PHARMACEUTICAL SCIENCES

Drug Release From Carbomer 934 Matrices

LORENA I. RUSSO, MS; EVONE S. GHALY, PhD

The main objective of this investigation was to describe the mechanism of drug release from Carbomer 934 hydrogel matrices and to evaluate the effect of polymer level, diluent type, and matrix restriction using customized device (that permits only one surface of the tablet to be exposed to the dissolution medium) on theophylline release from Carbomer matrices. Formulations containing theophylline (10%), Carbomer (10% , 30, 50%), direct compressible diluent (lactose fast flo, Avicel PH-101, Emcompress) and magnesium stearate (0.75%) were compressed at a target tablet weight of 450 mg and target hardness of 7-9 Kp. USP Apparatus 1, was used to test the drug release and Korsmeyer equation was used to describe the mechanism of drug release from Carbomer matrices. Results show that the release profile and release mechanism from Carbomer matrices were influenced by Carbomer level, diluent type, and matrix restriction. In general the release mechanism was anomalous (non-Fickian) except for 10% and 30% Carbomer level and in Avicel PH-101 matrices, where, the release mechanism appears to follow super case II where, the n exponent has value greater than 0.89. All formulations selected appear to follow zero order release only up to 120 minutes. Restriction of tablet surface resulted in a shift toward Fickian release. This study demonstrated that it is possible to modify the drug release mechanism and rate, by changing polymer level, diluent type, and imposing physical restriction on the surface of the matrix.

Key Words: Carbomer 934, Matrices, Sustained release, Mechanism of drug release, Direct compresion, Theophylline.

In spite of the advances in manufacturing technology of oral controlled release dosage forms, matrix tablets continue to be one of the most commonly used dosage forms for controlled oral drug delivery (1). Swellable controlled release systems in the form of tablets are widely used for controlled drug administration, mainly due to their optional performance and easy manufacturing (2).

Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. Several varieties of Carbomer with different molecular weights and viscous capacities, Carbopol 934, 940, and 941 have been studied in the formulation of sustained release tablets with low soluble active principles (3) and hydrosoluble drug (4). Carbopol 934 is commonly used in oral preparations, provides the widest range of modulation possibilities by controlling the technological variables (5-8). Carbopol 934 has been studied using theophylline and hydrochlorothiazide to determine the inter-lot variability of Carbomer 934 (9). As reported for Carbomer matrices, release kinetics depends on the solubility of the active principle in water. Water soluble drugs follow Higuchi's equation (4, 9-10) while water insoluble drugs follow zero order (3, 9).

Swellable matrices as drug delivery systems exhibit anomalous release (11). The resulting release mechanism depends on the relative importance of tablet relaxation (9, 11-13) and drug diffusion (9, 12-13). The existence of some molecular relaxation process in addition to the diffusion is believed to be responsible for the observed non-Fickian behavior (13).

The primary objective of this study is to describe the drug release mechanism from directly compressed matrices containing different levels of Carbomer 934 (10%, 30%, and 50% w/w), theophylline (10% w/w) and different direct compressible diluents (Lactose Fast Flo, Avicel PH-101 and Emcompress). A second objective was to investigate the effect of matrix restriction on the drug release mechanism and rate from selected formulations.

From the University of Puerto Rico, School of Pharmacy, San Juan, Puerto Rico

Address correspondence to: Evone S. Ghaly, PhD, University of Puerto Rico School of Pharmacy, PO Box 365067, San Juan, Puerto Rico, 00936-5067.

Materials

Except when noted, all chemicals were analytical grade and used as received. Theophylline anhydrous, lot number E1533 was selected as the model drug and was supplied by Searle Incorporation (Puerto Rico); Carbomer 934 (Carbopol 934, lot number 950204032) supplied by Rhone-Poulenc Rorer (Manati, Puerto Rico); Lactose Fast Flo, lot number 2RL322 supplied by Colorcon Inc. (Philadelphia, PA); Avicel PH-101, lot number 6206 supplied by FMC Inc. (International Food and Pharmaceutical Products Division, Wallingston, Ireland); Emcompress, lot number 113-648 supplied by Mendell Inc. (Patterson, N.Y.); and magnesium stearate, lot number B12220M16 supplied by Amend Drug Chemical Co. (Irvington, N.J.).

