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Effects of the molecular size of carboxymethylcellulose and pH on the release of a highly water-soluble drug, chlorpheniramine maleate from capsule formulations.

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Abstract

The objectives of this study were to evaluate the effects of dissolution medium pH on the release mechanisms and kinetics of chlorpheniramine maleate from sustained release capsules and to evaluate the effects of the molecular size of Sodium carboxymethylcellulose (CMC) on the release of the drug from its matrix. The conventional wet granulation method was used, with water as the granulating fluid. Granules were manually filled into hard gelatin capsules. Based on the best fit of release data to different mathematical models, an attempt was made to elucidate the mechanism of drug release. Marked differences in dissolution characteristics of the three molecular sizes of CMC were observed in two dissolution media of pH 1.2 and 7.5. Drug release parameters showed that the molecular size and pH of dissolution media strongly influenced the duration, rate of drug release and release mechanism. Drug release kinetics from CMC showed that, the low and medium molecular size CMC were released by Fickian diffusion, while the high molecular size was by non-Fickian transport. The molecular size of polymers such as carboxymethylcellulose should be carefully considered in sustained release formulations.

Key words: Carboxymethylcellulose, molecular size, pH, kinetics, matrix capsule.

Introduction

Recent theoretical and experimental advances in pharmaceutics and pharmacokinetics have highlighted the need for careful control of factors likely to affect the performance of drug delivery systems. In particular, there is increasing concern about any change likely to modify the rate of absorption. Some workers have even defined biological activity both in terms of rate and extent of drug absorption (1). Relatively small changes in the nature of a polymer are known to modify the dissolution processes, and hence drug release. Cellulose gum, which has a long history of use as a suspending agent in liquid pharmaceutical preparations, has also found utility as a tablet binder. Recent work has identified the usefulness of cellulose gum in sustained release applications (2, 3). Sodium carboxymethylcellulose (CMC), a modified form of cellulose has been used as a sustained release agent in drug formulation. It occurs in different molecular sizes, and the difference in molecular size affects its physical characteristics (2). The specific objectives of this study are: to evaluate the three molecular sizes of CMC (low, medium and high) as drug release retardants and study the effect of their molecular sizes on drug release, the effect of pH on the release profile of chlorpheniramine from CMC and to elucidate its release kinetics from capsulated granules.

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Materials and methods.

Materials

Chlorpheniramine maleate powder, (Evans, Nigeria) and sodium carboxymethylcellulose, Low, (CMC L: 90,000), medium, (CMC M: 250,000) and high, (CMC H: 700,000) molecular sizes. from Wako Chemical Company in Japan were used as the matrix polymer. Silicified microcrystalline cellulose (Prosolv HD90, Penwest Pharmaceuticals, England) and Talc (Syria-Aldrich, Germany) were used as the matrix diluents and lubricant, respectively.

Methods

Preparation of granules

Chlorpheniramine maleate, CMC-L or CMC-M or CMC-H and Prosolv HD90 were mixed in a blender (Braun, Germany). The powder mixtures consisting of 4% of chlorpheniramine, 40% of the polymer, and 55.5% of Prosolv HD90 were mixed for 10 minutes using a tumbler mixer (Karl Kolb, West Germany), and granulated with water for 5 minutes using an Erweka granulator (Erweka, Germany) fitted with a 1.6 mm mesh. Granules were dried at 50° C * for 60 minutes in a hot air oven (Salvis, England). The dried granules were rescreened through a 1.7 mm sieve and lubricated with 0.5% talc for 5 minutes using the tumbler mixer. The final blends were subjected to sieve analysis for 5 minutes at amplitude of 1.5 mm/g and interval of 10 seconds. The granules within the size range 0.25 1.0 mm was manually filled into No.O hard gelatin capsules. The capsule weight was adjusted to contain 12 mg of chlorpheniramine maleate per capsule. Fifty capsules were filled per batch.

Particle size analysis

Sieve analysis was carried out on each batch of granules using a nest of stainless steel sieves arranged appropriately on a sieve shaker (Reitch, Germany). Granules of 0.25 mm undersize were bottled and kept as fines, while those of 0.25-1.0 mm size range were stored and used for further experiments.

