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A Simple Oral Controlled Release Device that Releases Drug Via Zero Order Kinetics

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The present study was aimed at preparing a simple device that releases drug via zero order kinetics. The basic matrix forming material employed was glycerol monosterate in combination with either methylcellulose or ethylcellulose. The drugs used to evaluate the release characteristics of the resulting matrices were aspirin and propranolol hydrochloride.

Drug release from glycerol monostearate and metheylcellulose and from glycerol monosterate and ethylcellulose matrices was best explained by zero order kinetics. The matrices were easily prepared via direct compression after lubrication of the die and punches. Such zero order release oral devices can be used to deliver drug at a predetermined constant rate that will result in constant drug levels in the body for prolonged periods of time.

Key Words: Device, Controlled, Drug, Release, Kinetics.

INTRODUCTION

A controlled release device whether oral, transdermal, ocular, rectal or parenteral, that releases drug via zero order mechanism is most desirable. This is so because constant therapeutic levels of drug in the plasma are ensured provided the rate of drug release from the device is the rate – limiting step. A simple equation used to explain zero order kinetics is: **Q = kt**; where Q is the amount of drug released in time, t, and k is the release constant.

Zero order release mechanism is very difficult to achieve. Most oral rate controlled devices release drug via square root of time kinetics or first order kinetics. The majority of oral controlled release devices that have been prepared that release drug via zero order kinetics are complicated as they involve matrices of special geometry [1]. Kim [2] prepared compressed donut shaped tablets with zero order release kinetics while Van der Veen *et al* [3 – 4] prepared amylodextrin tablets with almost constant drug release rates.

In view of this the present research was aimed at preparing a ***simple*** oral controlled release device that releases drug via zero order kinetics over prolonged periods of time.

MATERIALS

Glycerol monosterate (GMS) was the basic oral controlled release matrix material and was supplied by Croda Chemical Company, Zimbabwe. ***Methylcellulose*** (MC) was used as a carrier for the GMS and Sigma Chemical Company, USA, supplied it. ***Ethylcellulose*** (EC) was another carrier for the GMS and like MC, was also supplied by Sigma Chemical Company, USA. ***Propranolol hydrochloride*** was used to evaluate the release characteristics of the matrices. Varichem Pharmaceutical Company, Zimbabwe, supplied this drug. ***Aspirin*** was also used to evaluate the release characteristics of the matrices and was supplied by Sigma Chemical Company, USA.

METHODS

Preparation of Binary Excipient

The carriers used were MC and EC. In each case, the GMS and carrier (either MC or EC) were geometrically mixed in a beaker until a free flowing binary excipient was formed. The ratio of GMS: MC was 1:22 while that for GMS: EC was 1:12.

Tablet Preparation

Once the binary excipient was formed it was mixed geometrically with the drug (either propranolol hydrochloride or aspirin) and compressed directly on a single punch Erweka tablet machine (Type EK 0, G.m.b.H, Germany) equipped with 9 mm flat faced punches. The tablet machine was manually operated. All tablets prepared were approximately 250 mg. This was achieved by individually weighed samples to a mass of 250 ± 3 mg and then manually compressing one sample at a time. Drug content ranged from 20 – 60 % $^{w}/_{w}$.

Dissolution Studies

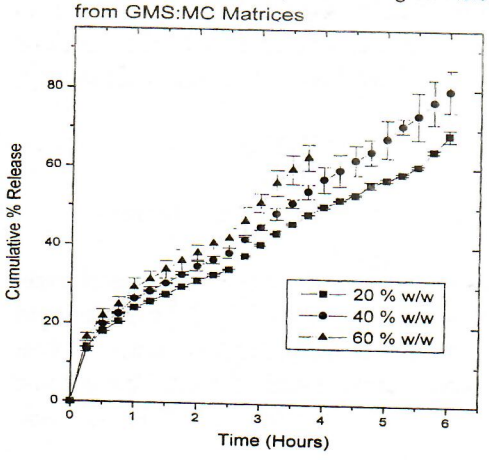
Dissolution evaluation was carried out 48 hours post – compaction. These studies were carried out using the rotating basket USP method I. The dissolution media was distilled water.