Methods

Preparation of blends. Twelve formulations including three control batches without Carbomer polymer were prepared. The batch size for each formulation was 0.5 Kg and the formulations contained theophylline anhydrous (10% w/w), Carbomer 934 (10%, 30%, and 50% w/w), direct compressible diluent (Lactose Fast Flo, Avicel PH-101, and Emcompress), and magnesium stearate (0.75%). All materials were screened through a #12 mesh except for magnesium stearate which was screened through a #30 mesh. Mixing of all formulations was performed by geometrical dilution in a V blender (PK processor, Patterson Kelly, model LB-5322) for 20 minutes. This mixture was then blended with magnesium stearate for an additional 5 minutes.

Tablet compression. The blends were compressed into tablets using a rotary Manesty B-3B machine equipped with 0.953 cm flat face punches and the machine speed 30 tablets per minute. Target tablet weight was 450 mg $\pm$ 5% and target hardness was 7-9 Kp and the diameter of the tablet varied from 3.5 mm to 7.5 mm based on the level of Carbomer in the formula.

In-vitro dissolution testing. The dissolution was carried out in 900 ml distilled water, phosphate buffer pH 7.4 and 0.1 N HCl at 37 $\pm$ 0.5° C using the USP rotational basket apparatus (Hanson Research, Model SR2, USA) at speed of 50 rpm. Filtered samples were withdrawn manually at predetermined time intervals and assayed using UV spectrophotometer (Beckman Instruments, model DU 65, USA) at 271 nm. Three replicates for restricted using customized device (only one surface of the tablet was exposed to the dissolution medium) and unrestricted tablet matrices (all surfaces of the tablet were exposed to the dissolution medium) were tested and their mean percent released was calculated.

Restricted matrix. A stainless steel (type 316) cylinder of 0.5 mm external diameter, 0.372 mm internal diameter and 0.800 mm length was used. In order to maintain the tablet in position without movement, an internal cylinder was designed. The internal cylinder piece has an external diameter of 0.370 mm so it can be inserted inside the cylinder. This piece has an O-ring to secure complete sealing. Three devices of similar dimensions were made in order to perform the dissolution testing in triplicates.

Mechanism of drug release. An equation derived by Ford Korsmeyer et al. (14) as well as Ritger and Peppas (11) was used to describe the mechanism of drug release from polymeric systems

$$M_t / M_\infty = K . t^n \qquad 1.$$

Where M_t / M_∞ is a fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristic of the release device and n is the release exponent indicative of the release mechanism (15). In order to calculate the release exponent n, the logarithmic form of equation 1 is used where

$$\log M_t / M_\infty = \log K + n \log t \qquad 2.$$

The release exponent takes various values depending on the geometry of the release device. Value of n for a cylinder less than or equal to 0.45 indicates Fickian diffusion, larger than 0.45 and less than 0.89 indicates anomalous (non-Fickian) transfer, 0.89 indicates case II transport (11) and larger than 0.89 indicates super case II type release (16-17) which is of particular interest because the drug release from such devices having constant geometry will be zero order.

