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EVALUATION OF ETHYLCELLULOSE AS MATRICES FOR CONTROLED RELEASE DRUG DELIVERY

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As the efficiency of a matrix forming polymer in sustaining drug release is a multiple function of physico-chemical nature of the active ingredient and pH of the surrounding environment, the study was undertaken to evaluate the effect of pH of dissolution media on the release profile of three drug molecules with diversified physico-chemical properties. Matrix tablets of diclofenac sodium, theophylline and diltiazem HCl were prepared using ethylcellulose as the matrix forming agent. The drug dissolution behavior of the matrix tablets were studied over 10 hours in buffer media of pH 1.2, 4.5 and 6.8. Elevation of pH of the dissolution medium increased the rate and extent of diclofenac release. However, for diltiazem HCl, increasing the pH showed the reverse pattern. Theophylline release, on the other hand, seemed to be unaffected by the pH of the dissolution media. This can be correlated with the physico-chemical characteristics of the drugs. Effect of compression force on drug release and tablet hardness was also studied. Increasing the compression force reduced drug release irrespective of the chemical nature of the drug molecule which can be attributed to the reduction of porosity and formation of continuous polymeric network within the matrix. Again, no significant change in tablet hardness was found with the increment of compression force. A near zero-order release kinetics were observed in all formulations investigated.

INTRODUCTION

The fluctuating drug concentrations in blood and tissues caused by conventional dosage forms lead to an insufficient influence on the mechanisms of disease and are related to the excessive use of a drug. Various oral dosage forms able to control the rate of drug delivery into the systemic circulation have been prepared and studied (Bidah and Vergnaud, 1991). In spite of the recent technological advances in the fabrication of oral controlled-release dosage forms, particular attention has been paid to the regulation of drug release rate by means of monolithic devices, whereby prior dispersion of the drug in a polymer matrix is carried out (Heilman, 1984). Preparation of drug embedded matrix tablet that involves the direct compression of drug, rate controlling polymer and additives is one of the least complicated approaches for the manufacturing of sustained release dosage forms (Lordi *et al.*, 1990). Direct compression technology is scientifically and economically appealing since it entails reduced labor, cost, time, operational space, and equipment, and further no utilization of heat or moisture. In these directly compressed monolithic systems, the active agent is dispersed, dissolved or distributed in an inert polymeric diffusion barrier (Frutos *et al.*, 2001). Drug release process is controlled by dual transfer mechanism, the liquid enters the polymer matrix, dissolves the drug and enable the drug to diffuse out through the liquid located in the polymer matrix (Droin *et al.*, 1985; Armand *et al.*, 1987; Saber *et al.*, 1988). Both these transfers are controlled by transient diffusion and the diffusivity of the drug which increases with the liquid concentration in the dosage form. As a result, drug delivery in the stomach is effectively controlled. Drug release is governed by polymer structure and properties (Higuchi, 1963; Gurny, 1982; Bain *et al.*, 1991; Stamm and Tritsch, 1986).

Ethyl cellulose is an inert hydrophobic polymer and its properties such as lack of toxicity, stability during storage and good compressibility make it suitable for designing sustained release matrices (Dubernet *et al.*, 1990; Upadrashta *et al.*, 1993). Ethylcellulose is widely used to control the dissolution rate of drugs from sustained-release preparations (Porter, 1989; Narisawa *et al.*, 1994). It has also been used as a matrix in the preparation of both water-soluble and sparingly water-soluble drugs using solid dispersion technique (Shaikh *et al.*, 1987).

It has previously been reported that, drug release from matrix systems is critically governed by physico-chemical nature of the drug molecule as well as by the pH of the dissolution medium (Quadir *et al.*, 2002; Reza *et al.*, 2003). The objective of this work is to evaluate the efficiency of ethylcellulose as a sole matrix former on sustaining the release of drugs having different physical and chemical properties at varying pH level. The effect of applied pressure and tablet hardness on drug release from directly compressed matrices was also investigated. Three drugs e.g. theophylline (TH) as a soluble neutral drug, diclofenac sodium (DS) as an acidic drug with strong pH dependant solubility and diltiazem hydrochloride (DH) as basic drug of acidic salt were used. All the three drugs chosen in this study are proven candidates to be formulated in sustained release dosage form and have been subjected to thorough

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investigation for their candidature (Verma *et al*., 1996; Chattaraj *et al.*, 1996; Shah *et al.*, 1997). The drug release process was kinetically interpreted by means of mechanistic models.

