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Development of a zero-order release oral compressed tablet with potential for commercial tabletting production

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Abstract

The release of caffeine and ibuprofen as model drugs from a unique core-in-cup oral drug delivery system has been examined to determine their time exponent (t^n) vs release profiles. The core-in-cup drug delivery system consisted of cores of various concentrations of two grades of hydroxypropylmethylcellulose (HPMC). HPMC K4M and HPMC K15M were used as the polymers in the core matrix. The flat disc-shaped core was then compressed with a previously compressed cup-shape tablet consisting of inert and impermeable carnauba wax and ethylcellulose. These drug delivery systems released active drug at a zero-order rate for periods of time between 8 and 23 h. The release rate was then compared to core only systems. The t^n exponents varied from 0.477 for the lowest core system to 0.997 for a 5% w/w HPMC K4M in ibuprofen core-in-cup system. Because the core, the cup, and the core-in-cup are compressed on an automated tabletting press, this drug delivery system can be easily scaled up to commercial production.

Keywords: Hydroxypropylmethylcellulose; Zero-order release; Core-in-cup system; Caffeine; Ibuprofen; Ethylcellulose; Automation method; Tabletting

1. Introduction

There are many oral drug delivery systems on the market today that provide some type of sustained or prolonged release of active drug. Most of the commercially available systems consist of simple compressed matrices incorporating active drug homogeneously mixed together with a hydrophillic polymer or mixture of polymers. The polymers are mainly cellulose derivatives of which hydroxypropylmethylcellulose (HPMC) is probably the most popular. These systems are usually simple to manufacture on a large scale and are mostly produced on a tabletting press. Because of the shape of the tablet (biconvex or disc) it is theoretically impossible for these tablets to release the active drug from it at a zero-order rate. This is because as the system erodes (which is the case with most polymers) the surface area exposed to the dissolution fluid continually decreases or the diffusion path of the drug (with water soluble drugs) increases in length. Whether the matrix releases drug via swelling control or erosion (or both), it is almost impossible to achieve a zero-order release (Langer, 1980). Most of these matrix-type tablets release drug according to the

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Higuchi (1962, 1963) square root of time kinetic model (Lapidus and Lordi, 1968; Rhine et al., 1980; Hsieh et al., 1983; Ford et al., 1987).

A possible means of altering the release kinetics from matrix systems is to alter the geometry of the matrix. This can be done by means of creating a system in which the drug is released from a constant surface area of constant drug concentration to the dissolution fluid, i.e., release from one side of a flat tablet, slab, base of cylinder, or inwardly releasing hemisphere. Many such systems have been fabricated in which all sides except a single flat side have been coated with a thin impermeable (to the active drug) polymer or other coating. Hsieh et al. (1983) produced inwardly releasing hemispheres of sodium salicylate in polyethylene, and bovine serum albumin in ethylene vinyl acetate matrices, which were coated with paraffin. The release of drug from this system was then conducted in saline solution. Zero-order release for 60 days at a rate of 0.5 mg/day was achieved from the polymer matrices containing bovine serum albumin. These systems, however, are difficult to manufacture and consist of a number of intricate steps in their production.

Devi et al. (1989) developed zero-order release matrix tablets of oxprenolol hydrochloride. Zero-order release was accomplished with swelling and erosion control of the polymer matrix. The formulation involved mixing oxprenolol hydrochloride with a combination of HPMC and NaCMC, and then compressing it into a tablet. By optimising the ratio between the drug and the polymers, the rates of advancement of the swelling front into the glassy core and the attrition of the rubbery state polymer were made equal so that the diffusional path length for the drug remained constant. Unfortunately, these systems are only applicable to drugs that are readily water soluble, as they rely on solubilization and then diffusion out of the matrix. It also seems likely that different combinations of polymers would be applicable to different drugs in order to match the rate of the advancement of the swelling front into the glassy core and the rate of attrition of the polymer.