Results and Discussion

All twelve formulations were successfully compacted into tablets. Figure 1 shows the dissolution profiles for matrices containing 10% theophylline anhydrous,

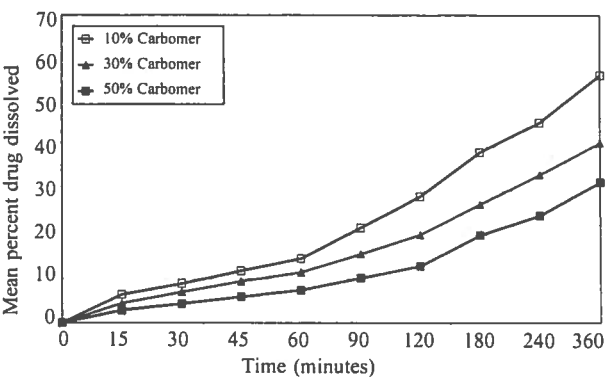

Figure 1. Dissolution profiles for matrices containing 10% theophylline, Carbomer 934 and lactose fast flo.

different levels of Carbomer 934 (10%, 30%, and 50%) and prepared with Lactose Fast Flo diluent. For Lactose Fast Flo and 10% polymer, the mean percent drug released (n = 3) at 4 hours of testing dissolution was 45.5%; for 30% polymer was 33.6%; and for 50% polymer was 24.3%. As the percent of polymer increased, the drug release from the matrix decreased. The same trend was true for Avicel PH-101 and Emcompress formulations.

Table 1 depicts the slopes and intercepts obtained from the linear regression of the dissolution data. The percent release rate for compacts prepared with Lactose Fast Flo and containing 10% polymer was 0.152% minutes^{-1} while the percent release rate for compacts of the same composition but containing 50% polymer was only 0.087% minutes^{-1}. The percent release rate for compacts prepared with Avicel PH-101 and containing 10% Carbomer was 0.263% minutes^{-1} while the percent release rate for compact of the same composition but containing 50% polymer was 0.093% minutes^{-1}. The same result was true for Emcompress formulations, the percent release rate for compacts prepared with Emcompress and containing 10% Carbomer was 0.128% minutes^{-1} while the percent release rate for compacts of the same composition but containing 50% polymer was 0.116% minutes^{-1}. The level of carbomer has a marked effect on the release rate of the drug. As the polymer level increased in the formulation, the drug release rate from the matrices decreased (see Table1).

Table 1. Slopes and Intercepts Obtained from Linear Regression of Dissolution Data (Unrestricted Matrices)

Formulation	% Release rate (minute-1)	Intercept	r2
Theophylline 10%, Carbomer 10% and Lactose Fast Flo	0.152	6.602	0.965
Theophylline 10%, Carbomer 30% and Lactose Fast Flo	0.109	5.086	0.975
Theophylline 10%, Carbomer 50% and Lactose Fast Flo	0.087	2.559	0.989
Theophylline 10%, Carbomer 10% and Avicel	0.263	2.611	0.953
Theophylline 10%, Carbomer 30% and Avicel	0.107	3.448	0.939
Theophylline 10%, Carbomer 50% and Avicel	0.093	6.704	0.923
Theophylline 10%, Carbomer 10% and Emcompress	0.128	11.630	0.953
Theophylline 10%, Carbomer 30% and Emcompress	0.133	8.188	0.992
Theophylline 10%, Carbomer 50% and Emcompress	0.116	7.198	0.980

The overall process of drug release is affected by the rate of water uptake and the diffusion of the drug through the swollen gel. Water uptake in the matrix is enhanced in presence of polymer due to its hydrophilicity. However the polymer swells as it absorbs water and the thickness of the gel layer formed varies according to the level of polymer in the matrix. High polymer level results in high gel formation. The gel formation increased the diffusional path length of the drug and also its viscosity affects the diffusion coefficient of the drug. The higher the level of polymer in the matrix, the lower the drug release from the matrix (see Table 1).

The effect of dissolution pH on drug release was also investigated. As depicted in Table 2, in acid medium it was apparent that the tortuosity of the matrix decreased due to the decreased of gel viscosity in acid medium. Also in acid conditions, a small proportion of the carboxyl group presents in the polymer chain may dissociates and produced flexible coil structure and consequently increased the drug release.

