Investigation of Two Naturally Occurring Hydrophilic Matrix Materials for Oral Controlled Drug Delivery Systems

R.T.J. CHIGWANDA* AND I. PFAIRA

Department of Pharmacy, Faculty of Medicine, University of Zimbabwe, P.O. Box MP 167,, Mt. Pleasant, Harare, Zimbabwe

The purpose of the present study was to investigate two naturally occurring hydrophilic matrix materials, gum tragacanth and agar, for controlled release characteristics. All the tablets prepared were 250 mg and contained 40% w/w drug. Dissolution studies were carried out using the USP rotating basket method.

Gum tragacanth was found to possess appreciable release sustaining characteristics depicted by drug release over a 5 hour period. In contrast drug release from agar matrices was complete within 30 minutes. However, matrices made from a combination of gum tragacanth and agar possessed controlled release properties of 2-3 hours.

Drug release from gum tragacanth matrices was best explained by the Higuchi mechanism. There was a gradual change in the release on combining the two matrix materials from Higuchi mechanism to first order mechanism. However, coating one face of the gum tragacanth:agar (1:1) matrices with ethylcellulose improved zero order kinetics of the matrices. This study showed that oral controlled release devices of the release sustaining type can be easily prepared from cheap naturally occurring hydrophilic materials.

Key Words: Hydrophilic matrix, Controlled release

INTRODUCTION

Modern science has always been in search of economical, efficient and safe means of providing for the health and well being of humankind. This includes finding of new drugs, modifying the existing ones and/or modifying drug delivery methods. The latter aspect has given rise to the field of "controlled release" whereby the rate at which a drug is made available to the absorption site is pre-determined. This may include pre-programming the release device so that it releases the drug at a pre-determined rate for a specified duration [1].

Among the various controlled release devices are those administered via the oral route. The majority of oral controlled drug delivery devices are made from either hydrophilic or hydrophobic matrix materials by compacting into tablets the matrix material processed or unprocessed) mixed with the drug [2]. A wide variety of different hydrophilic materials have been described for use in controlled release [3-8]. Some are synthetic (such as polyvinyl alcohol and polyvinylpyrrolidone), while the majority are either semi-synthetic (such as the cellulose derivatives which include hydroxypropylmethylcellulose phthalate and sodium carboxymethylcellulose) or natural (such as agar and gum tragacanth).

On contact with the dissolution medium or body fluids, these hydrophilic devices swell by polymer hydration and chain relaxation, forming a gel layer coat around a dry central core, with the two domains well defined [3]. The swelling of these matrices is influenced by cross-linking, heat treatment, pH, temperature and polymer substitution type [6]. Usually the amount of drug released from these devices is linearly related to the exposed external surface of the swollen matrix, with drug release kinetics sometimes dependent on the swelling kinetics. It is believed that the formation of the gel layer can be critical to the success or failure of the dosage form as a sustaining release device [3]. These hydrophilic matrices can deliver drug at a pre-determined rate for a defined period of time [4]. Mechanistically it is believed that there are two distinct synchronised processes, polymer swelling and its true dissolution, that result in hydrophilic matrices releasing drug via zero order [5]. This synchronised front behaviour was reported for hydrophilic polymers such as polyvinyl alcohol and sodium carboxymethylcellulose [5].

The present study was mainly concerned with the investigation of the potential of naturally occurring hydrophilic matrix materials, gum tragacanth and agar, in oral controlled drug delivery systems.

MATERIALS

Sodium salicylate, batch number 31173, supplied by Saarchem (Pvt.) Ltd., South Africa.

Gum Tragacanth, batch number 83110236, ethylcellulose, batch number 104F-0689, supplied by Sigma Chemical Company, USA.

Agar, batch number 92518, supplied by May and Baker Laboratory Chemicals, England.

METHODS

The assay of Sodium Salicylate was performed using a single beam UV-visible spectrophotometer (UV- 160 Shimadzu type, Japan) set at 315 um.

