jopat 12 2007 22 - 30

Journal Of Phytomedicine
And Therapeutics

Evaluation of the controlled release potential of *Adansonia digitata* mucilage: A super gel forming polymer

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Abstract

The suitability of *A. digitata* mucilage (ADM) as an excipient in the formulation of matrix tablets, the mechanism and kinetics of drug delivery were studied. Aminophyline was the prototype drug while these properties were compared to those of HPMC and Cp. ADM was used at concentration levels of 10, 15 and 30% of the tablet weight while HPMC and Cp were used at 30% concentration. The tablet friability, attrition and dissolution characteristics were evaluated. All the tablets formulated showed good physical properties. The ADM matrix tablets showed similar drug release and attrition pattern to those of Cp in both SIF and SGF. Generally the drug release retardation efficiency of the ADM tablets at equal polymer concentration was higher than those of Cp but less than that of HPMC in both SGF and SIF. The mechanism of release of aminophyline from ADM as in Cp and HPMC was by diffusion.

Key words: *Adansonia digitata* mucilage; Carbopol; Hydroxymethylpropylcellulose; Matrix tablets

Introduction

Hydrogels are hydrophilic polymers which can absorb a significant amount of water without dissolving or losing their structural integrity (1). Because of the need for innovations and improvement in biopolymers used for various biomedical applications, novel hydrogels from both natural and synthetic sources are continually being sought.

Hydrogels are widely used in pharmaceutical formulations especially in oral controlled release where they serve as matrix systems. Polysaccharides are favored for this purpose because of their biocompatibility and biodegradability (2, 3). Many of the naturally occurring hydrogels are obtained from plant sources and exist as polysaccharides (4).*Adansonia digitata* mucilage (ADM) is a naturally occurring hydrophilic polymer obtained from the leaves of *Adansonia digitata* (5). *A. digitata* is a tree that grows in most parts of Northern Nigeria where the leaves are used as vegetable and as a soup thickener as well as in parts of north and east Africa (6). Our earlier work on ADM shows that ADM exhibits different swelling characteristics in

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different pH environments with a characteristic swelling ratio of 12 and 5 in SIF and SGF respectively (7). These make ADM a potential controlled drug release excipient. This work is designed to evaluate the suitability of ADM in the formulation of matrix tablets by using it to modify the release profile of aminophyline a highly water soluble drug. This will be compared to the release properties of the drug from well characterized polymers, carbopol (Cp) and hydroxymethylpropylcellulose (HPMC). The release kinetics of the drug from ADM will also be determined.

Materials and methods

Materials

Lactose, hydroxypropylmethylcellulose (HPMC), aminophyline, ethanol were obtained from Sigma-Aldrich, Germany while carbopol (Cp), acetone, were obtained from Fisher, USA.

Methods

Preparation of ADM

ADM was prepared using a modification of our initial extraction method (5). The young leaves of *A. digitata* were collected and rinsed several times with distilled water to remove any adhering dirt. A predetermined quantity of the leaves was placed in a beaker containing ethanol maintained at 50 ^{O}C such that all leaves were totally submerged with constant agitation in a water bath (GFL, KarLK51b TUV, Scientific Services. Germany).The ethanol was changed several times until the leaves were totally free of any green pigment and then air dried. Mucilage was extracted by putting a 100 g quantity of the leaves into a 1L beaker containing 200 ml of distilled water maintained at 70 ^{O}C at a constant agitation for 2 h. The clear gummy exudate extracted was separated from the leaves by passing through a 150 mm mesh size sieve.The mucilage was then precipitated with 4 parts of acetone. The mucilage so obtained was washed three times with 50 ml of acetone to remove residual water and then air dried before pulverizing. The resulting material was stored in an air tight container and placed in a desiccator until used.

Preparation of Matrix tablets

Matrix tablets were produced by the blending technique (8). An appropriate amount of the polymer was homogeneously mixed with aminophyline and lactose in a Turbula mixer. (JEL, Germany) using the quantities indicated in Table. 1 for 30 min at a mixing rate of 15 rpm.

