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DRIED MOLASSES AS A DIRECT COMPRESSION MATRIX FOR ORAL CONTROLLED RELEASE DRUG DELIVERY I: MATRIX DEVELOPMENT AND DRUG RELEASE

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ABSTRACT

Investigation was conducted to evaluate dried molasses as a direct compression matrix for oral controlled release drug delivery system based on its tendency to form a gel-like layer around an inner dry core tablet when it comes in contact with fluid.

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Dried molasses matrix was modified by incorporation of hydroxypropylmethylcellulose (HPMC) at four concentration levels (12.5, 15.0, 20.0 and 28.57%) to obtain a gel layer of suitable characteristics, and compressed directly on an instrumented rotary tablet press. Theophylline was used as a model drug. Drug release study was performed using USP dissolution apparatus 2, rotated at 50 rpm, in distilled water, simulated gastric fluid pH 1.2, and simulated intestinal fluid pH 7.5. Theophylline was determined by a High Pressure Liquid Chromatographic method, utilizing beta-hydroxyethyl theophylline (BHET) as an internal standard. Results showed an inverse relationship between the rate of release and the level of HPMC, with release period ranging from 3 to 36 hours. Release rate was greatest in intestinal fluid, least in distilled water, and intermediate in gastric fluid.

INTRODUCTION

Since the introduction of the first oral controlled release dosage form in 1952 (1), a substantial number of competing drug delivery systems have been introduced into the market place.

The literature describes various methods and materials by which sustained release dosage forms could

be prepared (2-5). The materials most commonly employed include various coating materials, fats, fatty esters or alcohols, waxes, resins, gums, polymers and plastics. The general procedures include:

1. coating the active drug with substances which are resistant to, or slowly soluble in, gastro-intestinal fluids
2. forming a chemical complex with the drug
3. binding the drug to ion-exchange resins
4. embedding the drug in a matrix which gradually releases the active ingredients

Matrix systems, vehicles for drug delivery, have advantages in their ease of fabrication when compared to other controlled release systems such as encapsulated reservoir devices (6). Also, they become essential in order to achieve controlled release in cases such as macromolecules (7). The drug can be embedded in either a slowly eroding matrix, or a polymeric (non-disintegrating) matrix. A third type of matrix system is the hydrophilic matrix formulation, the concept of which is based on the formation of a hydrated gel-layer on the surface of the tablet. This then acts as a barrier and prevents the rapid dissolution of the inner drug core tablet.

It was the purpose of this study to investigate and evaluate the applicability of dried molasses as a

direct compression matrix for oral controlled release drug delivery systems which forms a pseudo-gel layer when it comes in contact with liquid.

BACKGROUND OF STUDY

Dried molasses (Ingredient Technology Corporation, Pharmaceutical Group, Pennsauken, New Jersey) is a natural product derivative which is widely available, and extensively used in the food industry as a flavor, sweetener, source of dietary fiber and natural color. In a previous work (8), a feasibility study was conducted to evaluate the potential use of this material as a direct tableting carrier.

Formulations prepared using several active ingredients did not disintegrate, but had erosion times ranging from 35 to 50 minutes. The dissolution study on a vitamin C formulation showed that about 90% of the drug was released over 3 hours. It was also observed that dried molasses matrix formed a pseudo gel-like mucilagenous layer around an inner dry core tablet when it came in contact with liquid.

EXPERIMENTAL

Development of the Matrix

Using theophylline as a model drug, initial experiments showed that the consistency of the molasses

gel did not prolong drug release for a sufficiently long period. Consequently, it was necessary to modify the matrix by incorporating various hydrophilic gums or gel-forming substances in order to obtain a suitable matrix for the study. Acacia (U.S.P. Powder, Amend Drug and Chemical Co., Inc., Irvington, New Jersey), guar gum (Type PK-200, Perny, Inc., Lodi, New Jersey), methyl cellulose (Dow Chemical USA, Midland Michigan), and hydroxypropylmethyl cellulose (Methocel F4M, Dow Chemical USA, Midland Michigan) were evaluated, and the latter was selected for further study based on its more desireable performance characteristics. Dried molasses powder was initially passed through a 60 mesh sieve (Newark Wire Cloth Co., Newark, New Jersey). HPMC was incorporated at four concentration levels: 12.5, 15.0, 20.0 and 28.57%. Weighed quantities of dried molasses, HPMC, and anhydrous theophylline (Sigma Chemical Co., St. Louis, Missouri) powders were blended in a cuboidal blender (Type KB-15, Erweka Apparatebau G.m.b.H., Germany) for 20 minutes, and compressed directly on an instrumented rotary tablet press (Pennwalt Corporation, Stokes Compacting Equipment Division, Warminister, Pennsylvania) using a set of 0.5 in. (1.27 cm) round standard concave tools to a tablet weight of 700 mg (containing 300 mg of drug). Tablet hardness was set at about 7.0 kg. For each

formulation, tablets were evaluated for weight variation, hardness, thickness and friability.

