCSA-2	0.4976	0.1474	0.9819

Table 4
Drug release parameters from Peppas Equation

For 25% wax-lipid loading				For 50% wax-lipid loading			
Formulations	**K_1**	**K_2**	**R^2**	**Formulations**	**K_1**	**K_2**	**R^2**
DGMS-1	0.3214	-0.0068	0.9956	DBW-2	0.5081	-0.0702	0.9852
DSA-1	0.5071	-0.0702	0.9821	DCW-2	0.1788	-0.0015	0.9914
DCA-1	0.2556	-0.0077	0.9940	DGMS-2	0.1864	-0.0007	0.9844
DCSA-1	0.1701	-0.0189	0.9969	DSA-2	0.2160	-0.0095	0.9833
				DCA-2	0.1519	-0.0012	0.9927
				DCSA-2	0.1549	-0.0055	0.9819

RESULTS AND DISCUSSION

Effect of Type and Loading of Hydrophobic Materials on Theophylline Release:

The effect of different wax-lipid based hydrophobic materials and their loading in the matrix tablet on the release of theophylline is illustrated in figure 1. The overall release rate of theophylline from different hydrophobic materials was found to be significantly different ($P<0.0001$). This indicates that, the physico-chemical composition of the wax and hydrophobic polymers imparts a significant impact on the rate and extent of drug release. Figure 1(a) shows the release of theophylline from matrices containing 25% wax-lipid load (i.e.100 mg hydrophobic material). At this wax-lipid concentration, cetostearyl alcohol imparted the strongest retarding effect on theophylline. About 62.35% of theophylline was released after 8 hours of dissolution period with an initial release of 16.60 % after one hour. The release was almost linear throughout the dissolution period. Cetostearyl alcohol is actually a mixture of aliphatic alcohols composed of 50-70% stearyl and 20-35% cetyl alcohols with small quantities of myristyl alcohol . The aliphatic portions of these long chain fatty alcohols imparts the cetostearyl matrix with sufficient hydrophobicity and impedes wetting of the matrix surface by dissolution fluid. Bees wax, consists of 70-75% of a mixture of various esters from C_{26}-C_{32} alcohols, particularly palmitic, hydroxypalmitic, d-β-dehydropalmitic and cerotic acid, could not impart any sustaining effect on

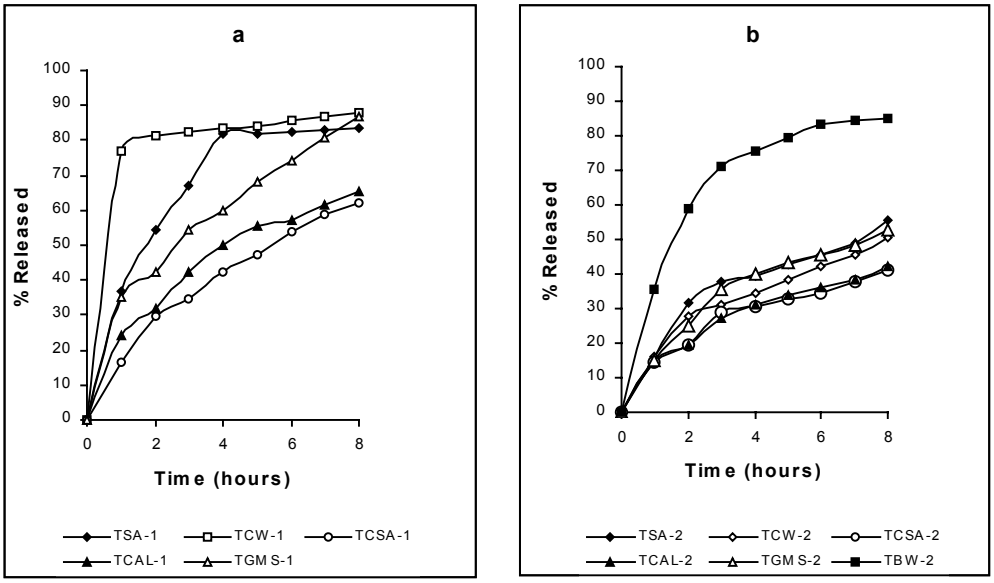

Fig.1: Release profile of theophylline from wax-lipid based matrix tablets (a) 25% wax-lipid load (b) 50% wax-lipid load.