A 250 mg quantity of the mix was directly compressed in a single punch tableting machine, (Shangha Tiaxiang & Chenta. Pharmaceutical Machinery Co. Ltd) fitted

with an 8 mm flat faced punch and die set such that each 250 mg tablet contained 100 mg aminophyline (Table 1). The tableting machine was set such that all tablets had a hardness of 6 ± 0.5 KgF, as determined with an Erweka hardness tester. The low polymer concentrations used for assessing the drug release retardation efficiency for the various polymers was chosen because of the sensitivity of polymer efficiency at such low concentrations (9).

Friability of matrix tablets

The weight loss for 10 tablets for each formulation was determined using an Erweka double drum friability tester (Erweka, Germany) set at 25 rpm for 4 min.

Attrition rate

The attrition of the matrix tablets was determined in SGF and SIF. Tablets were weighed and then dried to a constant weight (W_i) with a moisture balance (Ultra X, Germany). Each tablet was then subjected to attrition in an Erweka dissolution apparatus (Erweka, DT. Germany) at 50 rpm. The tablet was removed at hrly intervals and dried to a constant weight in the moisture balance (W_d). This was repeated until the entire tablet was totally lost. The tablet attrition was estimated on the basis of weight loss by the tablets.

$\%\text{Attrition} = (W_i - W_d) \times 100/Wi \quad \ldots 1$

W_i is initial weight of dried tablet

W_d is weight of dried tablet after attrition (10).

Attrition was characterized on a zero order model (11).

$\%\text{Attrition} = K_A t \quad \ldots . 2$

K_A is the attrition rate constant.

In vitro release studies

The USP (1990) (12) method for the dissolution of aminophyline tablets was adopted to determine the release profile of aminophyline in the various hydrogel matrices at a speed of 50 rpm and 900 ml of either SGF or SIF as medium. The amount of aminophyline released was assessed by taking samples from the dissolution medium every 30 min. for 10 h and quantitatively determining the drug concentration using a UV spectrophotometer (UV-160A. Shimadzu, Japan) at 276 nm and 273 nm for SGF and SIF respectively.

The kinetic mechanism of drug release from ADM was determined by fitting the release data obtained into equation 3.

$M_t/M = Kt^n \quad \ldots 3$

Where M_t/M is the fractional amount (0.1-0.7) of drug released at time t; K is a kinetic constant incorporating the characteristics of the polymeric system and n is a

constant which depends on and is used to characterize the transport mechanism. The characteristic values of n for a cylindrical tablet are n= 0.45 for Fickian (Case 1) release, >0.45 but <0.89 for non Fickian (Anomalous) release and 0.89 for Case II or Zero order release and > 0.89 for super case II release profile. Case II release is characterized by the dissolution of the polymeric matrix due to the relaxation of the polymer chain while the non Fickian release is characterized by the summation of both diffusion and polymer dissolution (13). Due to the differences in the drug release kinetics and test conditions, the constant K, is unsuitable for comparing release rates. The mean dissolution time (MDT) as given in equation 4 (14) was used to characterize the release rate of aminophyline from the various polymers in the different fluid systems using the values n and K obtained from equation 3.

$$MDT = (n/n+1).K^{-1/n} \quad \ldots . 4$$

Result and discussion

Tablet physical quality

All the tablets produced had friability values below the 1% limit which is an indication of good physical property. No evidence of lamination or capping was observed irrespective of the type of polymer used. A major factor in the capping of tablets is poor inter-particulate bonding which result from massive elastic recovery and also entrapment of air which occurs with small particles due to poor packing. Though the matrix tablets were prepared by direct compression of fine powder mix of the drug, the polymer and lactose, the tablets did not cap because of the enhanced cohesive and adhesive forces between polymerspolymer and polymer-drug or lactose particles (14).

Attrition profile

Swellable matrix tablets are all erodable systems and effect release of bioactive material by attrition and diffusion (10). Attrition which is as a result of surface stress in the dissolution medium is characterized by the loss of polymer and other insoluble component (11). In vitro and in vivo experiments have shown that the rate of weight loss and drug release from swellable matrix tablets in the human stomach is a primary consequence of both attrition and diffusion. The result (Figs. 1, 2) of the attrition studies indicates that the tablets underwent considerable but variable attrition at the various polymer concentrations investigated in both SIF and SGF. The percentage cumulative attrition for the three polymers investigated in both SIF and SGF were concentration dependent, decreasing with increasing polymer concentrations. The type of fluid affected the attrition profile of Cp and ADM matrix tablets (Figs. 1, 2).