RESULTS AND DISCUSSION

Student t – tests were carried out on the correlation coefficient data and results evaluated at 5 % significant level (p = 0.05). The calculated t values, t_{cal}, and the statistical table's t values, t_{tab}, at the appropriate degrees of freedom are quoted in the text.

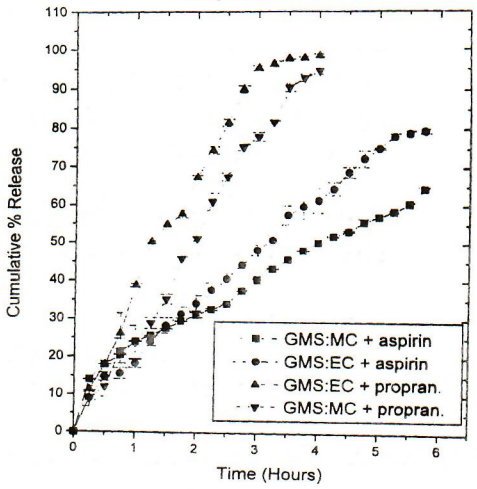
The effect of drug loading on GMS: MC matrices is summarized in figure 1.

Figure 1: Effect of Aspirin Loading on Release from GMS:MC Matrices



As expected, high drug levels had high release rates while the converse was true for low drug levels. GMS: MC matrices had lower release rates than GMS: EC matrices as shown in figure 2.

Figure 2: Effect of Type of Matrix and Drug on Release



This was unexpected since MC is relatively hydrophilic while EC is hydrophobic. This effect was apparent with both drugs (aspirin and propranolol hydrochloride). This anomaly was attributed to the possible interaction between GMS and MC forming a better release - sustaining matrix than GMS and EC. Propranolol hydrochloride showed faster release rates than aspirin with either matrix, as it is more water-soluble.

Aspirin release from GMS: MC and GMS: EC matrices was best explained by zero order kinetics ($p = 0.05$, $t_{cal} \geq 7.58$, $t_{tab} = 2.13$) and ($p = 0.05$, $t_{cal} \geq 8.50$, $t_{tab} = 2.13$) respectively (see also table 1). The same trend was obtained for propranolol hydrochloride release from GMS: MC matrices ($p = 0.05$, $t_{cal} \geq 5.14$, $t_{tab} = 2.13$) (see also table 2). These results showed that zero order kinetics were a ***matrix*** property rather than a drug property.

Drug release from either MC or EC on its own was accomplished within a matter of minutes and was not according to zero order kinetics. Hence the zero order kinetics was a GMS property rather than the carrier's property.

Table 1: Aspirin Release Kinetics from GMS:MC and GMS:EC Matrices (n = 3)

ZERO ORDER: Q = kt		
	GMS: MC	**GMS: EC**
	Mean ± sd	**Mean ± sd**
Slope %/hr	8.39 ± 0.04	13.43 ± 0.12
Intercept (%)	14.86 ± 0.02	7.22 ± 1.44
Correlation coefficient	0.99620 ± 0.00056	0.99656 ± 0.00155
FIRST ORDER: Log_{10} (100 % - Q) = kt		
	GMS: MC	**GMS: EC**
	Mean ± sd	**Mean ± sd**
Slope (hr^{-1})	-0.0777 ± 0.0007	-0.1232 ± 0.0026
Intercept	1.988 ± 0.001	2.044 ± 0.006
Correlation coefficient	0.99060 ± 0.00033	0.98633 ± 0.00231
HIGUCHI MECHANISM: $Q = kt^{0.5}$		
	GMS: MC	**GMS: EC**
	Mean ± sd	**Mean ± sd**
Slope (%/$hr^{0.5}$)	29.91 ± 0.15	41.05 ± 0.33
Intercept (%)	-8.16 ± 0.11	-20.06 ± 1.41
Correlation coefficient	0.98868 ± 0.00024	0.98781 ± 0.00089

