

In vitro Release Kinetics Study of Diltiazem Hydrochloride from Wax and Kollidon SR Based Matrix Tablets

Mohammad Safiqul Islam^{a*}, Selim Reza^b and Habibur Rahman^b

^aDepartment of Pharmacy, Noakhali Science and Technology University, Sonapur, Noakhali-3802, Bangladesh. ^bDepartment of Pharmaceutical Technology, University of Dhaka, Dhaka, Bangladesh.

Abstract

Extended-release matrix tablets of diltiazem hydrochloride (DTZ) were prepared using waxy materials alone or in combination with Kollidon SR. Matrix waxy materials were carnauba wax (CW), bees wax (BW), cetyl alcohol (CA) and glyceryl monostearate (GMS). Dissolution studies were carried out by using a six stations USP XXII type 1 apparatus. The in vitro drug release study was done in 1000 ml phosphate buffer of pH 6.8 for 12 h. Initial burst release was observed in case of waxy granules. Tablets prepared in combination of waxy granules and Kollidon SR sustained the drug release for more than 12 h. Addition of ludipress instead of Kollidon SR caused the drug release faster (for less than 12 h). Fitting the in vitro drug release data to Korsmeyer equation indicates that diffusion along with erosion could be the mechanism of drug release. Significant differences were found among the drug release profile from different polymeric matrices.

Keywords: Matrix granules; matrix tablets; diltiazem hydrochloride; Carnauba wax; Beeswax; Cetyl alcohol; Glyceryl monostearate.

Introduction

During the past few decades, various types of oral controlled release (CR) formulations have been developed to improve the clinical efficacy of drugs having short half lives as well as to increase patient compliance. These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions. This system is commonly used for manufacturing sustained release dosage forms because it makes such manufacturing easy. Their principal drug-release mechanism is based on drug diffusion through the matrix system. This diffusion is altered by the pH of the medium

and the body's physiological factors, all of which can cause difficulty in controlling the drug release rate. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for sustaining the drug release. Liquid penetration into the matrix is the rate-limiting step in such systems unless channeling agents are used. Waxy materials and Kollidon SR, due to their ease and safety of application have been used as rate retarding polymer and extensively studied by different investigators (1-4). The hydrophobic and waxy materials are potentially erodable and control the release of drug through pore diffusion and erosion. The release mechanism of drug from the matrix systems has been analyzed and explained with the help of different exponential models (5-10). Diltiazem hydrochloride is a calcium

* Corresponding author:

E-mail: nstpharmsafiq@yahoo.com

channel blocker drug used for the treatment of chronic stable angina pectoris and for angina pectoris caused by a coronary arterial spasm and systemic hypertension. Although 90% of an orally administered dose of diltiazem HCl is absorbed, only 40% of the oral dose reaches systemic circulation in an unchanged form. The mean absolute bioavailability of Diltiazem in normal subjects ranges from 33 to 44%. The drug undergoes rapid elimination that causes a short half-life (3.5 h), which dictates dosing at three times per day. Therefore, diltiazem HCl, with its low oral bioavailability, short half-life, and multiple daily dosing, is appropriate for a formulation in an extended-release, once-a day dosage form. As diltiazem hydrochloride is a highly water-soluble drug, its formulation into sustained release (SR) products is rather difficult. In this study waxy plasticizers like CW, BW, CA and GMS were used as plastic materials for preparation of granules and Kollidon SR and Ludipress were used for preparation of tablets. Kollidon SR derived from polyvinyl acetate dispersion (Kollicoat SR 30D) and appears as a spray dried non-hygroscopic powder consisting of polyvinyl acetate and polyvinyl pyrrolidone. It is particularly suitable for direct compression of sustained release matrix tablets. Ludipress is composed of lactose, povidone and crosspovidone. The unique composition of filler, binder and disintegrant and special properties of ludipress yield direct compression tablets of good hardness, very low friability and short disintegration times.

The aim of this study was to evaluate the influence of polymer content and polymer type on the release profile of drug as well as to establish a relationship between drug retaining efficacy of the polymer and physico chemical nature of the drug.

Experimental

Materials

Diltiazem HCl (USP) was generously donated by Drug International Ltd. Bees wax, Cetyl alcohol and Glyceryl monostearate were obtained from BDH, UK. Carnuba wax was obtained from Albright & Wilson Ltd. UK. Kollidon-SR and Ludipress were obtained from BASF

Bangladesh Limited. Aerosil (Silicon dioxide) and Magnesium stearate were procured from Hanau Chemicals Limited, Japan. Trisodium phosphate and Hydrochloric acid were obtained from Merck, Germany.

