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Modification of Mechanism of Drug Release from Processed Hydrogenated Vegetable Oil

R.T.J. CHIGWANDA[1*] AND J.N. STANIFORTH[2]

[1]*Department of Pharmacy, Faculty of Medicine, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Zimbabwe.*
[2]*Ventura Ltd, University of Bath, Claverton Down Rd, BA2 7AY, Bath, UK*

This study was aimed at altering the mechanism of drug release from processed hydrogenated vegetable oil from its predominant square root of time kinetics since release rate decreases with time due to the longer distance that the drug in the inner layers has to travel before eluting out. A variety of materials were incorporated into the oil so as to alter the release profile. The release from the various modified matrices was analysed.

Myverol, mainly glycerol monostearate, was found to alter drug release from processed hydrogenated vegetable oil matrices from Higuchi model type kinetics to Fickian diffusion coupled with relaxation model type kinetics. This occurred at a myverol concentration of 30% w/w. This change in release kinetics was attributed to the surfactact effects of myverol that weakened the hydrogenated vegetable oil matrix. A diffusion-relaxation controlled release system with appropriate lag times could be targeted to the various parts of the gastrointestinal tract.

Key Words: Processed hydrogenated vegetable oil; coupled with relaxation; Myverol.

INTRODUCTION

Hydrogenated vegetable oil (HVO) matrices release drug primarily via diffusion according to square root of time kinetics [1]. A simple equation that explains such a release mechanism is $Q = k\,t^{1/2}$; where Q is the amount of drug released at time t and k is a constant. Drug release rates from such devices decrease with time due to the longer distance that drug in the inner layers has to travel before eluting out. Research has been carried out in an attempt to achieve zero order kinetics ($Q = k\,t$; where Q, k and t are as above) from devices such as HVO matrices [1-5]. However, the methods used in all these cases are cumbersome and complicated as they involve the production of devices with special geometry and/or drilling holes in the devices.

A combination of two or more release mechanisms might be necessary in order to achieve an increase in release rate with time in a drug delivery device. A good example is a device that might release drug via the diffusion relaxation model [6]. The equation for such a mechanism is $Q = k_1 t^m + k_2 t^{2m}$; where Q and t are as above, k_1 is the diffusion constant, k_2 is the relaxation constant and m is the fickian diffusion exponent. For a device of diameter 8mm and thickness 2.8mm, $m = 0.46$ and $2m - 0.92$. The above equation then results in: $Q = k_1 t^{0.46} + k_2 t^{0.92}$. At the beginning of the drug delivery, release governed primarily by diffusion might be dominant followed by more relaxation kinetics thus increasing the release rate with time. Such a device could be ideal for proximal colonic drug targeting, as it will counteract the effects of gradual fecal consolidation by gradually increasing the release rate.

The present study was therefore aimed at modifying the release mechanism of a HVO

* Author to whom correspondence may be addressed.

matrix using simple method(s) so as to obtain zero order and/or increasing release rate with time, with the system capable of being targeted to a proximal colon.

MATERIALS

Sterotex K (hydrogenated castor oil) the HVO that functioned as the basic release sustaining matrix material; was supplied by Aston chemicals, UK.

PVP K-30 (polyvinylpyrrolidone) supplied by Dyken Chemicals, UK, was used as a binder.

Stearic acid supplied by Sigma Chemical Company, USA, was employed as an auxiliary binder.

Myverol (mainly glycerol monostearate) supplied by Eastman Chemical Company, USA, was used to alter the release mechanism of the HVO matrix.

Aerosil R974 (silica), supplied by Degussa, Germany, was utilized as a carrier for Myverol.