Seta et al. (1988) prepared core-in-cup compressed tablets of disc-shaped bilayer core matrices of captopril and hydroxypropyl cellulose (HPC) surrounded on the bottom surface and circumference wall (the cup) with an inactive mixture of ethylcellulose and carnauba wax. The two layers of the core contained different concentrations of captopril. It was found that this type of system released captopril in vitro at a zero-order rate over a period of 3–6 h. Shenouda et al. (1990) also prepared a similar core-in-cup type compressed tablet of dyphylline in HPMC as the core matrix and poly(ethyloxazoline) polymer as the inactive cup. Again, this type of system has the ability to release dyphylline in vitro at a zero-order rate of up to 7–8 h. In both the above studies, the core-in-cup tablets were produced by means of first compressing out the active core on a single punch tabletting press using round flat face punches to form a disc. The disc was then placed by hand in the centre of a larger round flat face punch in the die cavity of the press, filled with the inert polymer mixtures, and then compression coated by hand at high pressure. To place the core in the centre of the round flat punch called for careful and tedious placement and judgement. The problem with this compression coated method is that it cannot be automated and does not produce an even, elegant tablet. Both these properties are needed for commercial production of tablets.

This article describes a method that can be automated to produce core-in-cup tablets that have the ability to release soluble and insoluble drugs at a zero-order rate from an inert inactive cup.

The kinetics of drug release from the core-in-cup tablets are examined as to how well the rate of release fits the Korsmeyer et al. (1983) relationship depicted in Eq. 1 below:

$$(M_t/M_\infty) = k \cdot t^n \tag{1}$$

or,

$$\log(M_t/M_\infty) = \log k + n \log t \tag{2}$$

where M_t/M_∞ is the fractional release of the drug, t denotes the release time, k represents a constant incorporating structural and geometric characteristics of the release device and n is the time exponent indicative of the mechanism of

release. For example, $n = 0.5$ for square root of time kinetics and $n = 1.0$ for zero-order kinetics.

This classification has been successfully used by Ford et al. (1987) to characterize the release of a number of different drugs from HPMC matrices. If one plots the logarithm of the fractional release vs the logarithm of time (in min), the slope of the graph will give one the value of the n exponent. In order for Eq. 2 to be applicable the intercept of the graph must pass through the origin, i.e., log k must be zero. This correction to data can be achieved via correcting the sampling time data of cumulative fractional release vs the square root of time. The sampling times are then corrected by linear regression so that the graph passes through the origin (Ford et al., 1987).

2. Materials and methods

2.1. Materials

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Ltd, U.K. HPMC K4M and K15M have viscosities of 3500–5600 and 12 000–21 000 cP, respectively, as 2% solutions in water at 20°C. The polymers had already been screened through a No. 40 standard U.S. sieve.

Caffeine (E. Merck, Darmstadt) and ibuprofen (Boots Co, S.A. Pty Ltd) were ground and the fraction passing through a No. 150 standard U.K. sieve was used.

Ethylcellulose (Riedel de-Haën) was used as

Table 1
Codes and descriptions of different formulations tested

Code	Formulation	
	Core polymer/drug % w/w	Cup 10% carnauba wax/ethyl cellulose
5H4CC	5% HPMC K4M/caffeine	yes
10H4CC	10% HPMC K4M/caffeine	yes
15H4CC	15% HPMC K4M/caffeine	yes
5H15C	4% HPMC K15M/caffeine	yes
10H15CC	10% HPMC K15M/caffeine	yes
15H15CC	15% HPMC K15M/caffeine	yes
5H4cC	5% HPMC K4M/caffeine	
10H4cC	10% HPMC K4M/caffeine	
15H4cC	15% HPMC K4M/caffeine	
5H15cC	5% HPMC K15M/caffeine	
10H15cC	10% HPMC K15M/caffeine	
15H15cC	15% HPMC K15M/caffeine	
5H4CI	5% HPMC K4M/ibuprofen	yes
10H4CI	10% HPMC K4M/ibuprofen	yes
15H4CI	15% HPMC K4M/ibuprofen	yes
5H15CI	5% HPMC K15M/ibuprofen	yes
10H15CI	10% HPMC K15M/ibuprofen	yes
15H15CI	15% HPMC K15M/ibuprofen	yes
5H4cI	5% HPMC K4M/ibuprofen	
10H4cI	10% HPMC K4M/ibuprofen	
15H4cI	15% HPMC K4M/ibuprofen	
5H15cI	5% HPMC K15M/ibuprofen	
10H15cI	10% HPMC K15M/ibuprofen	
15H15cI	15% HPMC K15M/ibuprofen	