theophylline release (Kibbe, 1986). Total amount of theophylline in the matrix system was virtually released within the first hour of dissolution from bees wax matrix. Carnauba wax, on the other hand, composed of alkyl esters of wax acids (80%), chiefly myricyl cerotate, free monohydric alcohols (10%), lactose and resin (Tyler, 1976). This matrix system released 87.89% theophylline after 8-hour of dissolution period. However, an extensive burst release was observed with this system. About 76.81% of the active was liberated in the first hour of dissolution. The esters of these wax acids helps in the formation of different surface bonds i.e. hydrogen or Van Der Wall's bond between water molecule and the wax ingredients due to the presence of more electronegative oxygen in the ester moiety. This facilitated formation of surface bonds can be attributed to lower sustaining effect imparted by these waxes. Glyceryl monostearate released 34.95% of theophylline within first hour and the cumulative release after 8 hours was 86.68%. Surface active property of glyceryl monostearate (HLB value 3.8) can be held responsible for this higher extent of release (Martin, 1993). Theophylline release from stearic acid matrix was rapid, almost linear up to 4 hours after which a steady state was reached from where the drug release became extremely slow. About 81.74% of theophylline was released within first 4 hours and the total amount of drug released after 8 hours was 83.66%. The free carboxylic acid group (-COOH) present in stearic acid enhanced the formation of hydrogen bonding with surrounding dissolution medium and facilitated wetting of matrix and consequent higher release of theophylline. Cetyl alcohol, because of their lower hydrophilic characteristics than polymers containing carboxylic acid moiety, released lesser amount of drug (65.46% theophylline after 8-hours). Again, the molecular length and cross-sectional area for stearic acid is 25 A^o and 22 A^o respectively which is higher than those of cetyl alcohol (22 A^o and 21A^o respectively). This higher molecular dimension of stearic acid also contributed to enhanced formation of hydrogen bond and elevated extent of theophylline release (Martin, 1993). It can be noted that, at 25% level, waxes and hydrophobic materials used are not efficient enough in sustaining the release of drug. The release profile of theophylline from different matrix-forming agents of this class indicates the existence of a close

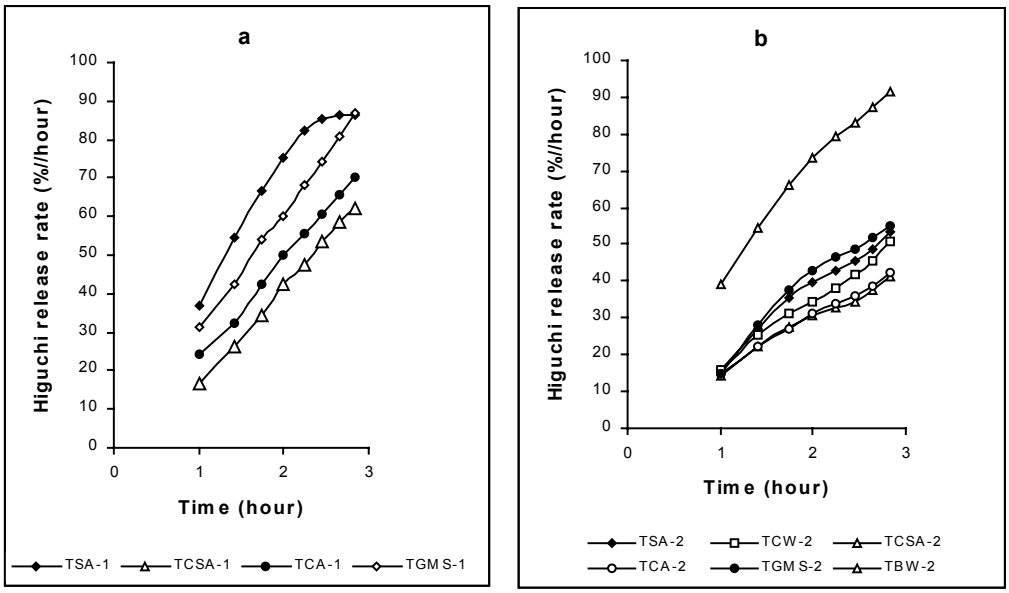

Fig. 2: Higuchi Release profile of theophylline from wax-lipid based matrix tablets (a) 25% level (b) 50% level.

relationship between chemical composition of the polymer and release pattern of the drug. An initial rapid release was observed with all the polymers that clearly necessitate the increment of matrix-retarding agents and/or incorporation of rate-modifiers to get a desirable release profile.