Table 2. Slopes and Intercepts Obtained from Linear Regression of Dissolution Data (Dissolution media of Different pH)

Formulation / dissolution medium	Release rate (% minute^{-1})	Intercept	r^2
Carbomer 30% and Lactose			
pH[a]	0.109	5.087	0.975
pH 1.2[b]	0.165	14.733	0.968
pH 7.4[c]	0.126	4.185	0.992
Carbomer 30% and Avicel			
pH 6[a]	0.107	3.448	0.939
pH 1.2[b]	0.178	20.726	0.934
pH 7.4[c]	0.168	10.610	0.803
Carbomer 50% and Emcompress			
pH 6[a]	0.116	7.198	0.980
pH 1.2[b]	0.145	14.074	0.970
pH 7.4[c]	0.124	3.198	0.998

[a]Distilled water, [b]0.1 N HCl, [c]Phosphate buffer

Figures 2 to 4 depict the effect of diluent type on drug release from matrices prepared with different levels of Carbomer 934. At 6 hours of testing dissolution, formulation prepared with Lactose Fast Flo and 10% Carbomer released 56.3% drug while formulation of the

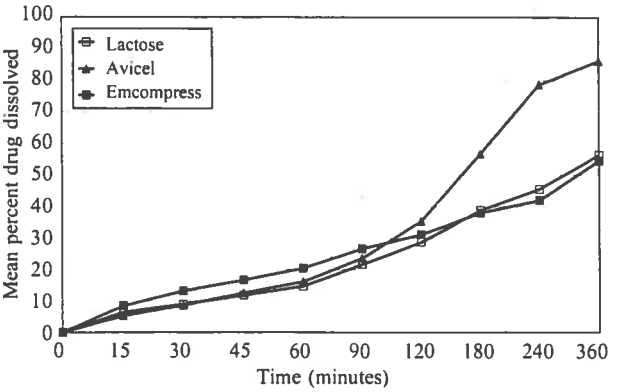

Figure 2. Dissolution profiles for matrices containing 10% theophylline, 10% Carbomer 934 and different diluents.

same composition but prepared with Avicel PH-101 released 86.3% and formulation prepared with Emcompress released 54.5%. Formulation prepared with Lactose Fast Flo and 30% polymer released 40.9% drug at 6 hour while formulation of the same composition but prepared with Avicel PH-101 released 37.4% and formulation prepared with Emcompress released 55.2%. Formulation prepared with Lactose Fast Flo and 50% polymer released 31.9% drug at 6 hour while formulation of the same composition but prepared with 50% Avicel PH-101 released 36.6% and formulation prepared with Emcompress released 46.1%. At 10% Carbomer level there was significant difference in drug release between matrices prepared with Lactose Fast Flo and Avicel PH-101 (56.3% vs 86.3%) or Emcompress and Avicel PH-101 (54.5% versus 86.2%). However there was no significant difference between Lactose Fast Flo and

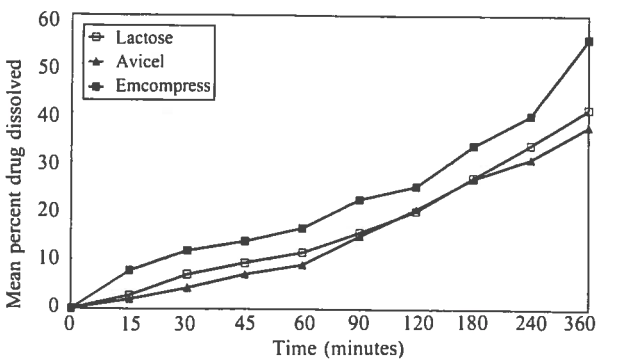

Figure 3. Dissolution profiles for matrices containing 10% theophylline, 30% Carbomer 934 and different diluents.