MATERIALS AND METHODS

Materials

Theophylline and diclofenac sodium were kind gifts from Square Pharmaceuticals Bangladesh Limited. Diltiazem HCl was generously donated by Drug International Ltd. Ethylcellulose (14 cp) was used as received from BDH, UK. Aerosil (colloidal silicon di oxide) and magnesium stearate were procured from Hanau Chemical Limited, Japan. Hydrochloric acid and tribasic sodium phosphate were purchased from Merck, Germany.

Preparation of matrix tablets

The active ingredients (diclofenac sodium / theophylline / diltiazem HCl), ethylcellulose, lubricant and flow promoters were blended together by dry mixing and made into tablets by direct compression (Shora *et al.*, 1980). To quantify the effect of applied pressure on tablet hardness and dissolution, the matrices were prepared under 1, 2, 3, 4 and 5 ton of compression pressure and compression time was kept at 30 seconds. For an individual active ingredient, 20 tablets were prepared at each level of compression pressure. The formulations of the tablets with their codes are listed in table-1. In all cases, the amount of each type of active ingredient is 100 mg and the total weight of the tablet is 406 mg. Properly weighed ethylcellulose, magnesium stearate, aerosol and the active ingredient were blended in a laboratory mixer 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 13 mm flat faced punch and die set. Before compression, the surface of the die and punch were lubricated with magnesium stearate. The preparations were stored in airtight containers at room temperature for further study.

Table 1

Formulations of the matrix tablets (per tablet in mg)

Ingredients	DS	TH	DH
Diclofenac sodium	100	-	-
Theophylline	-	100	-
Diltiazem HCl	-	-	100
Ethylcellulose	300	300	300
Magnesium stearate	2	2	2
Aerosil	4	4	4
Total weight	406	406	406

Hardness determination

Tablet hardness was determined by a standard Monsanto Hardness Tester and the breaking strengths were expressed in terms of kg/cm^2. Five tablets were tested for each of the formulation batches.

Dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 10 hours under sink condition using a six station USP XXII type I apparatus at 37±0.5°C and 50 rpm speed. Each of the formulation was tested separately in 1000 ml of dissolution medium, at varying pH condition. The dissolution media with pH of 1.2, 4.5 and 6.8 were prepared by mixing appropriate amounts of 0.1M hydrochloric acid and 0.2 M tribasic sodium phosphate. At every 1-hour interval samples of 5 ml were withdrawn from the dissolution medium and were replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for theophylline, 277 nm for diclofenac sodium and 238 nm for diltiazem HCl by 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.

RESULTS AND DISCUSSION

Effect of pH of dissolution media on drug release

The result of the dissolution experiment of ethylcellulose matrix tablets performed in media of different pH values viz. 1.2, 4.5 and 6.8 are illustrated in fig.1 (a-c). Figure shows that, release of diclofenac sodium, theophylline and diltiazem HCl varies as the pH was changed from 1.2 to 6.8. In case of diclofenac sodium, 23% drug was released after 10 hours of dissolution period at pH 1.2 (Fig. 1a). However, when the pH was increased to 4.5, release of diclofenac sodium was significantly elevated. About 68% of drug was released at this pH whereas at pH 6.8, cumulative accumulation of diclofenac sodium was 89% after the specified period. Release profile of theophylline from ethylcellulose matrix tablets at different pH is illustrated in Fig. 1(b). Matrix tablets containing theophylline released 95% and 92% of the active ingredient at pH 1.2 and 4.5 which indicates that, increasing the pH value from 1.2 to 4.5 could not impart any significant impact on release of theophylline from ethylcellulose matrix. Figure also shows that, the release pattern of theophylline at pH 1.2 and 4.5 was almost super imposable showing insignificant difference in the rate and extent of release. However, raising the pH of dissolution media to 6.8, reduced the release of theophylline to 80%. Diltiazem HCl, on the other hand, exhibited the release pattern reverse to that of diclofenac sodium (fig. 1c). Higher amount of diltiazem HCl was released in acidic pH and gradually decreased as the pH of the dissolution media was increased. Fig. 1c shows that, 99% and 93% of diltiazem HCl was released after 10 hours at the pH value of 1.2 and 4.5 respectively. On the other