Densities

A 50 g quantity of powder of the selected size range (0.25-1.0 mm) from each batch was carefully transferred into a 100 ml-measuring cylinder and the volume occupied noted. The cylinder was tapped 500 times using a stampfvolumeter and the new volume read. The bulk and tapped densities were calculated as the ratio of the granule mass and the respective volumes. The determination was repeated thrice and the mean values calculated.

Flow rate and angle of repose

The method of Chukwu (4) was adopted; 20 g of the granule, (size range 0.25-1.00 mm) was introduced into a glass funnel having a specific diameter of 14.5 mm efflux tube length of 7.5 mm and base diameter of 87 mm. The funnel tip was fixed at a constant height of 70mm above a smooth paperboard.

In each case, the granules were allowed to flow under gravity onto the paperboard with the time of flow measured using a stopwatch. The diameter of the cone formed by the granules was then measured. The experiment was repeated thrice and the mean values calculated

Granule friability

A 20 g quantity of granules of the size range 0.25-1.0 mm was placed in an Erweka friabilator (Erweka, Germany) rotating at 25 rpm for 4 minutes. The granules were subsequently shaken on a sieve shaker with a sieve of 0.25 mm aperture and the percentage passing through was taken as a measure of the granule friability (4).

Moisture uptake by granules

The method reported by Chukwu (5) was adopted with slight modification; A 1.0 g quantity of granules of the size range 0.25 1.0 mm was weighed into a petri dish suitably placed inside a very large desiccator kept at 30°C and 100% relative humidity. The granules were weighed every 24 hours until no further increase in granule weight was observed. The percentage moisture uptake was calculated from percentage increase in weight.

Capsulation

A 300mg quantity of the granules of size range 0.25-1.0 mm, equivalent to 12 mg of chlorpheniramine maleate, was filled manually into No. O hard gelatin capsules.

Absolute drug content

This was performed according to B.P 2001 method (6). The contents of five capsules of chlorpheniramine maleate, randomly selected from each batch, were emptied into a mortar, ground to fine powder, and a quantity equivalent to 12 mg of chlorpheniramine was weighed out. This was placed in a 100 ml volumetric flask and the dissolution medium, simulated gastric or intestinal fluids (SGF or SIF respectively) added up to the 100 ml mark. A one ml aliquot of each of the solutions was appropriately diluted and the absorbance and concentration determined spectrophotometrically (UV 160A, Schimadzu, Japan).

Release profiles

The in vitro drug release studies were performed using the basket method and an Erweka DT dissolution rate tester at a speed of 75 rpm. A 900 ml volume of SGF (pH 1.2) or SIF (pH 7.5) maintained at $37 \pm 0.5^{\circ}C$, was used as dissolution medium. Aliquots (3ml) of the dissolution medium were withdrawn at 30-minute intervals for 6 hours and subsequently at hourly intervals up to 8 hours. The withdrawn amount was respectively replaced with an equal volume of fresh dissolution medium kept at $37\ 0.5^{\circ}C$. The withdrawn samples were analyzed spectrophotometrically at 262 nm for the drug content using a Shimadzu UV 160A-spectrophotometer. The data presented are for triplicate determinations. For each dissolution study, the release data were analyzed by fitting in the appropriate release model. The release parameters were computed from the regressed line.

Release models

In order to describe the kinetics of the drug release from the sustained release formulations, various mathematical equations were used. The zero-order rate equation (Eq. 1) describes the systems where the drug release rate is independent of its concentration (7). The first-order equation (Eq. 2) describes the release from systems where release rate is concentration dependent (8). Higuchi (9) described the release of drugs from insoluble matrix as a square root of time dependent process based on fickian diffusion Eq. (3).

$Qt = Kot$ ..... (1)
$\ln Qt = \ln Qo\ K1.t$ ..... (2)
$Qt = K.St = KH.t$ ..... (3)

Where, Qt is the amount of drug released at time t, Qo is the initial amount of the drug in tablet, S is the surface area of the tablet and Ko, K1, KH are release rate constants for zero order, first-order and Higuchi equations respectively. In addition to these basic release models, there are several other models and equations described in the literature to characterize the drug release kinetics and mechanisms from different types of systems (10 - 16). However, in order to define a model, which will represent a better fit for the formulations, dissolution data can be further analyzed using the power law (17); $Mt/M = K.t^n$ where, Mt is the amount of drug released at time t, and M is the amount released at time t = , thus Mt/M is the fraction of drug released at time t, K is kinetic constant, and n is the diffusional exponent. The value of exponent n can be used to characterize the mechanism for both solvent penetration and drug release as shown in Tables 3a and b. (14).
Drug release data obtained was subjected to different drug release models in order to establish the drug release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit.