Table 2: Propranolol Hydrochloride Release Kinetics from GMS:MC and GMS:EC Matrices (n = 3)

ZERO ORDER: Q = kt		
	GMS: MC	**GMS: EC**
	Mean ± sd	**Mean ± sd**
Slope (%/hr)	25.67 ± 0.81	30.67 ± 0.91
Intercept (%)	0.24 ± 2.97	5.63 ± 1.73
Correlation coefficient	0.99544 ± 0.00062	0.99411 ±0.00205
FIRST ORDER: Log_{10} (100 % - Q) = kt		
	GMS: MC	**GMS: EC**
	Mean ± sd	**Mean ± sd**
Slope (hr^{-1})	-0.3002 ± 0.0067	-0.4060 ± 0.0203
Intercept	2.180 ± 0.010	2.189 ± 0.025
Correlation coefficient	0.95615 ± 0.00678	0.93974 ± 0.00438
HIGUCHI MECHANISM: $Q = kt^{0.5}$		
	GMS: MC	**GMS: EC**
	Mean ± sd	**Mean ± sd**
Slope (%/$hr^{0.5}$)	64.43 ± 2.05	70.62 ± 1.99
Intercept (%)	-35.33 ± 4.12	-30.58 ± 2.66
Correlation coefficient	0.98197 ± 0.00150	0.99151 ± 0.00378

Table 3: Effect of Aspirin Loading on Release Kinetics from GMS:MC Matrices (n = 3)

ZERO ORDER: Q = kt			
	20 % w/w	**40 % w/w**	**60 % w/w**
	Mean ± sd	**Mean ± sd**	**Mean ± sd**
Slope (%/hr)	8.39 ± 0.04	10.93 ± 1.06	12.27 ± 0.56
Intercept (%)	14.86 ± 0.02	13.08 ± 1.61	14.74 ± 1.28
Correlation coeff.	0.99620 ± 0.00056	0.99590 ± 0.00246	0.99181 ± 0.00080
FIRST ORDER: Log_{10} (100 % - Q) = kt			
	20 % w/w	**40 % w/w**	**60 % w/w**
	Mean ± sd	**Mean ± sd**	**Mean ± sd**
Slope (hr^{-1})	-0.0777 ± 0.0007	-0.1009 ± 0.0147	-0.0922 ± 0.0084
Intercept	1.988 ± 0.001	2.003 ± 0.020	1.956 ± 0.003
Correlation coeff.	0.99060 ± 0.00033	0.97264 ± 0.01813	0.97784 ± 0.00270
HIGUCHI MECHANISM: $Q = kt^{0.5}$			
	20 % w/w	**40 % w/w**	**60 % w/w**
	Mean ± sd	**Mean ± sd**	**Mean ± sd**
Slope (%/$hr^{0.5}$)	29.91 ± 0.15	33.80 ± 3.02	30.72 ± 1.41
Intercept (%)	-8.16 ± 0.11	-9.52 ± 3.29	-2.14 ± 0.56
Correlation coeff.	0.98868 ± 0.00024	0.97964 ± 0.01059	0.97558 ± 0.00082

Increasing drug concentration did not alter the zero order kinetics of the GMS:MC matrix as shown in table 3. At 20 % w/w drug ($p = 0.05$, $t_{cal} \geq 7.58$, $t_{tab} = 2.13$); at 40 % w/w drug ($p = 0.05$; $t_{cal} \geq 2.59$, $t_{tab} = 2.13$) and at 60 % w/w drug ($p = 0.05$, $t_{cal} \geq 8.57$, $t_{tab} = 2.13$). This is a very desirable quality in a matrix that enables it to be loaded with a variety of drug concentrations without compromising its release kinetics.

CONCLUSIONS

GMS devices are very easy devices to prepare and they release drug primarily via zero order kinetics. Variable drugs concentrations and different drugs can be incorporated into the matrix without significantly altering the zero order release kinetics of the device. Such oral controlled release devices can be used to obtain constant therapeutic drug levels within the plasma throughout the release period. GMS is readily available in developing countries such as oral controlled release devices economically.

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