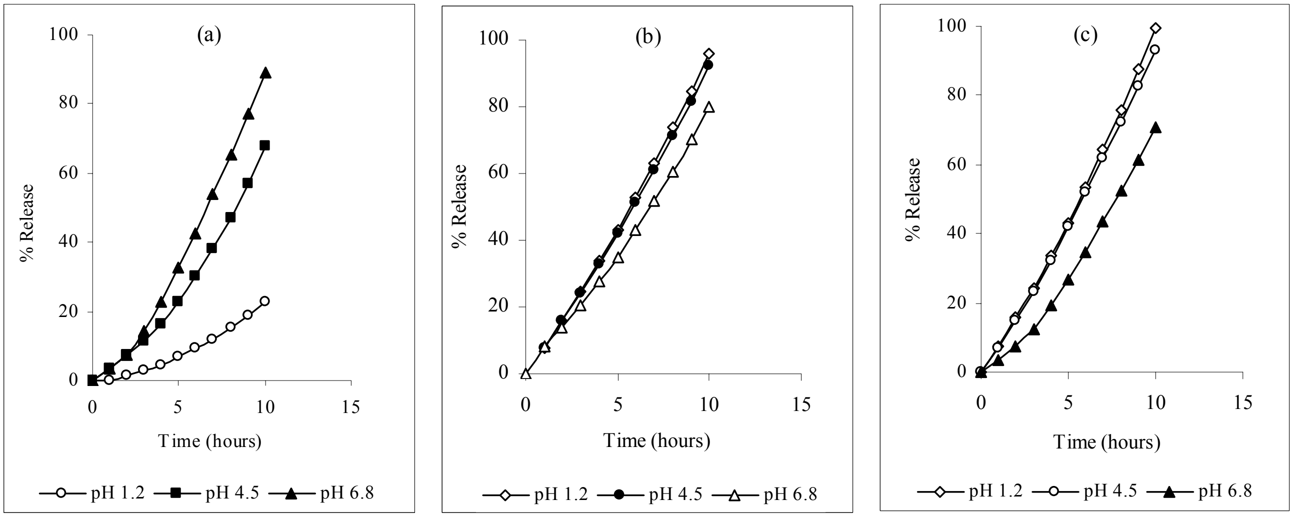

Fig.1: Effect of pH of dissolution media on the release profile of (a) Diclofenac sodium (b) Theophylline and (c) Diltiazem HCl.

hand, at pH 6.8, 70% of the active ingredient was accumulated after 10 hours of dissolution period. This disparity in release among the investigated drugs can be attributed to the differences in their physical and chemical properties particularly on their pk_a and solubility profile (Reza *et al.*, 2003). For a matrix system like ethylcellulose that possesses plastic and hydrophobic property, drug particles present in the surface of the matrix is initially released into the surrounding media generating many pores and cracks which facilitates further release of drug. Diclofenac sodium is reported to show pH dependent solubility. The molecule is a weak acid with pk_a value of 4.0 and is practically insoluble in acidic solution and dissolves readily in the intestinal fluid and water. Therefore, the lower solubility of diclofenac sodium in acidic media limits the initial release of surface drugs as well as the formation of channels within the matrix. Consequently, the overall release of diclofenac sodium is low in pH 1.2 and 4.5. Increment of pH to 6.8 caused diclofenac sodium to dissolve readily since the molecule is acidic in nature. Alkaline pH facilitates ionization of such molecule that ultimately results in greater solubility and higher release profile. Similar observation was also reported previously (Billah *et al.*, 1998). Diltiazem HCl, on the other hand, is an acidic salt of basic drug having the pk_a value of 7.7 and the molecule is freely soluble in water. Alderman reported that, the release kinetics of hydrosoluble drugs is mainly governed by diffusion from matrix system (Alderman, 1984). Diltiazem HCl present in the ethylcellulose matrix rapidly leaves the matrix at pH 1.2 and 4.5 because of its basic nature. The higher release profile obtained with diltiazem HCl can be attributed to the rapid ionization and higher solubility of the drug in acidic medium. Increment of pH of the dissolution media reduced the extent of ionization and solubility of diltiazem HCl. As a result both the rate and extent of diltiazem HCl release from ethylcellulose matrix was decreased in basic media.