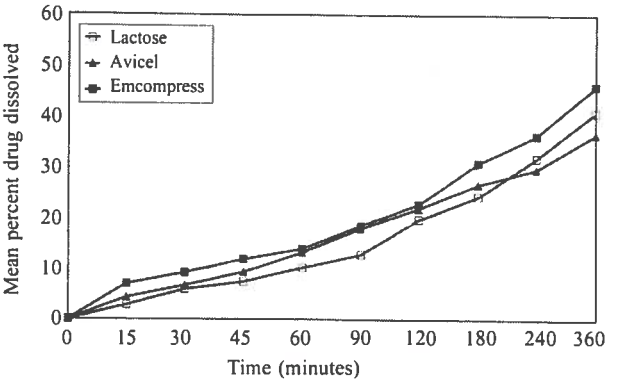

Figure 4. Dissolution profiles for matrices containing 10% theophylline, 50% Carbomer and different diluents.

Emcompress matrices (56.3% vs 54.5%). There was significant differences between matrices prepared with different diluents and containing 30% or 50% Carbomer. At 10% polymer level, Avicel PH-101 gave highest drug release at 6 hours (86.3%) while at 30% or 50% polymer level, Emcompress gave the highest percent drug release (55.2% and 46.1% respectively).

The high percent drug release from matrices containing 10% Carbomer and Avicel PH-101 may be due to disintegration property of Avicel PH-101 and the low level of Carbomer which was not effective in maintaining matrix integrity. The high drug release obtained from matrices containing 30% or 50% Carbomer and Emcompress may be due to the effect of Emcompress on gel formation. Presence of Emcompress appears to affect the uniformity of gel formation. In general the effect of diluent type on drug release depends on water solubility and the physical properties of the diluent. The presence of diluent decreased the tortuosity of the matrix, water soluble diluent as lactose dissolved and diffused outward forming channels, reducing the tortuosity of the matrix and increasing the release of the drug. Whereas water insoluble diluent remained in the matrix and reduced the swelling of the gel which in turn increased the drug release.

Matrices containing 30% Carbomer level and Lactose Fast Flo or Avicel PH-101 and matrix containing 50% Carbomer 934 and Emcompress were selected to study the effect of matrix restriction and to describe in more details the mechanism of drug release.

In order to determine if the decrease of drug release from restricted matrix was due to the reduction of the available area for drug release, the percent drug released per unit surface area from unrestricted and restricted matrices was calculated and is shown in Table 3. The results depicted in Table 3 showed that the drug release per unit surface area from restricted matrix was less than from unrestricted indicated that the differences in drug

Table 3. Mean Percent Drug Release Per Unit Surface Area (% cm-2)

Time (minutes)	30% Carbomer, Lactose Fast Flo Unrestricted:Restricted	30% Carbomer, Avicel PH-101 Unrestricted:Restricted	50% Carbomer, Emcompress Unrestricted:Restricted
15	2.63:2.8	0.97:2.04	3.59:2.36
30	3.91:3.15	1.96:2.20	4.72:3.14
45	5.26:4.09	3.24:2.299	6.10:4.25
60	6.42:4.88	4.11:4.25	7.18:4.84
90	8.72:6.77	6.80:5.83	9.59:6.15
120	11.17:8.19	9.32:7.09	11.69:7.40
180	15.03:11.65	12.19:9.27	15.85:9.22
240	18.77:15.28	14.02:11.96	18.62:11.0
360	22.85:21.73	17.08:18.10	32.87:13.5

release between unrestricted and restricted matrices is not due to differences in surface area. The differences obtained may be due to polymer swelling and existence of molecular relaxation specially in case of unrestricted matrix.

Figure 5 shows the dissolution profiles expressed as percent drug release for restricted and unrestricted matrices. Percent drug release at 3 hours from unrestricted matrices containing 30% Carbomer and Lactose Fast Flo was 26.9% while percent drug release from matrices of the same composition but restricted physically was 7.4%. For matrices containing 30% Carbomer and Avicel PH-101, the percent drug release at 3 hours was 26.7% while the percent drug release from matrices of the same composition but restricted was 5.9%. For formulation containing 50% polymer and Emcompress, the percent drug release was 30.9% while percent drug release from matrices of the same composition but restricted was 5.9%.