The attrition rate constant, K_{at} obtained by fitting the various attrition data into the

zero order equation plots is given on Table 2. The K_{at} values for ADM matrix tablets decreased with increasing polymer concentration in both SGF and SIF. The fluid type also had an appreciable effect on the K_{at} for tablets prepared with ADM and Cp with the attrition rate constants being consistently higher in SIF than for ADM and Cp. This could be due to the effect of the pH sensitivity of ADM and Cp to gelation and swelling. Due to the higher rate of swelling and gelation of ADM and Cp at high pH (7, 15) the degree of stress relaxation within the tablet matrix is also increased thus the hydrated polymer is more rubbery thus making the surface stress induced by rotation of the basket more effective in the SIF than in SGF hence the higher rate of attrition in SIF. At equal polymer concentrations (Table 1), the rate of attrition of matrix tablets prepared with ADM was less than that for HPMC in SGF and in both SGF and SIF in Cp (Figs. 1, 2). The kinetics of attrition in ADM, HPMC and Cp matrix tablets (Table 2) was evaluated based on zero order kinetics because the diminishing in the weight of the of matrix tablets as a result of the erosion of the matrix was due to surface stress induced by the rotation of the dissolution basket at a

Table 1: Formula for the formulation of aminophyline matrix tablets

Hydrogel	Drug (aminophyline)	Diluent (lactose)	Total weight
25 mg	100 mg	125 mg	250 mg
37.5 mg	100 mg	112.5 mg	250 mg
75 mg	100 mg	75 mg	250 mg

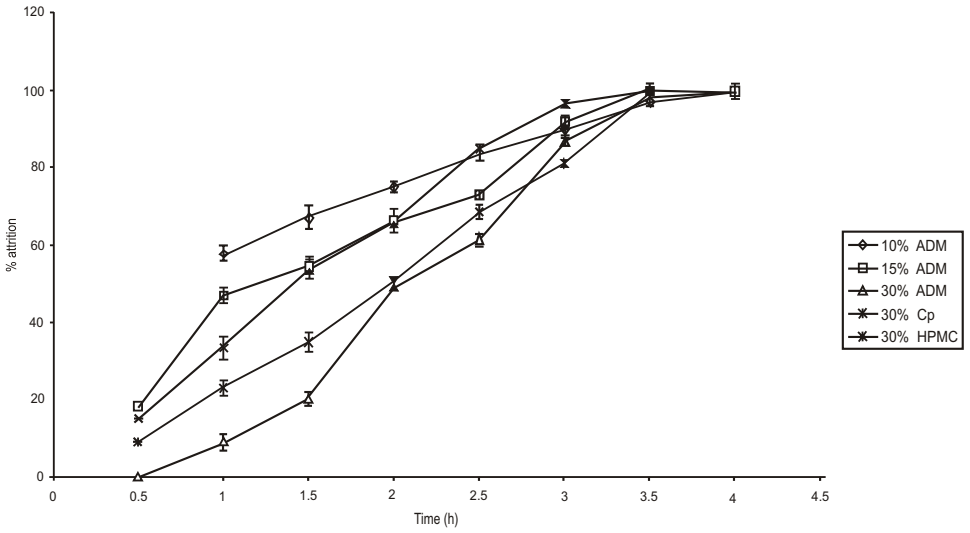

Fig. 1: Attrition profile of aminophyline from matrix tablets prepared with ADM, Cp and HPMC in SGF

Table 2: Release and attrition characteristics of matrix tablets formulated with ADM, HPMC and Cp in SGF and SIF