Increasing the wax-lipid level markedly decreased the rate and extent of drug release as can be observed from figure 1(b). In this case, highest amount of theophylline was released from bees wax matrix system (i.e. 85.22%) with initial release of 35.54%. Release profile of theophylline from cetostearyl alcohol and cetyl alcohol was almost superimposable on each other. The cumulative release after 8 hours was 41.07 and 42.18% respectively for these two matrices. As can be observed from the figure, 55.30, 50.79 and 52.68% of theophylline was released from stearic acid, carnauba wax and glyceryl monostearate matrices respectively. Except for bees wax matrix, increasing the wax-lipid level greatly reduced the initial release. The fact can be reasoned in the way that, an increase in the polymer content results in a decrease in the drug release rate due to a decrease in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug) (Boza, 1999). Increment in polymer content also increases the tortuosity of the matrix and drug diffusion path-length which in turn slows down diffusion and erosion from/of the matrix (Lee, 1999).

Kinetic Approach of Drug Release from Wax Matrices:

The mechanism of drug release from wax matrices has been a matter of controversy since wax systems tend to be crude and more heterogeneous than polymeric systems (Wong, 1992). It has been suggested that the mechanism of release from wax matrices involves the leaching of drug by the eluting medium. Fluid enters through the cracks and pores of the matrix with diffusion of drug through the matrix being insignificant (Dakkuri *et al*., 1978 a and b). Others have reported that release from a typical wax matrix is diffusion-controlled and is best described by Higuchi's $t^{1/2}$ model (Schwartz *et al*., 1968 a, b; Goodhart *et al*., 1974 and Parab *et al*., 1986).

In our study, Different kinetic equations (zero-order, first-order and Higuchi's equation) were applied to interpret the release rate from matrix system. The best fit with higher correlation was found with the well-known Higuchi equation, Eq. (1)

$$Q = 2C_0 (Dt/3.14)^{1/2} \quad (1)$$

Where Q is the amount of the drug released per unit area (cm^2), C_0 is the initial quantity of the drug (mg), D is the diffusion co-efficient and t is the time after application. As C_0 and D are essentially constant, the equation can be reduced to Eq (2)

$$Q = K' t^{1/2} \quad (2)$$

Where K' is the constant or the Higuchi release rate constant. The data, when treated with this above equation by plotting the percent of theophylline release (Q) against the square root of time ($t^{1/2}$), yielded a fairly good linearity confirming that the release permeation data followed the Higuchi model ($R^2 > 0.98$). This was true for all the formulations irrespective of polymer type and loading (Figure 2). However, the release profile of theophylline from carnauba wax and bees wax matrix system with 25% polymeric load cannot be shown because there were insufficient data point on the release profile between 10% and 80% release to provide accurate values.

For 25% wax-lipid level, extrapolation of the linear portion of the Higuchi plot showed a negative value on the time axis, indicating the presence of an initial burst release as mentioned earlier (Figure 2a). This finding is true for all the matrix system being studied at this hydrophobic level. The extent of initial release was least for cetostearyl alcohol. The higher rate and extent of theophylline released in this phase was due to greater extraction of theophylline from the vicinity of the matrix surface. Theophylline, being a soluble drug with pk_a value of 8.6 and solubility of 0.833%(w/v), immediately released when it came into contact of the dissolution media (Lund, 1984). Wax-lipid based matrices show negligible swelling property, and hydrophobicity of these matrix formers was not sufficient enough to control this rapid release. Higher proportion of ludipress in these formulations can also be considered as a major factor for this rapid release. Ludipress, being composed of lactose and kollidon CL, imparted a disintegrating effect on the matrix as soon as it is immersed into the dissolution medium generating numerous pores through which fluid diffused into and stressed the integrity of the matrix-surface. After liberation of the surface drug, the release of theophylline became extremely slow and steady as the hydrophobic polymers started impeding wetting and subsequent penetration of dissolution medium into the matrix. For 50% wax-lipid loading, extrapolation of the linear portion of the Higuchi plot again showed a negative value on the time axis indicating the presence of burst release. However, the extent of burst release was much lower than those found with 25% wax-matrix concentration. At this level, hydrophobic materials exerted potential repulsion of solvent-front from the matrix surface. Again, reduction of Ludipress also hindered the pore formation and disintegration process within the matrix. It should be mentioned that, the initial burst release of the drug from the hydrophobic system is often therapeutically undesirable because the total amount of drug released is remarkably influenced by this initial control of release from the dosage form (Talukder *et al.,* 1996). The presence of burst release for all the polymers being studied clearly indicates that hydrophobic materials at 25% level were not sufficient to produce a desirable pharmacokinetic profile. However, at 50% wax-lipid content, burst release can sufficiently be minimized and a provision to control theophylline release in a well-defined pattern can be explored as can be observed from Fig. 2(b).