Restricted matrices containing 50% polymer and Emcompress gave lowest release rate (0.021 % minute^{-1}) while restricted matrices containing 30% Carbomer and

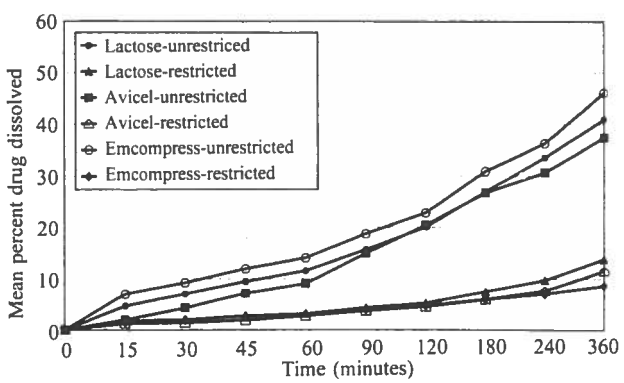

Figure 5. Dissolution profiles for selected matrices from unrestricted and restricted surface.

Table 4. Release Exponents, Intercepts and Correlation Coefficient (Unrestricted Matrices)

Formulation	Release exponent (n)	Release mechanism	Intercept (K)	r^2
Theophylline 10%, Carbomer 10%, Lactose	0.737	Non-Fickian (Anomalous)	0.00778	0.989
Theophylline 10%, Carbomer 30%, Lactose	0.712	Non-Fickian (Anomalous)	0.00647	0.997
Theophylline 10%, Carbomer 50%, Lactose	0.796	Non-Fickian (Anomalous)	0.00297	0.996
Theophylline 10%, Carbomer 10%, Avicel	0.957	Super Case II	0.00349	0.986
Theophylline 10%, Carbomer 30%, Avicel	0.935	Super Case II	0.00192	0.981
Theophylline 10%, Carbomer 50%, Avicel	0.700	Non-Fickian (Anomalous)	0.00679	0.981
Theophylline 10%, Carbomer 10%, Emcompress	0.583	Non-Fickian (Anomalous)	0.0182	0.995
Theophylline 10%, Carbomer 30%, Emcompress	0.607	Non-Fickian (Anomalous)	0.0144	0.995
Theophylline 10%, Carbomer 50%, Emcompress	0.622	Non-Fickian (Anomalous)	0.0117	0.993

Lactose Fast Flo gave highest release rate (0.03% minute^{-1}) and restricted matrices containing 30% Carbomer and Avicel PH-101 gave intermediate release rate (0.029% minute^{-1}). Accordingly matrix restriction can modify the drug release.

In order to determine the mechanisms of drug release from these matrices, it was necessary to plot log time versus fraction of drug released.

Table 4 depicts the release exponent (n) obtained from the slope of the straight line and the intercept (K). As expected, approximately all matrices showed non-Fickian (anomalous) drug release (see Table 4) except for matrices containing 10% or 30% Carbomer and Avicel PH-101 where the release mechanisms appear to be super case II (n=0.975 and 0.935 respectively). Additionally, the values of n (release exponent) for lactose fast flo matrices were the lowest (showing tendency for Fickian release), Emcompress matrices showed intermediate exponent release values and Avicel PH-101 showed high exponent release values.

All selected formulations were investigated further, the dissolution data was plotted as mean percent drug release

Table 5. Release Rate Constants, Release Rate Exponents, and Release Mechanisms for Restricted Matrices

Formulation variable	Release rate (% minutes-1)	Release exponent (n)	Release mechanism
Carbomer 30% and Lactose Fast Flo	0.036	0.679	Non-Fickian (Anomalous)
Carbomer 30% and Avicel	0.029	0.728	Non-Fickian (Anomalous)
Carbomer 50% and Emcompress	0.021	0.566	Non-Fickian (Anomalous)

versus time (zero order kinetic), versus square root of time (diffusion), and as log percent drug release versus time (first order kinetic). The data obtained showed that all selected formulations appear to follow zero order up to 120 minutes of testing dissolution. After 120 minutes the erosion rate was not constant and the drug release was dependent on polymer relaxation.