Tablet Preparation

Tablets used in the dissolution studies were prepared via direct compression using a manually operated single punch tablet machine (Earweka, Type E, GMBH, Germany), equipped with 9 mm punches. The machine was manually operated because only six tablets per batch were prepared. Also, formulation for each tablet was individually weighed on an analytical balance (Sartorius Analytica, Type A, 2005, GMBH, Germany), and then carefully tipped into the dye before manually turning the fly-wheel for compaction. This was carried out so as to obtain the target tablet weight of 250 mg and to achieve constant compaction forces. Each formulation sample weighed 252.5 - 253.0 mg. The drug (sodium salicylate) content was kept constant at 40% w/w as preliminary studies had shown that this was the optimum concentration. The matrix material was dry mixed with the drug before the direct compression.

Dissolution Testing

Dissolution testing was carried out 48 hours post-compaction using the USP (method II) rotating basket method operated at 50 revolutions per minute for at least 4 hours in most cases with sampling carried out every 15 minutes. In all cases, unless otherwise mentioned, 3 tablets were assayed in one run. The dissolution data for blank tablets (tablets containing the matrix material minus the drug.) was subtracted from the dissolution data of the tablets made from the matrix material plus the drug.

Analysis of Data

All release data was evaluated according to the Hignchi mechanism: $Q = kt^{1/2}$ where Q is amount of drug released in time t and k is a constant; first order mechanism: $\log_{10}(100\%\text{-}Q) = kt$, where Q and t are as above and k is a constant as well; zero order mechanism: $Q = kt$, where Q and t are as above and k is a constant. Analysis was carried out up to the maximum drug release. The above evaluations were carried out with the aid of a microcomputer software programme, Microcal Origin, Microcal Software, Inc. student t-tests at the 5% significant level were carried out on some of the release kinetics data. The calculated t values, t_{cal}, were compared with values in the statistical table, t_{tab}, at the appropriate degree of freedom and probability, p, of 0.05.

RESULTS AND DISCUSSION

A 10 point calibration curve for aqueous solutions of sodium salicylate gave a correlation coefficient of 0.9998 for concentration range 0-200 mg/litre. The summary of the sodium salicylate release kinetics from the various hydrophilic matrices is shown in table 1.

TABLE 1 : Sodium Salicylate (40% w/w) Release Kinetics

	GUM TRAGACANTH MATRIC		
	slope	intercept	corr. Coeff.
Zero order	11.05 +1-0.68	31.04+1-1.68	0.94520 +1-0.00230
Higuchi	34.15 +/-2.02	7.6 1+/-2.9 1	0.98170+1-0.00140
first order	-0.1 29+/-0.01 3	1 .90+/-0.02	0.97370+/-0.00800
	GUM TRAGANTH: AGAR (1:1) MATRIX		
	slope	intercept	corr. Coeff.
Zero order	15.87+1-2.49	35.67+1-3.90	0.95 120+/-0.00630
Higuchi	41.76+A6.47	11.09+1- 3.07	0.98395+1-0.00598
first order	-0.285+1-0.192	1.96+1-0.15	0.96959+1-0.02340
	GUM TRAGACANTH: AGAR (2:1) MATRIX		
	slope	intercept	corr. Coeff.
Zero order	16.91+1-0.83	33.77+1-5.79	0.94722+1-0.01077
Higuchi	44.70+1-2.36	7.29+1-4.65	0.98399+1-0.00754
first order	-0.254+1-0.080	1 .92+AO.02	0.98271+1-0.01593