3. Results and discussion

Moisture sorption profile of chlorpheniramine granules
Figure 1 shows the moisture sorption profile of the chlorpheniramine granules at 100% relative humidity. The percent water uptake by the granules was inversely proportional to the molecular size of CMC. This result is consistent with our earlier finding (3). The maximum percent moisture uptake by CMC-L was 151.52 compared to 136 for CMC-M and 74.0 % for CMC-H. This parameter is important as many water swellable controlled-release polymers including CMC are highly hygroscopic and especially as the controlled-release mechanism of CMC involves gelling and swelling after it comes in contact with the dissolution fluid.

Low molecular size (CMC-L),
Medium molecular size (CMC-M),
High molecular size (CMC-H)

Micromeritic properties of chlorpheniramine granules.

Table 1 shows the micromeritic properties of the chlorpheniramine maleate granules. The granules used for the investigation were those between 0.25 mm and 1.00 mm in size. The amount of granules of particle size > 0.5 mm increased with increase in molecular size of CMC. However at < 0.5 mm,the relationship was CMC-M > CMC-L and CMC-H. Bulk and tapped densities are useful parameter for estimating the packing behavior of powders and granules. An increase in tapped density is usually an advantage in capsule and tablet technology because of reduced volume of fill (4). While the angle of repose increased with increase in molecular size, the effect was the opposite with the flow rate, which decreased with increase in molecular size. Adhesiveness of CMC, which increases with increase in molecular size (2) could have contributed to the high value of angles of repose of CMC-H. With the other parameters such as bulk and tapped densities, Carr's index and Hausner's quotient, CMC-M had lower values than CMC-L and CMC-H. This indicates that molecular size of CMC influences the flow properties of the granules. As expected, flowability increased with decreased angle of repose due to reduced interparticulate friction.

CMC-M granules had the highest porosity with a value of 83% while CMC-L had the lowest. The higher the porosity of a bed, the faster the rate of penetrant into the system, which will facilitate the eventual dissolution of the polymer fraction (18). This probably explains the faster drug release from CMC-M (fig.2a). However, because of the higher adhesiveness/viscosity of the CMC-H, which most certainly overcame the positive forces of fluid penetration and swelling (1), its degree of moisture uptake and drug release was not consistent with its porosity. Hence, CMC-L despite its lower porosity value had higher moisture uptake than CMC-H.

Table 1. Some micromeritic properties of chlorpheniramine granules

Parameter	CMC- L	CMC M	CMC - H
Bulk density (g/dl)			
Tapped density (g/dl)			
Carrs index (%)	16.67	14.81	15.63
Flow rate (g/s)		1	
Angle of repose (o)			
Particle density (g/dl)			
Hausner quotient	1.2	1.17	1.19
Porosity (%)	66	83	77
Absolute drug content (%)	12.00 0.005	11.93 0.24	11.93 0.36

Low molecular size (CMC-L), Medium molecular size (CMC-M), High molecular size (CMC-H)

Low molecular size (CMC-L),
Medium molecular size (CMC-M),
High molecular size (CMC-H)

Effect of molecular size and pH on drug release.

Table 2 shows the effect of molecular size on the $t_{50\%}$ and $t_{70\%}$ (time for 50% and 70% of drug to be released) values as well as the maximum drug released (C_{max}) after 8 hours in the SGF and SIF. The time for 50% of chlorpheniramine to be released in SGF from CMC-L was 26.8 min. The corresponding $t_{50\%}$ values for CMC M and CMC H respectively were found to be 14.6 and 47.8 min. CMC-H had the highest values of both $t_{50\%}$ and $t_{70\%}$ followed by CMC-L and CMC-M respectively. The result of drug release here corroborates the reported porosity of CMC-M compacts. Maximal drug release was however not dependent on the molecular size of CMC.