In order to better understand the mechanism of drug release, the dissolution data for restricted matrices (selected formulation) was plotted as log time versus log fraction of drug released (see Figure 6). Both release rate constant and exponent n were obtained from the linear regressions of restricted selected formulations as shown in Table 5. Avicel PH-101 formulation gave highest release exponent as shown in Table 5 (n = 0.935 for unrestricted and 0.728 for restricted matrix) while Emcompress formulation gave lowest release exponent (0.622 for unrestricted and 0.566 for restricted matrix) and Avicel PH-101 release exponent was intermediate (0.935 for unrestricted and 0.728 for restricted matrices).

Fickian diffusion release mechanism was found for restricted system containing Lactose Fast Flo and 30% Carbomer from 30 minutes up to 120 minutes. Restricted system containing Avicel PH-101 and 30% Carbomer followed the Fickian diffusion from 30 minutes up to 180

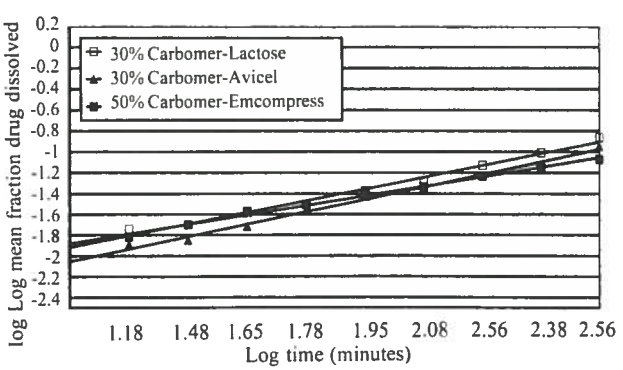

Figure 6. Dissolution profiles for selected matrices plotted as log mean fraction drug released versus log time (restricted surface).

minutes of dissolution testing while restricted systems containing Emcompress and 50% Carbomer followed the Fickian diffusion through all time of dissolution testing (15 minutes to 360 minutes).

Conclusions

Theophylline-Carbomer 934 matrices were successfully prepared by direct compression method. The release mechanism from all Carbomer matrices was anomalous (non-Fickian diffusion) except for matrices prepared with 10% and 30% Carbomer level and Avicel PH-101 where, the release mechanism appears to follow super case II. A shift in the mechanism of drug release towards Fickian diffusion was achieved by imposing a physical restriction o0f the matrices surface.

This investigation demonstrated that it is possible to modify the release profile and mechanism of drug release from Carbomer 934 matrices by changing polymer level, type of diluent and imposing physical restriction on the surface of the matrix.

Resumen

El principal objetivo de esta investigación fue describir el mecanismo de liberación de las drogas a través de matrices hidrogel de Carbomer 934. Otro objetivo fue evaluar el efecto del nivel de este polímero, tipo de diluyente y restricción de la matriz utilizando un aparato especializado, (que permite exponer solamente una de las superficies de la tableta al medio de disolución) que mide la liberación de teofilina a través de las matrices de Carbomer. Las formulaciones que contienen teofilina (10%), Carbomer (10%,30%,50%), diluyente comprimido directamente ("Lactosa fast flo, Avicel PH-101, Emcompress") y estearato de magnesio (0.75%) fueron comprimidas a un peso final de 450 mg y una dureza final de 7-9 Kp. El aparato # 1 de la Farmacopea de de Estados Unidos para examinar la liberación de la droga fue ultilizado para describir el mecanismo de liberación de la droga en matrices y se utilizó la ecuación Korsmeyer. Los resultados demuestran que el perfil de liberación y el mecanismo de liberación de matrices Carbomer fueron influenciados por el nivel de Carbomer, por el tipo de diluyente y por larestricción de la matriz. En general. el mecanismo de liberación fue anormal (non-Fickian) excepto para un 10% y 30% del nivel de Carbomer y en matrices de Avicel PH-101. En estas situaciones el mecanismo de liberación parece seguir un super caso II, donde el exponente n tiene un valor mayor de 0.89. Todas las formulaciones seleccionadas parecen seguir una liberación de cero hasta 120 minutos. La restricción en