supplied. All other reagents used were standard laboratory grade.

2.2. Formulations

Flat disc-shaped tablets (cores) were made consisting of 95% w/w, 90% w/w and 85% w/w of caffeine (soluble model drug) or ibuprofen (insoluble model drug) in either HPMC K4M or HPMC K15M. Table 1 lists all the different formulations used in this study.

20 g of each combination was prepared. The cores were compressed in a tabletting press to a thickness of 1 mm and a diameter of 7 mm, therefore, the weights of the cores varied slightly according to the density of the core mixture. Table 2 lists the average weights of the cores together with their standard deviations. Cups were made of 10% w/w carnauba wax in ethylcellulose. The average weights of the cups are also listed in Table 2.

Table 2
Mean weights of cores and cup used in the different formulations

Formulation	Mean weight (mg) ± SD ($n = 20$)
HPMC K4M/caffeine	
5H4cC	92.28 ± 2.66
10H4cC	88.27 ± 1.98
15H4cC	87.10 ± 2.09
HPMC K15M/caffeine	
5H15cC	94.15 ± 2.45
10H15cC	90.41 ± 1.86
15H15cC	88.27 ± 2.36
HPMC K4M/ibuprofen	
5H4cI	91.10 ± 2.62
10H4cI	90.92 ± 1.55
15H4cI	87.34 ± 3.52
HPMC K15M/ibuprofen	
5H15cI	85.42 ± 2.57
10H15cI	86.25 ± 1.06
15H15cI	85.22 ± 2.49
Ethylcellulose/carnauba wax	
Cup	284.06 ± 4.31

Table 3
Mean crushing strength of cores, and core-in-cup used in the different formulations

Formulation	Mean crushing strength (N/m^2) ± SD ($n = 10$)	
	Cores	Cup-in-core
HPMC K4M/caffeine		
5H4CC	44.61 ± 4.34	152.41 ± 7.51
10H4CC	48.61 ± 6.53	158.70 ± 4.36
15H4CC	40.70 ± 3.42	145.24 ± 5.58
HPMC K15M/caffeine		
5H15CC	38.32 ± 9.42	145.26 ± 7.97
10H15CC	43.02 ± 3.86	150.25 ± 5.19
15H15CC	41.42 ± 4.80	147.55 ± 5.96
HPMC K4M/ibuprofen		
5H4CI	41.98 ± 8.92	149.40 ± 8.18
10H4CI	38.16 ± 6.15	142.63 ± 7.75
15H4CI	42.94 ± 7.46	150.43 ± 6.38
HPMC K15M/ibuprofen		
5H15CI	44.30 ± 4.07	154.79 ± 9.55
10H15CI	46.11 ± 8.48	152.12 ± 9.77
15H15CI	46.22 ± 3.09	150.65 ± 3.72
Ethylcellulose/carnauba wax		
Cup	90.25 ± 5.31	N/A

2.3. Preparation of compressed tablets

All powders for the cores were thoroughly mixed and granulated in an Erweka FGS granulator fitted with a 500 μm stainless-steel screen. 90% v/v alcohol was used as granulating agent. Once the granules were dry and passed through a 500 μm screen, they were compressed into cores on a Manesty F3 tabletting press using 7 mm diameter flat round punches. The press was set to compress the cores to a thickness of 1 mm. The hardness of the cores were then measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce a tablet of approximate hardness of around 40 N/m^2. Table 3 lists the crushing strength values of the cores as well as the final core-in-cup tablets.