The $t_{50\%}$ values in SIF were 52.4, 83.5, and 139.1 minutes for CMC-L, CMC-M and CMC-H respectively, indicating an inverse relationship between the molecular size of CMC and drug release. This is consistent with the result of earlier studies (18). CMC gum solution is known to maintain its normal viscosity over a wide pH range. However cellulose solutions exhibit their maximum viscosity and best stability at pH 7 to 9. Below pH 4, the less soluble free acid carboxymethylcellulose predominates and may significantly increase viscosity (7). A combination of this inherent property of the drug and of the matrix former is responsible for the variation in drug release from CMC matrix. The reduced drug release from SIF compared to SGF is due to the decreased solubility of the drug base in SIF. The cumulative drug released (C_{max}) at 8 hours in SIF were, 100, 78 and 86.9% for CMC-L, CMC-M and CMC-H respectively. The complete release noticed in CMC-L is consistent with its lower viscosity and the faster rate of matrix hydration and drug diffusion from it.

Table 2 Release parameters of Chlorpheniramine maleate

	SGF			SIF		
Parameter	CMC-L	CMC-M	CMC-H	CMC-L	CMC-M	CMC-H
$T_{50\%\,(min)}$	26.8	14.6	47.8	52.4	83.5	139.1
$T_{70\%\,(min)}$	57.3	21.9	70.6	60.0	162.2	255.7
$C_{max\,(\%)}$	100.0	100.0	100.0	100.0	78.0	86.9

Low molecular size (CMC-L), Medium molecular size (CMC-M), High molecular size (CMC-H)

Drug release kinetics

Fig. 2 shows the cumulative percent drug released versus time. The curves suggest that none of the batches followed zero order drug release kinetics. This is confirmed by the poor correlation coefficients in the low and medium molecular sizes (Table 3). However, the high correlation coefficient of the low and high molecular sizes for the first and zero order release kinetics in SIF and SGF respectively, shows the involvement of these mechanisms. This differing release kinetics was noticed between the medium and high molecular sizes in a different study (3). Similarly, the poor correlations of the data for medium and high molecular sizes in the first order and Higuchi models show the non applicability of these models. Drug release data from different batches were analyzed using equation 4 and the results show that the low and medium molecular size granules followed Fickian kinetics at pH 1.2 (SGF) with n = 0.12 0.34 (Table 3). There was however a shift in the diffusion kinetics from Fickian to non-Fickian transport at higher pH (SIF).

Table 3: Regression analysis and correlation coefficient values for dissolution data of Different batches of chlorpheiramine granules according to various kinetic models in SGF and SIF

SGF	Zero order		First order		Higuchi model		Korsenmeyer
	R	k	r	k	r	k	n
CMC-L	0.7561	0.7337	0.9803	6.6829	0.4858	0.012	0.34
CMC-M	0.6761	1.0181	0.8686	7.9053	0.4553	0.006	0.12
CMC-H	0.9327	0.6828	0.0465	6.5575	0.5574	0.0245	0.63
SIF							
CMC-L	0.4406	0.9542	0.9287	6.6302	0.8071	0.0519	0.82
CMC-M	0.8409	0.3477	0.2469	4.1469	0.5198	0.0299	0.93
CMC-H	0.7326	0.2816	0.6823	3.5942	0.5072	0.0364	0.95

Low molecular size (CMC-L), Medium molecular size (CMC-M), High molecular size (CMC-H)
r, correlation coefficient, k, rate constant, n, release exponent

Conclusion

Drug release from CMC in both SGF and SIF were found to be affected by a combination of the pH of the dissolution medium, molecular size of CMC, solubility of CMC or the drug in the dissolution medium. Of these, it appeared that, pH of the dissolution medium had a dominant effect, followed by the solubility of the CMC. This is probably responsible for the lower drug release in SIF even though, the free acid CMC in SGF could have retarded drug release more. The kinetics of drug release from the CMCs of three molecular sizes at different pH levels were established and drug release was found to be Fickian controlled from the low and medium molecular sizes, whereas, it followed non-Fickian anomalous diffusion patterns from the high molecular size. However, the value of diffusion exponent n changed with change in pH of dissolution media.

It is concluded therefore that, pH of the dissolution media, as well as the molecular size of CMC play a significant role in describing the in-vitro drug release from the capsule matrix.

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