Methodology

Preparation of matrix granules

Matrix granules were prepared by melt granulation method as previously reported procedure (11). The specified amount of waxy materials were taken in a beaker and melted by heating. Diltiazem hydrochloride was then dispersed in the melted wax with continuous stirring. The ratios of drug: wax used to prepare the different formulations were 1:1 and 1:2. The wet mass was then passed through sieves to collect the granules of particle size 1.21mm.

Preparation of matrix tablets

The method of tablet production has previously been described by several authors (12, 13) that provided reproducible experimental results in terms of in vitro release. The matrix granules, release retardants, filler, lubricant and flow promoters were blended together by dry mixing in a laboratory mixer for 10 min and made into tablets by compression at a fixed compression force 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 tons and 30 s respectively. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. The formulations of the tablets with their codes are listed in Table 1. In all cases, the amount of the active ingredient is equivalent to 120 mg DTZ and the total weight of the tablet is 406 mg. 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 for a period of 12 h using a six stations (1) USP XXII type apparatus at $37 \pm 0.5^\circ\text{C}$ and 50 rpm speed. The dissolution studies were carried out in triplicate for 12 h in phosphate buffer of pH 6.8 under sink

Table 1. Formulation of different batches of matrix tablets containing 120 mg DTZ, 4 mg Aerosil and 2 mg Mg-stearate.

Code	Wax	Granules (equivalent to 120 mg Diltiazem HCl)	Kollidon SR (mg)	Ludipress (mg)
FWD01	CW	240	160	-
FWD02	BW	240	160	-
FWD03	CA	240	160	-
FWD04	GMS	240	160	-
FWD05	CW	360	40	-
FWD06	BW	360	40	-
FWD07	CA	360	40	-
FWD08	GMS	360	40	-
FWD09	CW	240	-	160
FWD10	BW	240	-	160
FWD11	CA	240	-	160
FWD12	GMS	240	-	160
FWD13	CW	360	-	40
FWD14	BW	360	-	40
FWD15	CA	360	-	40
FWD16	GMS	360	-	40

condition. At every 1-h interval 5-ml samples were withdrawn from the dissolution medium. To maintain the volume constant, 5 ml of fresh medium was added in each case. After filtration and appropriate dilution, the sample solution was analyzed at 238 nm by a 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.

Analysis of release data

Different kinetic models (zero-order, first-order and Higuchi's) were applied to interpret the release profile from matrix system. The best fit with higher correlation ($r^2 > 0.98$) was found with the Higuchi's equation. However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow 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 equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior

from polymeric systems (14).

$$\text{Log} (M_t / M_f) = \text{Log} k + n \text{Log} t \quad (1)$$

Where, M_t is the amount of drug release at time t ; M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. Talukder et al applied this equation to evaluate the drug release mechanism from xanthan gum matrix tablets (15). Some Authors (16) used this equation for wax matrix granules whereas others (3, 13) applied for kollidon SR matrix system.

To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 1. A value of $n = 0.45$ indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (16).

Mean dissolution time (MDT) was calculated from dissolution data using the following

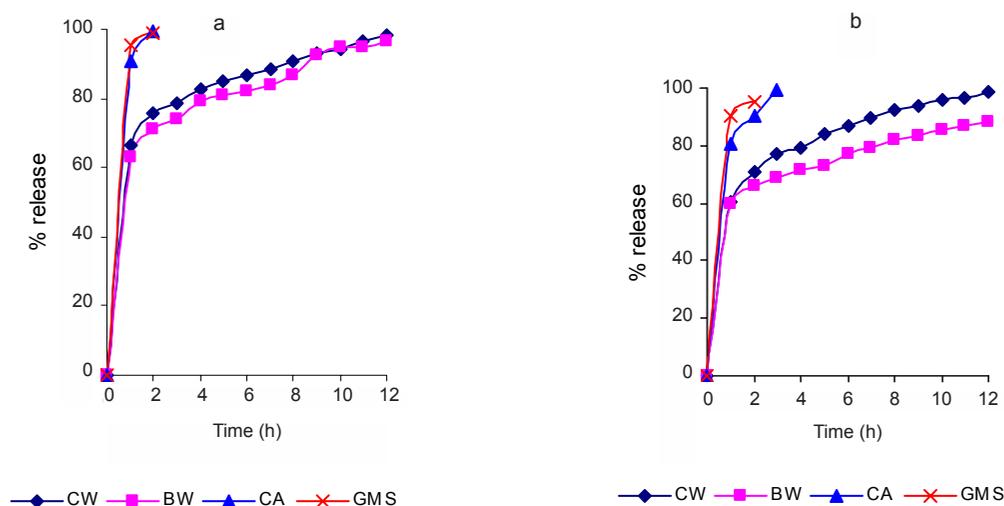


Figure 1. Effect of waxy materials on the release of DTZ. from matrix granules; (a) DTZ : Wax = 1:1, (b) DTZ : Wax = 1:2

equation (Mockel and Lippold) (17).