Parameters	10% ADM		15% ADM		30% ADM		30% HPMC		Cp	
	SGF	SIF	SGF	SIF	SGF	SIF	SGF	SIF	SGF	SIF
n	0.4665	0.5648	0.4124	0.4086	0.4384	0.5648	0.4994	0.4495	0.4418	0.3861
Kr	0.29	0.7458	1.0465	1.1834	0.2191	1.6158	0.6152	1.3495	0.9077	1.6947
r	0.9925	0.9877	0.9979	0.9856	0.9837	0.9957	0.9811	0.9833	0.9906	0.9907
MDT	0.1125 ±0.03	0.2147± 0.06	0.217± 0.02	0.4380± 0.01	0.4789± 0.02	0.4153± 0.01	0.826± 0.01	0.81279± 0.01	0.363± 0.012	0.4110± 0.012
K_{at}(%h^{-1})	38.52 ±1.17	47.32± 2.46	33.01± 1.46	39.78± 2.2	21.21± 1.95	38.79± 0.89	25.73± 0.86	29.72± 0.86	33.84± 1.76	49.48± 1.92
x	0.9355	0.9981	0.9073	0.9628	0.9565	0.9565	0.9969	0.9969	0.9874	0.9874

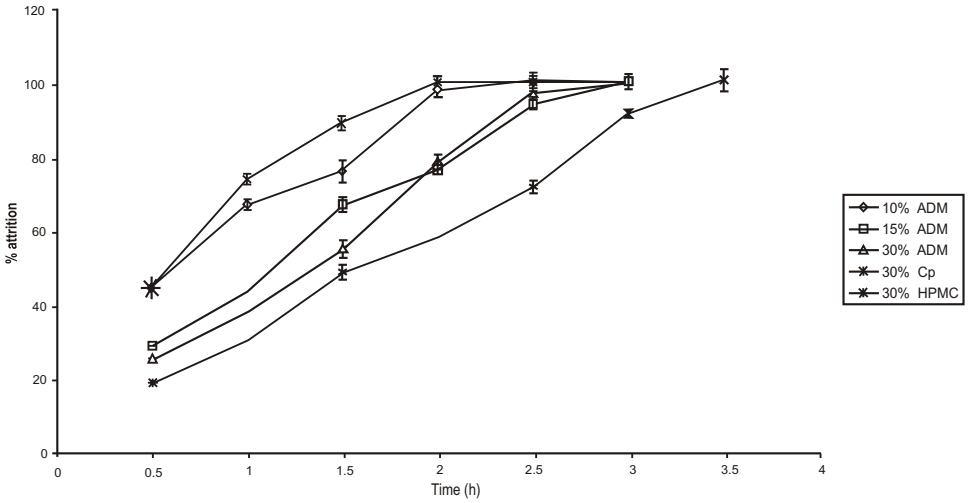

Fig. 2: Attrition profile of aminophyline matrix tablets prepared with ADM, Cp and HPMC in SIF

constant speed (13).

Release studies

The various matrix tablets formulated with ADM, HPMC and Cp showed variable time dependent release profiles (Fig. 3, 4). The amount of aminophyline released from the matrix tablets formulated with ADM decreased with increasing polymer concentration in both SGF and SIF. The rate of drug release by both ADM and Cp matrix tablets was consistently higher in SIF than in SGF as shown by the MDT values (Table 2). The results were similar to those obtained for attrition assessment and are consistent with the pH sensitivity of ADM and Cp.

The release profile of the various matrix tablets (Figs. 3, 4) showed that at the

polymer concentration used, HPMC was most efficient in retarding the release of aminophyline from the matrix followed by ADM. The release behavior of ADM in SIF and SGF closely resembles that of Cp. The slow rate of release of aminophyline from ADM and Cp matrix tablet in SGF relative to SIF is due to the slow rate of hydration and swelling in SGF (15). The time required to achieve 100 % release of aminophyline was consistently lower at the various polymer concentrations than that required to achieve 100 % attrition irrespective of the polymer type. This indicates that the primary mechanism of drug release from the various matrix tablets is by diffusion. The K_{at} and MDT values for attrition and drug release respectively (Table 2) supports this. This is in line with earlier reports that the release of a water soluble drug from Cp and HPMC matrix systems is basically diffusion controlled (11, 15). The kinetics of aminophyline release from the various matrix tablets were similar, and predominantly indicating diffusion ($n = 0.45$) or a combination of diffusion and dissolution of the matrix system ($n > 0.45 < 0.89$) in both SGF and SIF. This similarity in the kinetics of release of aminophyline from matrices irrespective of the type of polymer used is probably because they are