The ethylcellulose and the carnauba wax were thoroughly mixed and directly compressed into cups with a top punch which was sparkeroded,

machined, and polished so that it produces a cup-shaped tablet of 11 mm outer diameter, and an inner hollow core of 7.5 mm diameter and 1 mm depth. The bottom punch consisted of a flat round 11 mm diameter punch. The press was set to produce a tablet of an approximate hardness of 90 N/m^2. Table 3 lists the crushing strength values of the cups.

Once the cores and the cups were compressed, the cores were placed inside the cups and fed into the tabletting press to finally be compressed into a single core-in-cup tablet. The cores and cups were then compressed between flat round punches of 12 mm diameter. The slightly larger punches and die cavity ensured that the core-in-cup tablet of 11 mm diameter could easily be fed into the 12 mm die cavity. The press was then adjusted to produce an approximate hardness of 140 N/m^2. Fig. 1 graphically describes the various steps in the production process of the core-in-cup compressed tablets.

The inactive cups and the active cores, as well as the two being compressed together, can be accomplished automatically on a tabletting press that can be modified with feed shoes that feed the cores into the cups and then feed these into a die cavity to be compressed together. It is also a very simple method using exceedingly few adjuvants, and is applicable to a wide variety of drugs. Fig. 1 graphically describes the compression of the core-in-cup tablets and the dimensions of the punches and dies used to produce these compressed tablets.

2.4. Release studies

The BP 1988 paddle method was utilised in all the release studies. A volume of 500 ml of deionized water, equilibrated at 37 ± 0.5°C, was used as the release medium. All experiments were carried out at 50 rpm. The release rates of the tablets were monitored using a six beaker Caleva model 7ST dissolution tester. At appropriate time intervals 2.0 ml samples were withdrawn for analysis. For the release of caffeine from the tablets, the samples were analyzed spectrophotometrically at a wavelength of 242 nm using a Beckman DU 650 spectrophotometer. Linearity was established for aqueous solutions of caffeine in the range of 0.625–20 $\mu g/ml$. For the release of ibuprofen from the tablets, 2 ml methanol was added to the sample withdrawn, mixed well on a

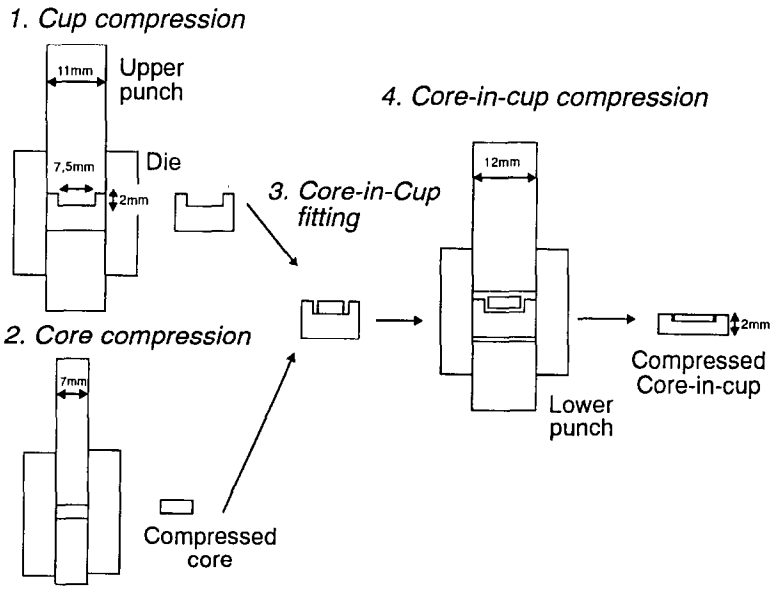

Fig. 1. Schematic diagram of core-in-cup production and dimensions of punches used and ctablets produced.

vortex mixer, and measured at a wavelength of 216 nm. Linearity was established for 50% v/v methanol in deionized water ibuprofen solutions in the range of 0.625–20 μg/ml. The release profiles of a minimum of three tablets from each of three different batches ($n = 9$) were analyzed. The rate of release of caffeine and ibuprofen from cores only was also analyzed.