$$MDT = (n / n + 1) . k^{-1/n} \quad (2)$$

Statistical analysis

To compare the means of all release data and to assess statistical significance between them single-factor analysis of variance (ANOVA) was carried out at 5% significance level.

Results and Discussion

Effect of waxy materials on DTZ release from granules

Figure 1 (a) and Figure 1 (b) show the effect of different concentrations of CW, BW, CA, and GMS (50%, 66.67% w/w) on release rate of DTZ from wax matrix granules. The amount of the matrix forming polymer influenced the drug release from matrix granules. Drug release is inversely proportional to the amount of rate retarding polymer present in the matrix system, i.e. the rate and extent of drug release increases with decrease in total polymeric content of the matrix. The formulations containing 66.67% polymeric content are more sustained than that of the formulations containing 33.33% polymeric content. The overall rate of release of a particular drug at a specific polymeric content was found to be significantly different for different polymers.

It was found that the release is highest from GMS based matrix granules and lowest in case of CW based matrix granules and the sequence of rate retarding of the waxy materials is BW>CW>CA>GMS.

No significant difference ($P < 0.05$, single factor ANOVA) in release rate was observed between granules containing either 50% or 66.67 % of CW or BW or CA or GMS.

Physicochemical properties of the drug

The release-retarding efficiency of the polymers depends on the physicochemical nature of the drug molecule. DTZ is an acidic salt of basic drug having a pKa value of 7.7 and the molecule is freely soluble in water. One researcher reported that, the release kinetics of water soluble drugs is mainly governed by diffusion from hydrophilic matrices (18). DTZ present in the surface of matrix tablet rapidly leaves the matrix system because of its higher solubility. The class and nature of the matrix forming polymers influenced the release profile of active ingredient.

Effect of Kollidon SR and waxy materials on DTZ release from matrix tablets

Types of polymers used to prepare the matrix were also found to impart differential effect on

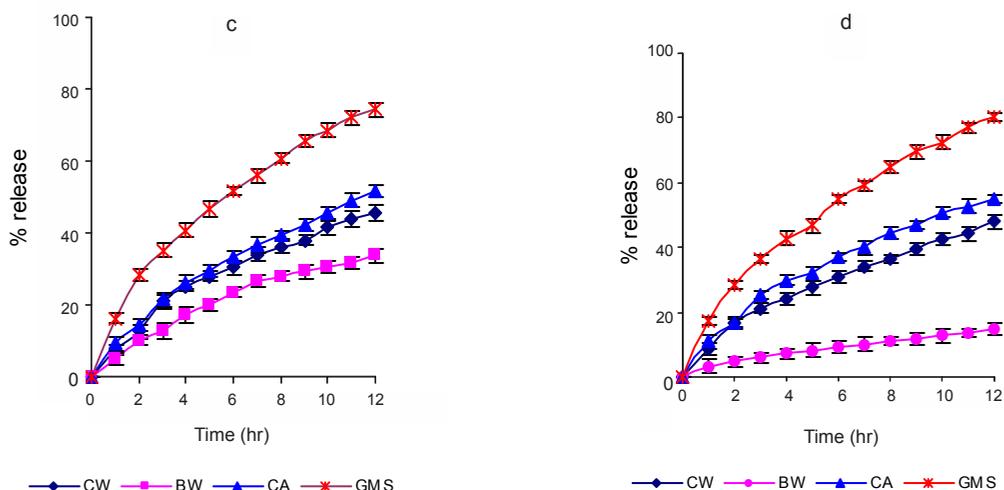


Figure 2. Effect of waxy materials and Kollidon SR on the release of DTZ from matrix tablets; (c) FWD01-FWD04, (d) FWD05-FWD08.