A significant proportion of theophylline was released over the entire pH range selected for the experiment. The fact is attributable to the chemistry, higher pk_a value (pk_a 8.6) and solubility profile of theophylline in both acidic and basic type of dissolution media. It has been reported that, theophylline shows the solubility of 12.76 mg ml^{-1} in acidic media while 9.13 mg ml^{-1} in basic media (Lund, 1984). Consequently, the rate and extent of dissolution was high in both acidic and basic dissolution media. Again, Theophylline, being an anhydrous drug molecule, has not been influenced by pH induced ionization. As a result, changing the pH of the dissolution media did not significantly influence the drug release pattern. Ethylcellulose, being a polymer with insoluble and inert plastic characteristics, did not change its drug retaining activity due to the change of pH. The fact can be substantiated by the fact that, release profile of drug molecules, irrespective of their chemical nature, were almost linear with time.

Effect of compression force on the release of drugs from ethylcellulose matrix tablets

The importance and influence of compression force on drug release is well reported (Dabbagh *et al.,* 1996; Katikaneni *et al.,* 1995). The effect of compression forces on the release characteristics of diclofenac sodium, theophylline and diltiazem HCl were studied by applying 2 ton and 5 ton pressure. Dissolution was carried out at pH 6.8 so that, optimum release was obtained for all the classes of drugs. Effect of compression force on drug release rate (% released/time) is illustrated in fig. 2. It was found that, an increase in the compression force, decreased the rate of drug release irrespective of chemical nature of the molecule. The decrease in the release rate, though not significant enough, may be due to a decrease in porosity and simultaneous increase in matrix tortuosity owing to the formation of continuous matrix at higher applied forces (Deasi *et al.*, 1966). Similar observation was reported by Katikaneni et al. with ethylcellulose matrix tablets loaded with pseudoephidrine (Katikenani *et al.*, 1995).

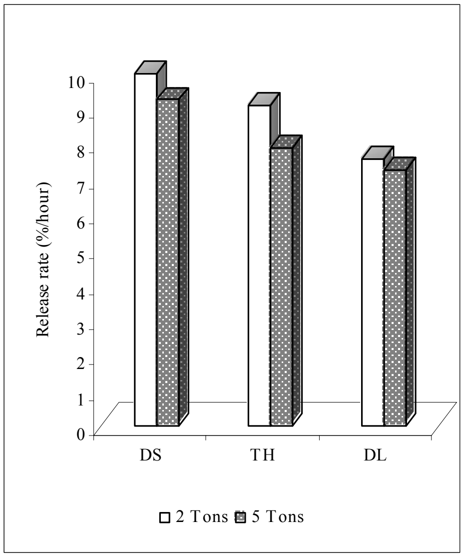

Fig. 2: Effect of comparession force on drug release rate. DS: Diclofenac sodium.

Effect of compression force on tablet hardness

The effect of different compression force i.e. 1, 2, 3, 4 and 5 ton on tablet hardness (kg/cm^2) is illustrated in table-2.

Table 2
Effect of compression force on tablet hardness (Kg/cm^2)

Compression force (tons)	Hardness (kg / cm^2)		
	DS	TH	DH
1	15.1	15.0	15.0
2	15.7	15.4	15.8
3	16.2	16.0	16.1
4	16.8	16.5	16.7
5	17.1	17.2	17.0

From the table, it can clearly be seen that, tablet hardness varies only slightly with compression force within the experimental range. This is to be mentioned that, the number of interaction points or the bonding surface area governs the tablet hardness (Ritgers and Peppas, 1987). Kartikaneni *et al.* (1995) reported that, for ethylcellulose matrix tablet, hardness varies significantly with drug loading in the matrix, viscosity grades and particle size of ethylcellulose since these parameters conspicuously affects porosity and tortuosity of the matrix (Ritgers and Peppas, 1987). Since in this experiment, the viscosity and drug loading parameter were kept constant, increment of applied pressure did not impart significant impact on hardness of the matrix tablets as the points of interaction and bonding surface remained unchanged.