The Higuchi release rate (% hour $^{-1/2}$) was calculated from the slope of higuchi release curves of the polymers. At 25% wax-lipid level, the Higuchi Release rate (% hour $^{-1/2}$) was highest with stearic acid and glycerol monostearate (30.97 and 29.94% hour $^{-1/2}$) matrix. The release rate was 22.69 and 23.45 % hour $^{-1/2}$ for cetostearyl alcohol and cetyl alcohol respectively. The Higuchi release rate was found to decrease considerably with increment of wax-lipid concentration. Stearic acid and GMS was found to release theophylline at the rate of 19.08 and 19.21 % hour $^{-1/2}$ respectively at this fat-wax level. However, beeswax, at 50% w/w of the matrix, released theophylline at a faster rate than any other hydrophobic materials (30.98 % hour $^{-1/2}$). Cetostearyl alcohol, Cetyl alcohol and Carnauba wax showed the Higuchi release rate of 14.43, 14.93 and 17.43 % hour $^{-1/2}$ respectively. The effect of different wax-lipid based matrix systems on Higuchi release rate can be placed in the descending order of: Bees wax > Carnauba wax > GMS > Stearic acid > Cetyl alcohol > Cetostearyl alcohol.

Two factors, however, diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential Eq. (1), which is often used to describe the drug release behaviour from polymeric systems:

$$M_t / M_\infty = Kt^n \quad (3)$$

Where Mt/Mα is the fractional (0.1-0.7) drug release at time t; K is a constant incorporating the properties of the macromolecular polymeric systems and the drug and n is a kinetic constant which depends on and is used to characterize the transport mechanism. The value of n for a tablet, n = 0.45 for Fickian (Case I) release, >0.45 but <0.89 for non-Fickian (Anomalous) release and 0.89 for Case II (Zero order) release and >0.89 for super case II type of release (Ritger and Peppas, 1987). Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport (Non Fickian) refers to the summation of both diffusion and dissolution controlled drug release. From the above equation the n and K values for different formulations have been calculated to identify the drug release mechanism. Akbuga (1993) applied this equation to evaluate the drug release mechanism from chitosonim malate matrix tablets while Fickian release and / or case II release is presumed to contribute to drug release from wax matrix granules as reported by Sato *et al* (1997). These investigations clearly rationalize the application of biexponential equation to wax-matrix tablets.

In Table 3, the values of n, K and the correlation co-efficient (R^2) obtained with wax-lipid matrix tablets are summarized. The value of correlation coefficients R^2 (>0.98) are high enough to evaluate theophylline dissolution behaviour from wax matrix by Eq. (3). The table shows that, at 25% polymeric level, cetyl alcohol, stearic acid and GMS demonstrated the tendency of drug release by Fickian or case I mechanism (square root of time kinetics) as observed from their n values. Cetostearyl alcohol matrix system, on the other hand, showed a greater deviation from case I or Fickian kinetics (n = 0.6211) and showed much adherence to anomalous or non-fickian release. This suggests that, at this polymeric load, some level of swelling and dissolution of matrix must be operating within the system which causes it to deviate from the Fickian release and remain in moving boundary condition (Sujja-areevath, 1996). Presence of higher proportion of ludipress in the system also enhances the penetration of water into the matrix and facilitates the contact of cetostearyl alcohol with eluting media. Increasing the wax-lipid load, however, brought about changes in the kinetics of drug release and consequently in the value of release exponent. At 50% level, all the hydrophobic materials being studied showed a clear trend to release drug by Fickian or case I mechanism. Cetostearyl alcohol, at this level, also showed an adherence to