GUM TRAGACANTH: AGAR (1:1) MATRIX (Coated one face with 20% ethylcellulose)			
	slope	intercept	corr. Coeff.
Zero order	12.91+1-0.17	10.8+1-4.73	0.99053+AO.00603
Higuchi	34.05+/-0.23	-9.06+/-4.50	0.99670+/-0.00324
first order	-0.092+/-O.OO5	1.97+1-0.02	0.99645+/-0.00 100
GUM TRAGACANTH : AGAR (1:1) MATRIX (Coated with 20% ethylcellulose +5 mm hole)			
	Slope	intercept	corr. Coeff.
Zero order	4.12+1-1.13	0.41+1-1.45	0.99580+/-0.00191
Higuchi	9.77+1-2.71	-5.53+1-1.10	0.98433+/-0.005 14
first order	-0.019+/-0.006	2.00+/-0.01	0.99583+/--0.00118
GUM TRAGACANTH :AGAR (1:1.5) MATRIX (Coated with 4% ethylcellulose +5 mm hole)			
	slope	intercept	corr. Coeff.
Zero order	*18.52+/~1.14	*8.75+I~0.94	*0.99100+AO.00369
Higuchi	*47.39+I~2.97	*-17.18+A2.54	*0.99778+/-0.00144
first order	*-0.161+A0.022	*2.02+AO.03	*0.99356+/-0.0071 1

NB: All +/- values are standard deviation values

*n = 6 where in all the other values n=3

	slope units	intercept units
Higuchi	%/hr.0.5	%
zero order	%/hr	%
first order	hr.-1	

The gum tragacanth matrix on its own showed controlled release characteristics of the release sustaining type of over 5 hours while agar showed a short duration. However, matrices of gum tragacanth and agar did show these release sustaining characteristics. On contact with the dissolution fluid all the un-coated tablets gradually swelled and eroded with time. However, the rate of swelling appeared to be greater than the rate of erosion of the matrix.

Sodium salicylate release from gum tragacanth matrices was best explained by the square root of time release mechanism (corr. coeff. = 0.98170). The addition of agar to the matrix material increased the drug release rate of the tablets. This was probably due to the better hydrophilic properties of agar than gum tragacanth. However, the gum tragacanth:agar (1:1) matrix release kinetics was still best explained by the Higuchi mechanism (corr. coeff = 0.98395), showing that drug release from such a matrix was still primarily governed by diffusion rather than erosion.

Sodium salicylate release from gum tragacanth:agar (2:1) matrix could be explained by either the Higuchi or first order mechanisms (t_{cal} = 0.13, t_{tab} = 2.13, at p = 0.05, between 0.98399 $\pm$ 0.00754 and 0.98271 1 0.01593 respectively). This probably showed that besides diffusion, the concentration of the drug remaining in the matrix could also have effect on release.

Coating one face of the gum tragacanth:agar (1:1) matrix with a water insoluble polymer such as ethylcellulose greatly improved zero order kinetics (corr, coeff. = 0.99053) although the release kinetics were still better explained by either the Higuchi or first order mechanisms (t_{cal} = 0.13, t_{tab} = 2.13, at p = 0.05, between 0.99670 $\pm$ 0.00324 and 0.99645 $\pm$ 0.00100 respectively). However, the above matrix that was

completely covered with 20% ethylcellulose except a 5mm hole on one face, had release kinetics that were better explained by either the zero order or first order mechanisms (t_{cal} = 0.02, (t_{tab} = 2.13, at p =0.05 between 0.99580 ± 0.00191 and 0.99583 ± 0.00118 respectively). The 5mm hole probably eliminated the effects of increasing distance with time by increasing the surface area available for drug dissolution with time.

The matrix containing more agar than gum tragacanth (gum tragacanth:agar (1:1.5) matrix) had release kinetics best explained by the Higuchi mechanism (corr. coeff. = 0.99778). The intercept (-17.18) also indicated a lag phase before drug release. This is to be expected since before drug release, a wetting phase occurs. These results indicate that controlled release devices of the sustained release type can easily be obtained from naturally occurring cheap hydrophilic matrices such as gum tragacanth. The release mechanisms can be altered by changing the proportions of the hydrophilic matrix components or by coating with a simple water insoluble polymer such as ethylcellulose without altering the geometry of the device.

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