Kinetic approach of drug release from ethylcellulose matrix

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

$$Q_t = Q_0 + K_0 t \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where Q_t is the amount of drug release at time t, K_0 is the apparent dissolution rate constant and Q_0 is the initial concentration of the drug in the solution resulting from a burst effect. In this case, drug release runs at a constant rate. The data, when treated with this equation by plotting the percent of theophylline release (Q) against time (hours), yielded a fairly good linearity confirming that the release permeation data followed the zero-order model ($R^2 > 0.99$). This was true for all the formulations irrespective of the physico-chemical nature of the drug and range of compression force applied. The value of Q_0 was negligible for all the formulations indicating the absence of burst effect and implies that ethylcellulose exerted a strong retarding effect on drug release from the beginning of dissolution (table-3). Although it is desirable for a controlled release device to deliver drug in zero-order kinetics, it is extremely difficult to attain such pattern as the kinetics of release is affected by the physico-chemical composition of surrounding medium and processing variables (Reza *et al.*, 2003).

Table 3
Drug release parameters from zero order (q_0) and biexponential equation (n, r^2).

Formulations	n	R^2	Q_0 (zero order)
DS	1.01	0.9956	-0.2145
TH	1.00	0.9931	-0.3564
DH	1.04	0.9874	-0.1014

So far as the zero-order release rate (% release/time) is concerned, it was found that, at pH 6.8, diclofenac sodium showed the highest rate of release (9.2%/hour) while diltiazem HCl showed the least (7.2%/hour). The physico-chemical nature of the drug molecule again can be held responsible for this observation. Generally, the net release rate observed is a cumulative effect of drug's solubility (influenced by its structure, molecular weight and pK_a), polymer property (hydrophilicity/lipophilicity, molecular weight, tortuosity) and the relative ratio of drug and polymer in the tablet. Diltiazem HCl, being a basic drug of acidic salt as well as its high molecular weight (450.0) may be considered as the predisposing causes for this slower rate of diltiazem HCl release.

The dissolution data were also fitted according to the well-known exponential equation, Eq. (2) which incorporates the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix:

$$M_t / M_\infty = Kt^n \quad \text{(2)}$$

Where M_t / M_α is the fractional (0.1-0.7) drug release at time t; K is a rate 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).

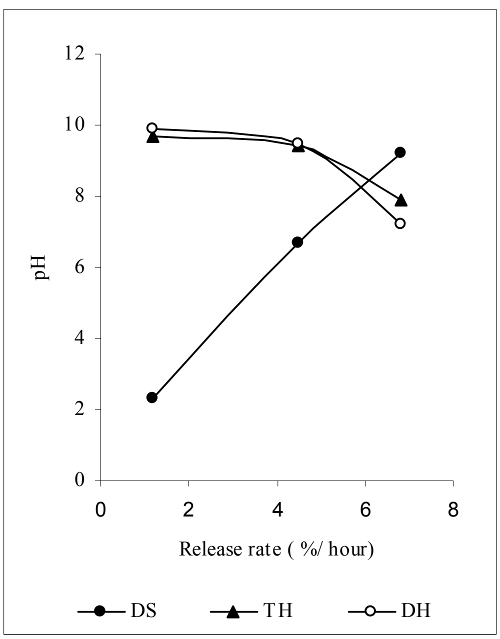

Fig.3: Effect of pH on zero order release rate of different drug molecules

In table-3, the values of n and the correlation co-efficient (R^2) obtained with ethylcellulose matrix tablets are summarized. The value of correlation coefficients R^2 (>0.98) are high enough to evaluate drug dissolution behaviour from wax matrix by Eq. (2). Dissolution data of all the experimental drugs at pH 6.8 was treated with this equation. The model cannot be applied for pH 1.2 and 4.5 because at these pH conditions there were insufficient data point on the release profile for diclofenac sodium to provide accurate values. The values of n for different formulations presented in table-3 clearly shows a clear adherence of drug release to zero order or case II kinetics. This observation was true irrespective of chemical nature of the drug molecule and compression forces applied in this experiment.

CONCLUSIONS

Directly compressed ethylcellulose matrix tablet loaded with active ingredient of diversified physicochemical nature showed sustained drug release over a period of 10 hours in both acidic and basic dissolution medium. An increase in the compression force resulted in decreased release rate irrespective of pH condition and chemical property of drug. However, increment of compression force did not impart significant effect on tablet hardness. Drug release from ethylcellulose matrix followed a zero-order release mechanism. However, a number of critical parameters such as flow property of the tablet mixture, granulation process, tabletting conditions and porosity of the tablet will markedly affect drug release pattern from a matrix tablet. These factors, although beyond the scope of this study, should be taken under consideration during manufacturing process in industrial setup.

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