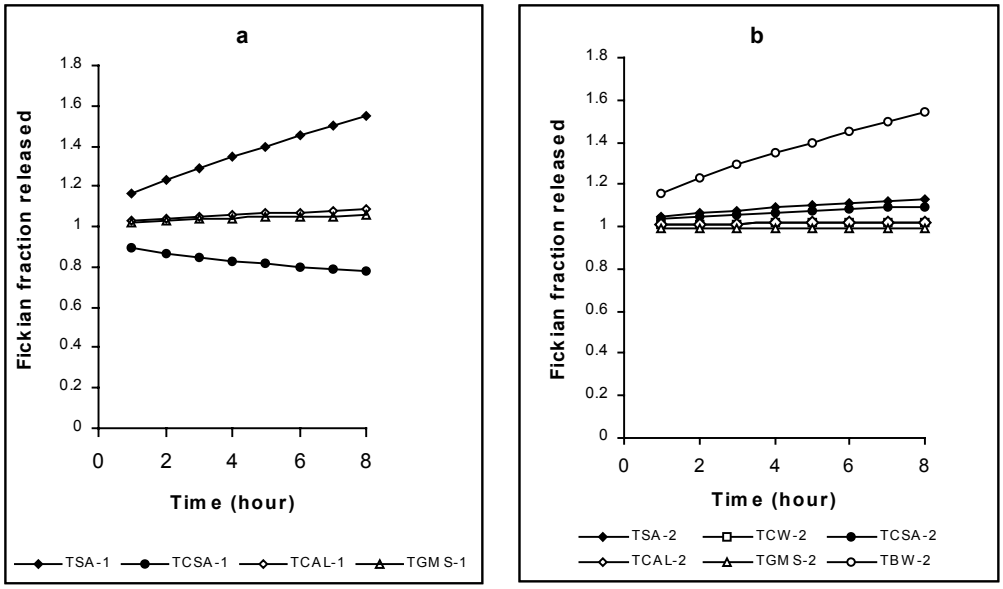

Fig.3: Fickian release fraction from wax-lipid based matrix tablets (a) 25% wax-lipid load (b) 50% wax-lipid load.

Fickian diffusion. The insignificant swelling and/ or relaxation property of cetostearyl alcohol has been compensated by increment of polymeric load due to the formation of solid monolithic matrix which decreased wetting and water penetration into the matrix to initiate hydration of cetostearyl matrix surface.

To quantify and materialize the amount of drug released by Fickian diffusion and by polymer relaxation, if operating, the release data were also fitted with Eq. (4) using a software package of nonlinear regression analysis (CurveExpert, Version 1.34, D.Hyams, Microsoft Corporation, US).

$$M_t / M_\infty = K_1 \sqrt{t} + K_2 t \qquad (4)$$

The first and the second terms on the right hand side of Eq. (3) represent the Fickian diffusion and the case II relaxation contributions, respectively (Peppas and Sahlin, 1989). K_1 and K_2 are the kinetic constants. The values of these constants along with the R^2 values are presented in Table 4. At 25% level, all the hydrophobic materials except cetostearyl alcohol, showed a negative value of K_2 which is associated with the dissolution as well as relaxation of polymer chains (Sutananta, 1995). Relatively higher value of K_2 was found only with cetostearyl alcohol which indicates some level of polymer relaxation and swelling in such matrix and supports its tendency to release drug by Non-Fickian kinetics. Other hydrophobic materials being studied showed the interpretable value of diffusion contribution (K_1) indicating that Fickian or case I kinetics is the predominant mechanism of drug release from these matrices. In case of 50% hydrophobic load, all the matrices along with the cetostearyl alcohol, released drug by diffusion controlled process as observed from their higher values of diffusional contribution (K_1) and non-positive value of swelling component (K_2). Lee (1980, 1981) formulated a drug release model from erodible matrices, which has diffusion contribution but no swelling or relaxation component.