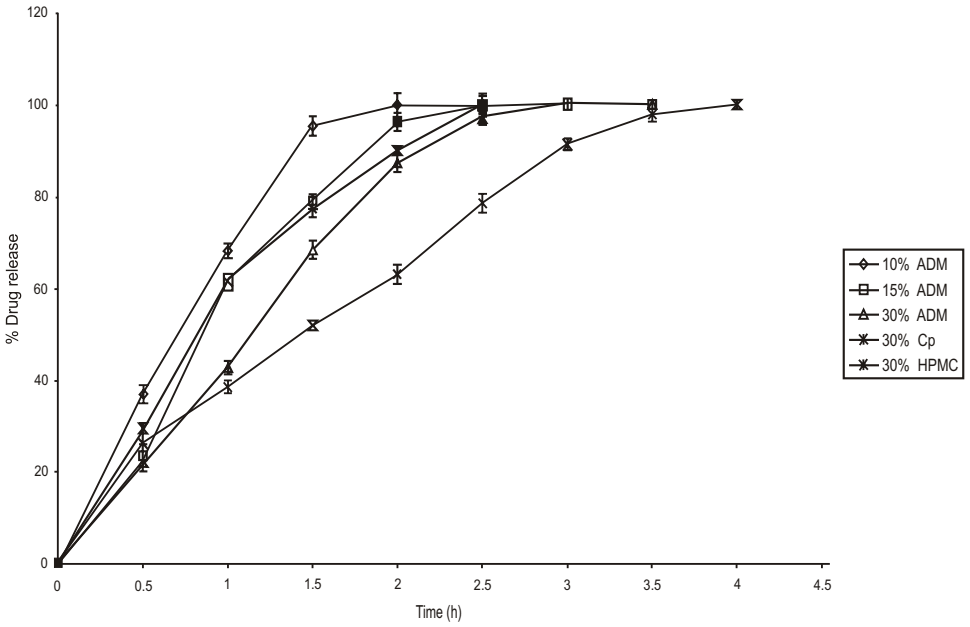

Fig. 3: Release profile of aminophyline from matrix tablets prepared with ADM, Cp and HPMC in SGF

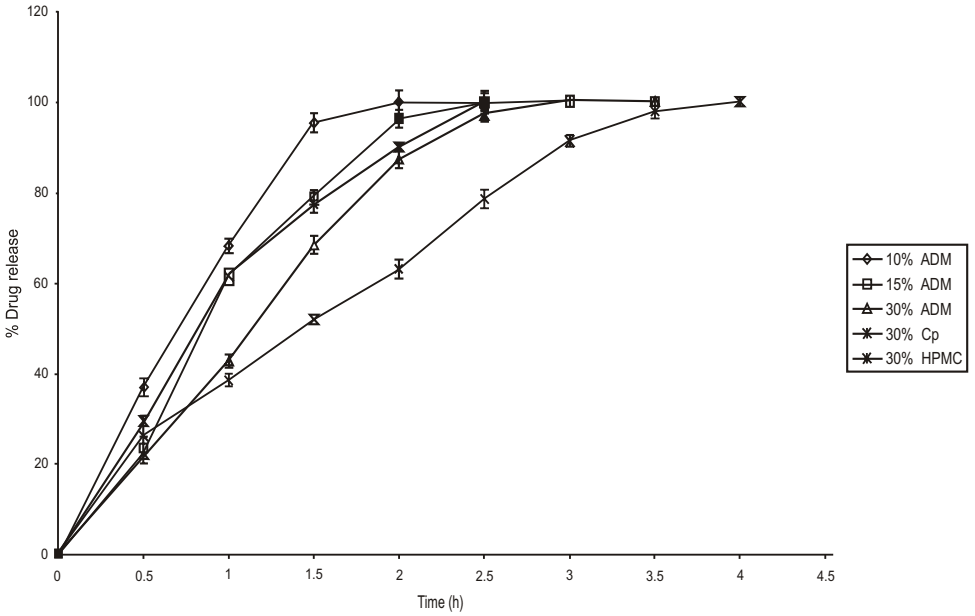

Fig. 4: Release profile of aminophyline from matrix tablets prepared with ADM, Cp and HPMC in SGF

all hydrogels.