matrix disintegration. Formulation FWD01-04 contains 120 mg CW, BW, CA, GMS respectively with 160 mg kollidon SR. The difference between the release rate of GMS and CA based matrix tablets is not significant and also it is not significant between BW and CW based matrix tablets. But the overall release rates, i.e. among the CW, BW, CA, GMS based matrix tablets were found significantly different ($P < 0.0005$, single factor ANOVA, $F_{\text{calculated}} = 9.58$ and $F_{\text{critical}} = 2.82$). This may be due to the large difference among CA and GMS based matrix tablets with CW and BW based matrix tablets. After 1st h dissolution 7.51%, 5.06%, 9.18% and 16.33% (Figure c) and after 12 hours dissolution 45.75%, 33.7%, 51.54% and 74.26% DTZ (Figure c) were released from formulations FWD01, FWD02, FWD03 and FWD04 respectively. Comparing with respective granules Figure 1 (a, b) they become more sustained.

From figure 2 (c, d) and figure 3 (e, f) it is clear that release retarding order of polymers is $BW > CW > CA > GMS$. Bees wax show greater rate retarding efficiency than the others. The beeswax based granules were quite sticky and after compression they were tightly bound with kollidon SR. Formulations FWD05-08 contain 360 mg of CW, BW, CA, GMS respectively with 40 mg kollidon SR. Due to different types

of wax materials release rate was also found significantly different ($P < 0.00001$, single factor ANOVA, $F_{\text{calculated}} = 21.51$ and $F_{\text{critical}} = 2.82$). After 1st hour dissolution 8.9%, 3.25%, 11.02% and 17.33% and after 12 h dissolution 48.09%, 14.64%, 55.14% and 80.26% DTZ (Figure d) were released from formulations FWD05, FWD06, FWD07 and FWD08 respectively.

Formulations FWD01-FWD04 show greater drug release retarding properties (where Kollidon SR is 160 mg) than that of formulations FWD05, FWD07, FWD08 where the Kollidon SR is 40 mg but amount of waxy materials is double. Formulation FWD06 show greater drug release retarding properties than formulations FWD01-FWD04. This is also due to the sticky property of bees wax based granules.

Effect of Ludipress on DTZ release from matrix tablets

In case of formulations FWD09-FWD16 ludipress is used instead of Kollidon SR that has no release retarding property. Ludipress contains lactose and kollidon CL. Lactose caused a decrease in the tortuosity of the diffusion path of the drug and Kollidon CL, by its swelling effect, weakened the matrix integrity (19). These two factors can be ascribed for the higher release rate of drug with formulations containing ludipress.

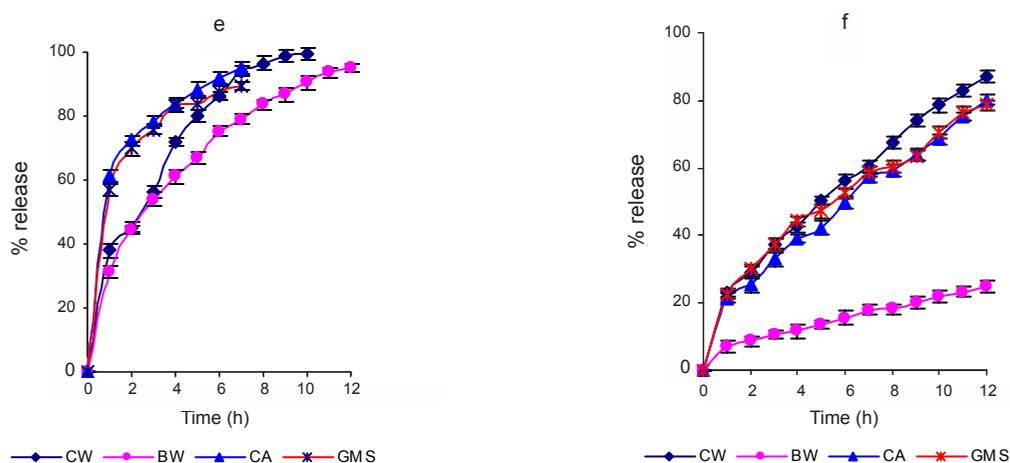


Figure 3. Effect of Waxy materials and Ludipress on the release of Diltiazem HCl from matrix tablets; (e) (FWD09-FWD12): 1:1 DTZ and waxy materials were used in granules, (f) (FWD13-FWD16): 1:2 DTZ and waxy materials were used in granules.

Analogous result has been reported with previous investigations (3).