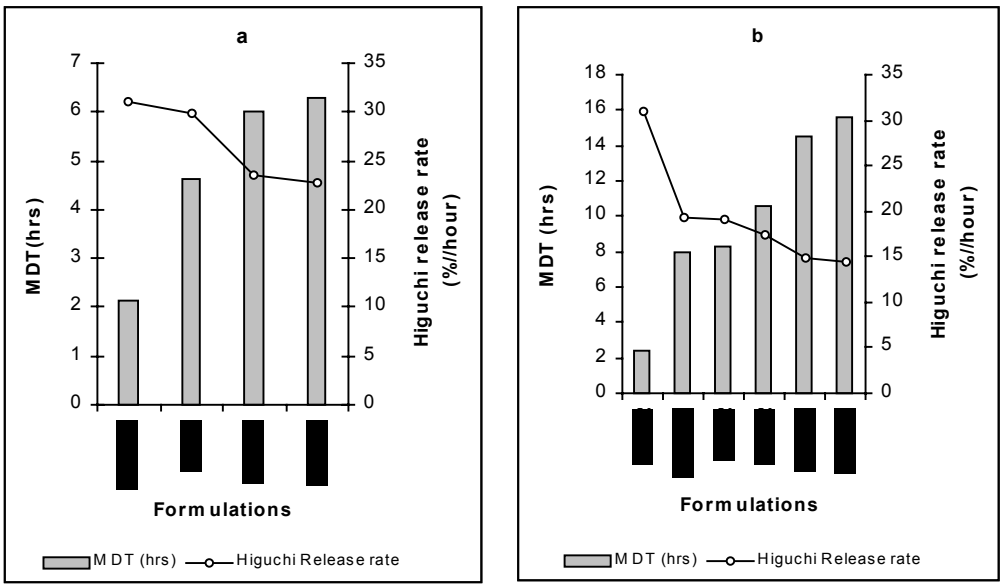

Fig. 4: Relationship between MDT and Higuchi release rate from wax-lipid matrix tablets (a) 25% wax-lipid load (b) 50% wax-lipid load.

Again, from the values of K_1 and K_2 obtained from Eq. (4), it is possible to calculate the fraction of Fickian release by using the following equation (Akbuga, 1993):

$$F=1/(1+k_1 t^m/k_2) \quad (5)$$

Where F is the Fickian fraction released at a particular time t and the value of m is considered as 0.45 for wax matrix tablets in this study. The Fickian release fraction are plotted as a function of time and illustrated in Fig. 3. The figure shows that, at 25% level of hydrophobic material, the fraction of Fickian release increases with time for stearic acid matrix while decreases abruptly for cetostearyl alcohol as dissolution time elapses. The fact for cetostearyl alcohol may be due to the swelling and relaxation of such matrix at this particular level as mentioned earlier. The Fickian fraction released for cetyl alcohol and GMS remained constant throughout the dissolution period. On the other hand, at 50% fat-wax level, bees wax system showed an abrupt increase in the release of Fickian fraction with time while cetostearyl alcohol and stearic acid system showed a moderate increase in such release. Again, the Fickian fraction release of theophylline by cetyl alcohol and GMS remained fairly constant throughout the dissolution period.

Although the constant K used in Eq. (3) is one of the measures of the drug release rate, it should not be used for comparison because there are different kinetics in different test conditions. Therefore to characterize the drug release rate in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution data according to Möckel and Lippold using the following equation.

$$MDT = (n/n+1).k^{-1/n} \quad (6)$$

MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the matrix forming agent. A higher value of MDT indicates a higher drug retarding

ability of the polymer and vice-versa. In our study, the MDT value was also found to be a function of wax-lipid type, loading and physico-chemical property of the wax-lipid itself. It is explicitly understood that, Higuchi release rate will show a reverse trend of MDT values for a set of matrix systems and Fig. 4 shows this inter-relationship between the MDT value and higuchi release rate irrespective of matrix type and wax-lipid loading. Supportive to drug release data, it was found that, at both 25% and 50% fat-wax level, cetostearyl alcohol based matrix system (i.e. TCSA-1 and TCSA-2) showed the highest value of MDT which is indicative of the strongest retardation impact it exerts on theophylline irrespective of wax-lipid concentration. This can be attributed to the some level of swelling and relaxation of long chain molecules within cetostearyl alcohol matrix as a small case II relaxation contribution was found earlier with this hydrophobic matrix at 25% loading. Due to this swelling, the diffusion path length gets longer in the cetostearyl matrix, which results in decreasing release rate and consequent elevation of MDT value. At 25% level, stearic acid showed the least MDT value (2.13 hour) whereas at 50% fat-wax level, the lowest MDT value was found with beeswax matrix (2.41 hour).

CONCLUSIONS

Among all the hydrophobic materials being studied, only carnauba wax and bees wax are used extensively in pharmaceuticals to control the release of drug. The approach of the present study was to make a comparative evaluation among the most available wax-lipid based hydrophobic materials those can be potential candidates as release retarding agents. The study implies that, the kinetics and mechanism of release exclusively depends on the physico-chemical type and loading of these materials. A critical wax-filler ratio is necessary to get an acceptable release profile and counter the complexities of burst effect. The wide range of matrix-formers available in this group endows the formulator with higher degree of flexibility, greater scope of optimization and wider approach to comply with compendial specifications. The study also reveals that, it is possible to formulate matrix tablet by appropriate combination of these hydrophobic matrices with rate-controlling agents to get an acceptable pharmacokinetic profile in the fluctuating *in vivo* environment.

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