Conclusion

Elegant matrix tablets with good physical characteristics similar to those prepared with Cp and HPMC were prepared with ADM. The attrition and drug release characteristics of ADM matrix tablets closely resembles those of Cp than HPMC in both SIF and SGF. The effective and comparative retardation of aminophyline release from ADM matrix at relatively low concentrations makes it a potential controlled release excipient. The higher rate of drug release relative to rate of attrition indicates that the main mechanism of release is diffusion.

Acknowledgment

We wish to acknowledge the technical assistance and support of Mrs. Abigail Nnurum, Mrs. Rekiya Akuboh, Mrs. Theresa Ezeh and Mr. Abuh Garba of the Department of Pharmaceutical Technology and Raw Material Development, National Institute for Pharmaceutical Research and Development (NIPRD) Abuja.

References

1. Wu, X., Huang, S., Zhang, J. and Zhuo, R. (2004). Preparation of novel physically

crooslinked hydrogels composed of poly (vinyl alcohol) and amine-terminated polyamidoamine dendrimer. Macromol. Biosci. 4, 71-75.

2. Watering, P., Metters, A.T, Scheonmkers, R. G. and Hubbell, J.A. (2005). Poly(ethylene glycol) hydrogels formed by bconjugate addition with controllable swelling, degradation, and release of pharmaceutically active protein. J. Control. Release. 102, 615-627.
3. Mousa, S. I., Lenaerts, V. Cartilier. L. H. (1998). Effect of some physical parameters on the swelling properties of cross-linked amylose matrices. Int.. J. of Pharmaceutics 173. 35 - 41.
4. Al-Taani, B. and Tashtoush, S. (2003). Effect of microenvironment pH of swellable and erodable buffered matrices on the release characteristics of diclofenac sodium. .Pharm. Sci Tech. 4:3, 43 61.
5. Builders, P. F., Isimi, C. Y. Toge, B. K. and Kunle, O. O. (2002). Some physicochemical properties of Adansonia digitata mucilage: A potential pharmaceutical excipient. J. of Phytomed. and Therap. 7:1 and 2 56-62.
6. Keay, R. W. J. (1989). Useful trees of Nigeria. Clarendon Press, oxford. pp. 136-137.
7. Builders, P. F., Adikwu. M. U., Egieyeh, A. and Kunle, O. O. (2006). The swelling properties of Adansonia digitata mucilage: A super gel forming polymer. Afr. J. Pharmaceut. Res. Dev. 2:1, 88-93.
8. Mc Ginity, J.W., Cameron, C. G. and Cuff, G. W. (1983). Controlled Release theophylline tablet formulations containing cicrylic resins. (1) Dissolution properties of tablets. Drug.dev. and Ind. Phram. 9:1&2 57-68.
9. Rowe, C. R., Sheskey, P. J. and Weller, P. J. Handbook of Pharmaceutical excipents. 4th Ed. Pharm. Press Amer. Pharm. Assoc. P. 89-92 and 297-300.
10. Remon, P.J., Ameye, D., Vervaet, C., Foreman, P., and Pringels. E. (2005). Starch/Carbopol spray-dried mixtures as excipients for oral sustained drug delivery. J. Control. Release. 103, 635 641.
11. Vazquez. M., Casalderrey, M., Duro, R. and Gomez-Amoza, J. (1996). Attenolol release from hydrophilic matrix tablets with hydroxypropylmethylcellulose (HPMC) mixtures as gelling agent: effect of viscosity of the HPMC mixtures. Eur. J. Pharm. Sci 4, 39-48.
12. The United States Pharmacopeia, 1990. (The National Formulary) United States Pharmacopeial Convention Inc. 22nd Revision. Mack Printing Company, Easton, P. A. 18042. P. 69.
13. Reza, S., Abdul Quadir, M., Haider, (2003). Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled release drug delivery. J. Pharm. Pharmaceut. Sci. 6:2, 274-291.
14. Marshall, K. Compresion and consolidation of powdered solids In: Lachman, L., Lieberman, H. A. and King, J. L. The theory and practice of industrial pharmacy. 3rd Ed. P. 66 99.
15. Perez-Marcos, B., Gutierrez, Gutierrez, C., Gomez-Amoza, J. L., Martnez-Pacheco, R., Souto, C. and Concheiro, A. (1991). Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices. Inter J. Pharm. 67, 113-121.