METHODS

Preparation of the processed HVO

The Sterotex K was processed with PVP K30 (7.5%w/w) and stearic acid (5% w/w). The PVP was gradually dissolved in water with the acid at (60^0C). The volume of water used in each case was equivalent to 20% v/w of the total processed HVO. Molten stearic acid was gradually added to the aqueous binder solution while stirring vigorously. The resulting dispersion was added to the HVO in a high speed mixer granulator (Kenwood, Type FP600, Kenwood Ltd, UK). The mixture was granulated for approximately 2 minutes before being tray dried overnight in a convective oven (Baird and Tatlock Ltd, UK). In the case of the formulation containing myverol (30%w/w), the molten stearic acid was mixed with the molten myverol and the rest was carried out as described above. myverol was also processed with Aerosil R974 (ratio: 60:32 respectively) to produce a free flowing formulation that had its release pattern analyzed. The silica was gradually incorporated into the molten myverol while stirring until a free flowing formulation had been formed.

Tablet Preparation

Tablets were made on a manually operated instrumented Manesty E2 tablet machine equipped with 8mm flat faced punches. All the tablets made had an approximate weight of 150mg. Tablets were made at compaction forces ranging from 3 to 18 kN.

Dissolution testing

This was carried out 24 hours post compaction according to the USP dissolution method II.

RESULTS AND DISCUSSION

One way analysis of variance was performed on some of the data obtained and the results were evaluated at 5% significant level (p=0.05). The calculated F values, F_{cal}, and the statistical tables' F values, F_{tab}, at the appropriate degrees of freedom at p=0.05 are quoted in the text.

The release kinetics of propranolol hydrochloride from processed HVO is summarized in table 1. This kinetics confirm the fact that square root of time kinetics best describe drug release from processed HVO matrices.

In order to assess alteration of drug release from HVO matrices containing glycerol monostearate, drug release from glycerol monostearate compacts without HVO was investigated first. Unlike the processed HVO tablets that remained intact at the end of the dissolution process, processed glycerol monostearate tablets disintegrated first. The results pertaining to propranolol hydrochloride release from processed gycerol monostearate are summarized in figure 1. The tablets were made at 9 kN. The carrier for the myverol was

Table 1: Release Kinetics data from Processed HVO tablets (n=6)

Square root of time mechanism (Q=kt^0.5)		
	Mean	sd
Slope (%/hr ^0.5)	33.1	0.67
Intercept (%)	5.57	0.96
Correlation coefficient	0.99958	0.0003
First Order Mechanism {log10 (100% - Q) = kt}		
	Mean	sd
Slope (hr^-1)	-0.111	0.004
Intercept	1.901	0.005
Correlation coefficient	0.99838	0.00064
Zero order mechanism (Q = kt)		
	Mean	sd
Slope (%hr)	5.39	0.16
Intercept	43.13	1.36
Correlation coefficient	0.95031	0.00434

silica (ratio: 60:32 respectively). The curves in figure 1 had two distinct regions, 1 and 2. Both regions had constant drug release rates: F_{cal}=0.30, F_{tab} ≈1.98, p = 0.05 and F_{cal} = 1.58, F_{tab} ≈ 1.63, p = 0.05 respectively. The initial phase (region 1) was attributed to drug release

Figure 1: Drug release and release rate from processed glycerol monostearate compacts

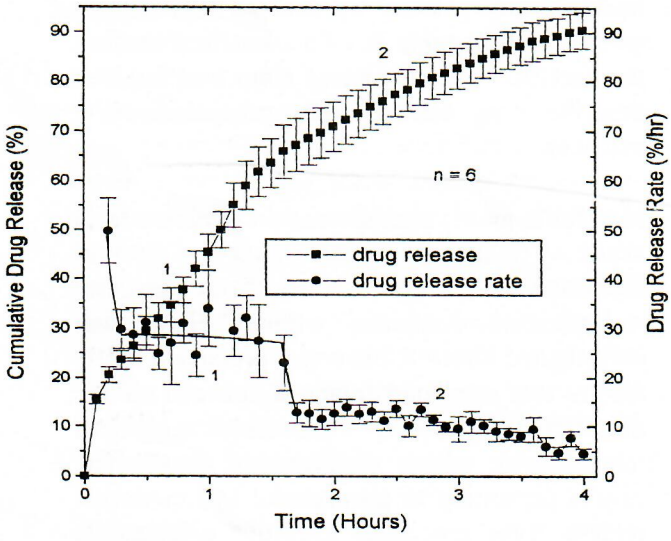
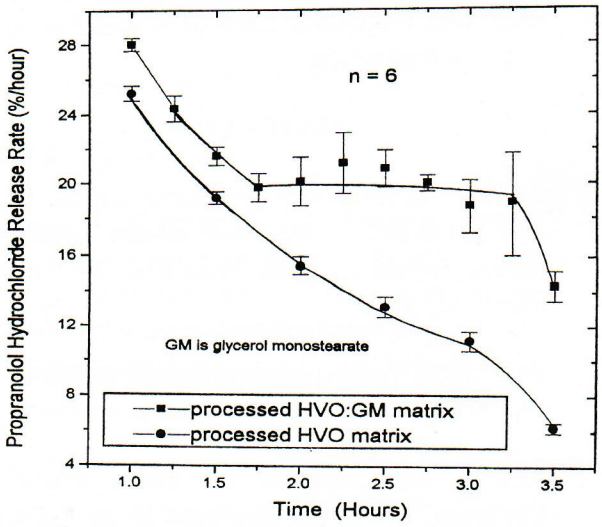