2.5. Calculation of time exponents

The release rate exponents of drug release from the core-in-cup tablets were examined as to how well the rate of release fits the relationship of Korsmeyer et al. (1983) depicted in Eq. 2.

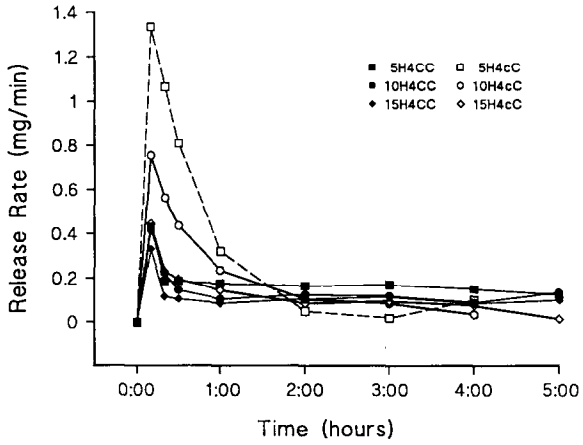

Fig. 2. Caffeine release rates from HPMC K4M drug delivery systems.

Table 4
Mean time exponents and release rates of core matrices and core-in-cup systems used in the different formulations

Formulation	Exponent n value ± SD ($n = 9$)	Mean release rate (mg/min) ± SD ($n = 9$)
HPMC K4M/caffeine		
5H4CC	0.973 ± 0.046	0.174 ± 0.036
5H4cC	0.562 ± 0.041	
10H4CC	0.988 ± 0.089	0.115 ± 0.042
10H4cC	0.594 ± 0.033	
15H4CC	0.987 ± 0.057	0.105 ± 0.033
15H4cC	0.617 ± 0.023	
HPMC K15M/caffeine		
5H15cC	1.026 ± 0.096	0.115 ± 0.045
5H15cC	0.534 ± 0.031	
10H15CC	1.056 ± 0.013	0.106 ± 0.035
10H15cC	0.516 ± 0.098	
15H15CC	1.058 ± 0.082	0.081 ± 0.048
15H15cC	0.477 ± 0.069	
HPMC K4M/ibuprofen		
5H4CI	0.997 ± 0.032	0.126 ± 0.025
5H4cI	0.496 ± 0.031	
10H4CI	0.984 ± 0.039	0.094 ± 0.035
10H4cI	0.451 ± 0.099	
15H4CI	0.979 ± 0.019	0.081 ± 0.020
15H4cI	0.409 ± 0.026	
HPMC K15M/ibuprofen		
5H15CI	0.987 ± 0.062	0.091 ± 0.024
5H15cI	0.540 ± 0.061	
10H15CI	1.015 ± 0.050	0.078 ± 0.016
10H15cI	0.553 ± 0.069	
15H15CI	1.041 ± 0.021	0.055 ± 0.042
15H15cI	0.499 ± 0.031	

Plots of the logarithm of the fractional release vs the logarithm of time in min were plotted for each formulation. The time exponent was then calculated from the slope of the plot via linear regression. In order for Eq. 2 to be applicable the intercept of the graph must pass through the origin, i.e., log k must be zero. This correction to data was achieved via correcting the sampling time data of cumulative fractional release vs the square root of time. The sampling times were then corrected by means of linear regression so that the graph passed through the origin, as per Ford et al. (1987). This correction, however, is only applicable to those systems that release drug via square root of time kinetics. For the core-in-cup systems which release drug mainly via zero-order kinetics, the data were corrected from the plot of fractional release vs time plot. The sampling times were then corrected by means of linear regression so that the graph passed through the origin. In order to determine whether the drug was released mainly via zero-order or square root of time kinetics, the plot with the best correlation coefficient was used. Only the linear portions of the graphs were used to calculate the time exponents. The mean release rates of the core-in-cup tablets were calculated via linear regression of the linear portion of the plot of cumulative fractional release vs time.