la superficie de la tableta resultó en un cambio hacia una liberación Fickliana. Este estudio demostró que es posible modificar el mecanismo y la velocidad de liberación de la droga, cambiando el nivel del polímero y diluyente e imponiendo restriccion fisica a la superficie de la matriz.

References

1. Li L. In vitro controlled release of theophylline from tablets containing a silicone elastomer latex. Int J Pharm 1992;87:117-124.
2. Colombo P. Catellani P. Peppas N. Maggi L. Conte U. Swelling characteristics of hydrophilic matrices for controlled release new dimensionless number to describe the swelling and release behavior. Int J Pharm 1992;88:99-109.
3. Perez-Marcos B. Gutierrez C. Gomez-Amoza J. Martinez-Pacheco R. Souto C. Concheiro A. Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices. Int J Pharm 1991;67:113-121.
4. Perez-Marcos B. Iglesias R. Gomez-Amoza J. Martinez-Pacheco R. Souto C. Concheiro A. Mechanical and drug release properties of atenolol-Carbomer hydrophilic matrix tablets. J Controlled Release 1991;17:267-276.
5. Khanm GM. Jiabi J. Carbopol 974 P-NF Controlled release matrix Tablets III: Influence of co-excipients on release rate of the drug. J Controlled Release 1998;54:185-190.
6. Deshpand AA. Shah NH. Rhodes CT. Malick W. Development of a novel controlled release system for gastric retention. Pharm Res 1997;14: 815-819.
7. Goskonda VR. Reddy IK. Durrani MJ. Wilber W. Khan MA. Solid state stability assessment of controlled release tablets containing Carbopol 971 P. J Controlled Release 1998;54:87-93.
8. Perez-Marcos B. Ford. JL. Amstrong DJ. Elliot PN. Rostron C. Hogan JE Influence of pH on the release of propanolol hydrochloride from matrices containing hydroxypropylmethyl-cellulose K4M and Carbopol 974. J Pharm Sci 1996;85:330-334.
9. Perez BM. Guitierrez C. Gomez-Amoza J. Souto C. Concheiro A. Rowe R. Interlot variability of Carbomer 934. Int J Pharm 1993;100: 207-212.
10. Huang. Schwartz J. Studies on drug release from a Carbomer tablet matrix. Drug Dev Ind Pharm 1995;21:1487-1501.
11. Ritger P. Peppas N. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Controlled Release 1987;5:37-42.
12. Coombo P. Conte U. Gazzaniga A. Maggy L. Sangalli M. Peppas N. La-Manna A. Drug release modulation by physical restriction of matrix swelling. Int J Pharm 1990;63:43-48.
13. Lee P. Kinetics of drug release from hydrogel matrices. J. Controlled Release 1985:2:277-288.
14. Korsmeyer R. Gurny R. Doelker E. Buri P. Peppas N. Mechanism of solute release from porous hydrophilic polymers. J Pharm Sci 1983;15:23-35.
15. Ford J. Rubinstein M. McCaul F. Hogan J. Edgar P. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Int J Pharm 1987;40:223-234.
16. Rango-Rao K. Padmalatha D. Buri P. Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. J Controlled Release 1990;12:133-141.
17. Ranga R. Padmalatha D. Buri P. Cellulose matrices for zero order release of soluble drugs. Drug Dev Ind 1988;14:2299-2320.