In case of formulations FWD09-FWD12 the rate was not significantly different ($P < 0.05$, single factor ANOVA, $F_{\text{calculated}} = 0.45$ and $F_{\text{critical}} = 2.90$). On the other hand in case of formulations FWD13-FWD16 where the amount of ludipress is lower than that of formulations FWD09-FWD12 the effect of waxy polymeric type on drug release was found to be significantly different ($P < 0.00005$ single factor ANOVA, $F_{\text{calculated}} = 14.84$ and $F_{\text{critical}} = 2.81$).

Release kinetics

The release rate kinetic data for all the models is shown in Table 2. Drug release data of matrix tablets of formulations FWD04, FWD09, FWD13-FWD16 showed good fit into the Higuchi equation ($r^2 > 0.98$). Tablets of formulations FWD01-FWD03, FWD05-FWD08 and FWD10-FWD12 showed high linearity with Korsmeyer equation ($r^2 > 0.98$) and indicated combined effect of diffusion and erosion mechanisms for controlled drug release. Value of release exponent “n” determined from the various matrices ranged from 0.2247 to 0.7511 and the k values ranged from 0.0314 to 0.6140 (Table 2). Values of “n” and “k” were found to vary with type and concentration of

polymers.

The overall effect of polymer on release (FWD01-FWD16) was also significantly different ($P < 0.00005$, single factor ANOVA). It means null hypothesis is nullified and alternative hypothesis is accepted i.e. the variation in formulations in polymeric type and content (FWD01-FWD16) have significant effect on release profile.

Mean dissolution time (MDT) value is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. MDT value is higher (114.27 h) in case of formulation FWD06 and is lower (1.61 h) in case of formulation FWD11. This finding can be attributed to the higher water repelling property of BW and CW and kollidon SR compared to CA, GMS.

Conclusion

From the results of the present study it appears that the release of DTZ was significantly influenced by the characteristics of the polymer used. Carnauba wax and Bees wax and Kollidon SR show greater rate retarding property in comparison with cetyl alcohol and glyceryl monostearate. In USP 29 the dissolution medium used for DTZ extended release tablet is distilled

Table 2. Mathematical modeling and drug release kinetics of DTZ sustained-release matrix tablets.*

Formulations	r^2 †				k ‡	n #	Order of release	MDT (h)
	Zero	1 st order	Higuchi	Korsmeyer Model				
FWD01	0.9478	0.9784	0.9843	0.9966	0.0754	0.7511	non-Fickian	13.40
FWD02	0.9484	0.9637	0.9782	0.9847	0.0569	0.7510	non-Fickian	19.52
FWD03	0.9661	0.9923	0.9858	0.9953	0.0949	0.6908	non-Fickian	12.35
FWD04	0.9393	0.9954	0.9963	0.9935	0.1770	0.5926	non-Fickian	6.92
FWD05	0.9580	0.9859	0.9909	0.9916	0.0981	0.6407	non-Fickian	14.63
FWD06	0.9677	0.9752	0.9888	0.9982	0.0314	0.6059	non-Fickian	114.27
FWD07	0.9554	0.9893	0.9898	0.9936	0.1139	0.6486	non-Fickian	11.21
FWD08	0.9521	0.9958	0.9939	0.9975	0.1807	0.6086	non-Fickian	6.29
FWD09	0.8737	0.9413	0.9849	0.9746	0.3597	0.4682	non-Fickian	2.83
FWD10	0.8722	0.9888	0.9923	0.9955	0.3231	0.4508	non-Fickian	3.81
FWD11	0.678	0.9631	0.9067	0.9994	0.6140	0.2247	Fickian	1.61
FWD12	0.6675	0.9122	0.9022	0.9805	0.5818	0.2322	Fickian	1.94
FWD13	0.9642	0.9824	0.9920	0.9871	0.2084	0.5626	non-Fickian	5.85
FWD14	0.9616	0.9742	0.9818	0.9699	0.0626	0.5262	non-Fickian	66.79
FWD15	0.9663	0.9743	0.9823	0.9766	0.1872	0.5577	non-Fickian	7.22
FWD16	0.9376	0.9822	0.9949	0.9946	0.2156	0.5082	non-Fickian	6.90

*Analyzed by the regression coefficient method.

† Correlation coefficient.

‡ Kinetic constant incorporating structural and geometric characteristic of the tablet.

Diffusional exponent indicative of the mechanism of drug release.

MDT indicates mean dissolution time in hour.

water. In this experiment we used buffer of pH 6.8. This pH is closer to water pH. It was demonstrated that combination of both waxy materials and Kollidon SR could be successfully employed for formulating sustained-release matrix tablets of DTZ.

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