3. Results and discussion

Table 4 lists the calculated time exponents as calculated from the results using Eq. 2 as well as the average release rates using Eq. 1 for the zero-order core-in-cup systems.

Fig. 2 and 3 show the release rate of caffeine from the cup-in-core tablets when HPMC K4M and HPMC K15M were used in the core, as well as the release from the cores without the cup coatings. The results indicate that the rate of release of caffeine (a soluble drug) is released from the core-in-cup tablets at a near zero-order rate of release for 80% of the release time. This occurred irrespective of which concentration of HPMC K4M was used. This near zero-order rate of release is confirmed for the release of caffeine from the HPMC matrix core-in-cups from Eq. 2.

When HPMC K15M is used as the matrix polymer there is a slight negative deviation in the rate of release (i.e., the rate decreases slightly with time) which results in an exponent n of greater than 1. For these systems, the larger than 1 the exponent n is, the less closer it is to zero-order release, just as it does for a fraction less than 1 for a positive deviation. Deviation of the time exponent n away from 1 occurs more with core-in-cup tablets containing HPMC K15M than with HPMC K4M. This is because there is more swelling of the HPMC K15M in the release

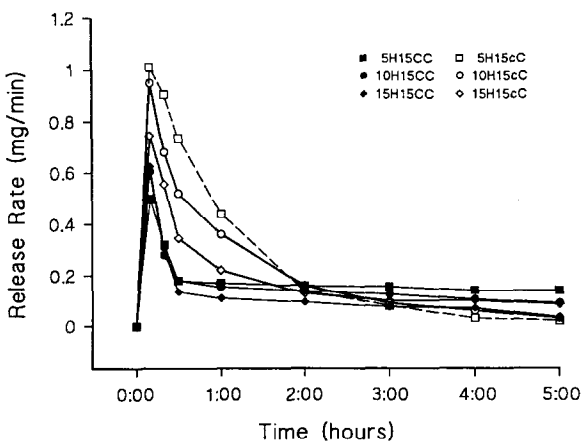

Fig. 3. Caffeine release rates from HPMC K15M drug delivery systems.

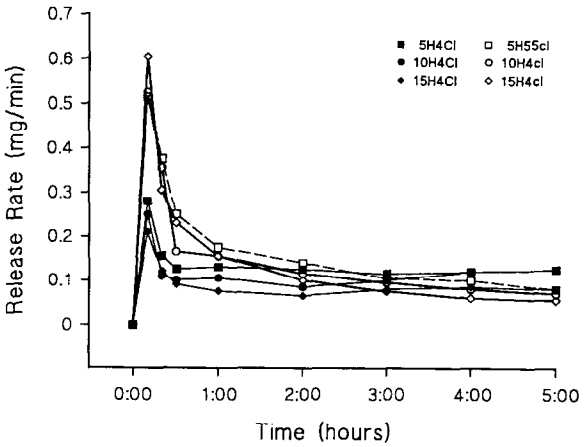

Fig. 4. Ibuprofen release rates from HPMC K4M drug delivery systems.