Figure 2: Release rates from processed HVO:GM matrix and processed HVO matrix



from the eroding tablets while the second phase (region 2) was possibly due to drug release from the smaller particles. In the latter phase the glycerol monostearate was probably in the cubic phase form hence the low sustained release fashion [7].

Glycerol monostearate concentrations below 30% w/w were found to have no marked effect on the release mechanism of processed HVO while those greater than 30% w/w enhanced release without modifying the release mechanism. Processed HVO tablets 1.50 – 3.25 hours (F_{cal} = 0.49, F_{tab} = 2.25, p = 0.05) (figure 2). All the tablets at all compaction forces used, gradually disintegrated with time. This was possibly due to glycerol monostearate acting as a surfactant and plasticizaer, weakening the HVO matrix structure. The diffusion relaxation model as shown in table 2 best described drug release from processed HVO tablets containing 30% glycerol monostearate.

CONCLUSIONS

Glycerol monostearate at 30% w/w concentration can alter the mechanism of drug release of processed HVO from square root of time kinetics to Fickian diffusion coupled with

Table 2: Release kinetics from Processed HVO: Glycerol Monostearate Matrices

Zero order machamins (Q = kt)		
	Mean	Sd
Slope (%/hr)	23.3	1.68
Intercept (%)	22.28	1.73
Correlation coefficient	0.99288	0.00323
Square root of time mechanism (Q = kt^0.5)		
	Mean	Sd
Slope (hr^0.5)	54.09	3.73
Intercept%	-5.77	3.16
Correlation coefficient	0.99852	0.00088
Diffusion - relaxation model (Q = k1t^0.46 + K2t^0.92)		
	Mean	Sd
k1 (%hr^0.46)	36.57	2.5
k2	10.42	2.9
Intercept%	0.15	0.12
Correlation coefficient	0.99975	0.00007

relaxation model type kinetics. This was attributed to the surfactant effects of glycerol monostearate that weakened the HVO matrix. Diffusion - relaxation controlled release system with appropriate lag times could be targeted to the various gastrointestinal regions where the drug will be released at a predetermined rate.

REFERENCES

[1] P.J. Lockwood. The development and characterization of directly compressible oral controlled drug delivery systems. Ph.D. Thesis, Univ. Bath, UK (1990).

[2] D.S.T. Hesieh, W.D. Rhine and R.S. Langer. J. Pharm. Sci. 1983: (72) 17-22.

[3] A.G. Hansson, A. Giardino, J.R. Cardinal and W. Curatolo. J. Pharm. Sci. 1988: (77) 324-32.

[4] S. Bechard and J.N. Mc Mullen. J. Pharm. Sci. 1988: (77) 228-222.

[5] J.N. Staniforth, UK Patent, Publication No. GB 2 222 948B, (1993).

[6] N.A. Peppas and J.J. Sahlin. Int. J. Pharm. 1989: (57) 169-172.

[7] D..M. Wyatt and D. Dorschel. Pharm. Technol. 1992: (16) 116.