medium. The higher the concentration of HPMC K4M or HPMC K15M polymer in the core, the lower the rate of release and the longer the time of near zero-order release. The unique high rate of release initially is due to the occurrence of an immediate release of drug from the surface of the polymer matrix core as it comes into contact with the release medium. During manufacture some of the drug particles are exposed at the surface of the matrix and not trapped within. Also, the HPMC swells out very slightly as it comes into contact with the aqueous solution, even though its concentration in the core is low. This allows an immediate release of drug via diffusion in the initial period of release as well as a larger initial surface area exposed to the release medium. Consequently, after approx. 60 min this swelling above the circumference walls of the cup is eroded to a flat constant surface area. The HPMC K15M swells more than the HPMC K4M, therefore, more caffeine is released via diffusion control for the HPMC K15M tablets than the HPMC K4M tablets. The release of caffeine from the tablets, however, settles down to a near zero-order rate of release after 30–60 min. This is due to the fact that the release of caffeine from the polymer matrix is mainly due to erosion of the polymer and constant diffusion through the slightly swollen polymer surface.

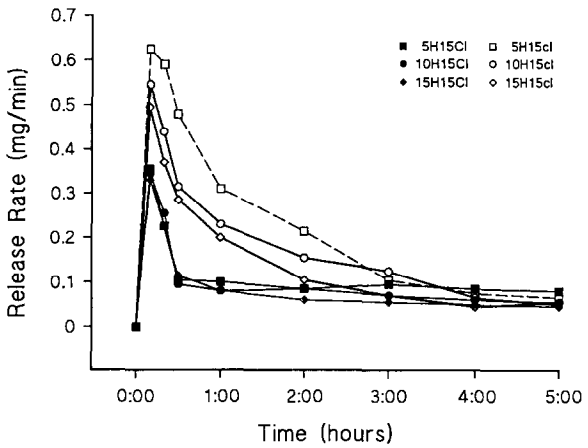

Fig. 5. Ibuprofen release rates from HPMC K15M drug delivery systems.

The rates of release of ibuprofen from HPMC K4M and HPMC K15M core-in-cups and cores only are shown in Fig. 4 and 5. The results are very similar to that of caffeine, except that the rate of release over the linear period for both polymers are closer to zero-order than that for caffeine. The time exponents n vary from 1.041 to 0.997. This is well in line with predicted theory in that the release of ibuprofen from the polymer matrix is predominantly through erosion of the polymer surface. The reason for this is that ibuprofen is not very soluble in aqueous solution and negligible drug is released via diffusion from the polymer matrix.

Again, like the release of caffeine from the core-in-cup tablets, the release of ibuprofen from the HPMC K4M tablets is closer to perfect zero-order than the release of ibuprofen from the HPMC K15M tablets. The difference, however, for all practical purposes is less than that for the caffeine core-in-cup tablets.

In comparing all the core-in-cup tablet formulations with the core-only formulations, one can see that there is a vast difference in the constant release of both the aqueous soluble caffeine and insoluble ibuprofen. The core-only formulations release drug at a rate equivalent to square root of time kinetics. This can be explained by the fact that as the core tablet erodes the surface area of the tablet decreases with time and hence less drug is released with time. Therefore, there is no doubt that this core-in-cup formulation is a superior formulation to the traditional matrix type of compressed tablet.

It is possible, through the manipulation of the grade of HPMC polymer used (or any other hydrophillic polymer or mixture of polymers that erodes constantly with time), the quantity of HPMC polymer used, and the exposed surface area of the core of the HPMC polymer matrix, to produce a core-in-cup compressed tablet that can release a constant amount of drug over a predetermined period of time. In this study, the time of constant release varied from approx. 8 h for the 5% w/w HPMC K4M in caffeine core-in-cup tablets, to approx. 23 h for the 15% w/w HPMC K15M in ibuprofen core-in-cup tablets. Therefore, it is possible to produce a zero-order compressed tablet that only needs to be taken once or twice daily depending on where the drug is absorbed in the gastrointestinal tract and its residence time. With the current advancement of robotics and automated technology it will be reasonably easy and inexpensive to fully automate the manufacture of this core-in-cup compressed tablet. Each set of punches, however, will be specific for each core-in-cup tablet, as it is the diameter and depth of the cup indentation that determine the amount of drug and polymer to be included in the tablets.

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