Assay of Theophylline

A High Pressure Liquid Chromatographic (HPLC) method was employed because of color interference with UV absorbance. The method was a modification of that described by Orcutt et al (9) for theophylline in biological fluids. Beta-hydroxy ethyl theophylline (Sigma Chemical Co., St. Louis, Missouri) (BHET) was used as an internal standard. HPLC analyses were performed using a 30 cm x 3.9 mm i.d. Bondapak C_{18} column (Waters Associates, Inc., Milford, Massachusetts), WISP Auto Sampler (Model 710-A, Waters Associates, Inc., Milford, Massachusetts), programmed to inject 5 microliters of sample. Absorbance was measured at 270 nm and full scale sensitivity of 0.01A. Peak heights were computed using an integrator (Model 3390A, Hewlett Packard Co., Avondale, Pennsylvania).

The mobile phase consisted of 7% acetonitrile and 93% of acetate buffer, pH 4.0. The flow rate was set at 1.5 ml/min.

Standard Curves

The standard curves were prepared with theophylline in distilled water, gastric fluid, and

intestinal fluid over a concentration range of 0.5 to 70 g/ml. BHET was prepared at a concentration of 50 g/ml in each of the dissolution fluids. The theophylline standard curves were obtained by plotting the peak height ratio (peak height of theophylline to peak height of BHET) against concentration. The slope, intercept and correlation coefficient were obtained by linear regression.

In Vitro Release Study

The in vitro release study was performed using the USP XXI/NF XVI rotating paddle (Hanson Research Corp., Northridge, California) method (10). 900 ml of dissolution fluid (distilled water, gastric fluid or intestinal fluid) was placed in the dissolution vessels and allowed to equilibrate to 37°C. The paddles were rotated at 50 rpm. At specific time intervals, a 5 ml sample was withdrawn from each vessel, and immediately replaced with an equivalent volume of fresh fluid. The samples were filtered through a 0.45 m filter, and after appropriate dilutions, assayed for drug content.

RESULTS AND DISCUSSION

Development of the Matrix

The direct compression of various blends of HPMC with dried molasses and drug showed no manufacturing

TABLE I

PHYSICAL PROPERTIES OF TABLETS

Parameter	Formulations			
	A	B	C	D
Mean Weight (mg)	701.15	700.00	701.39	703.42
Standard Deviation	3.42	3.13	2.30	3.98
Mean Hardness (kp)	7.32	7.28	7.46	7.51
Mean Thickness (mm)	5.43	5.49	5.53	5.65
Friability (%)	1.02	0.85	0.63	0.54
Theophylline Assay (mg)	306.25	300.92	296.51	303.86

weight, hardness and thickness are means of twenty tablets

assays are means of two determinations

A - contains 12.50% of HPMC
B - contains 15.0% of HPMC
C - contains 20.0% of HPMC
D - contains 28.57% of HPMC

problems. Table I gives a summary of the measured physical properties of the tablets. The small variations in weight and thickness indicated a good flow characteristic. The friability values ranged from 0.54% to 1.02% which are acceptable values. The mean

mass of drug present was close to theoretical and ranged from 98.85% to 102.08%. This also indicates a uniform distribution of drug within the matrix.

Assay of Theophylline

The HPLC method for the assay of theophylline proved suitable for solid dosage forms where components of the tablet matrix could pose a problem. The method is rapid, accurate, sensitive and specific for theophylline. At a flow rate of 1.5 ml/min, and an operating pressure of 1500 psi, theophylline and BHET had retention times of 7.6 and 9.5 minutes, respectively.

Standard Curve

The relationship between the peak height ratio and concentration was linear over the concentration studied. The correlation coefficient values ranged from 0.995 to 0.997. The results also showed that the sensitivity of the assay method was similar in all the dissolution fluids and was independent of the dissolution fluid pH.

In Vitro Release Study

The incorporation of HPMC in dried molasses matrix gave a gel-layer of suitable cohesiveness and strength depending upon the concentration of HPMC. Generally,

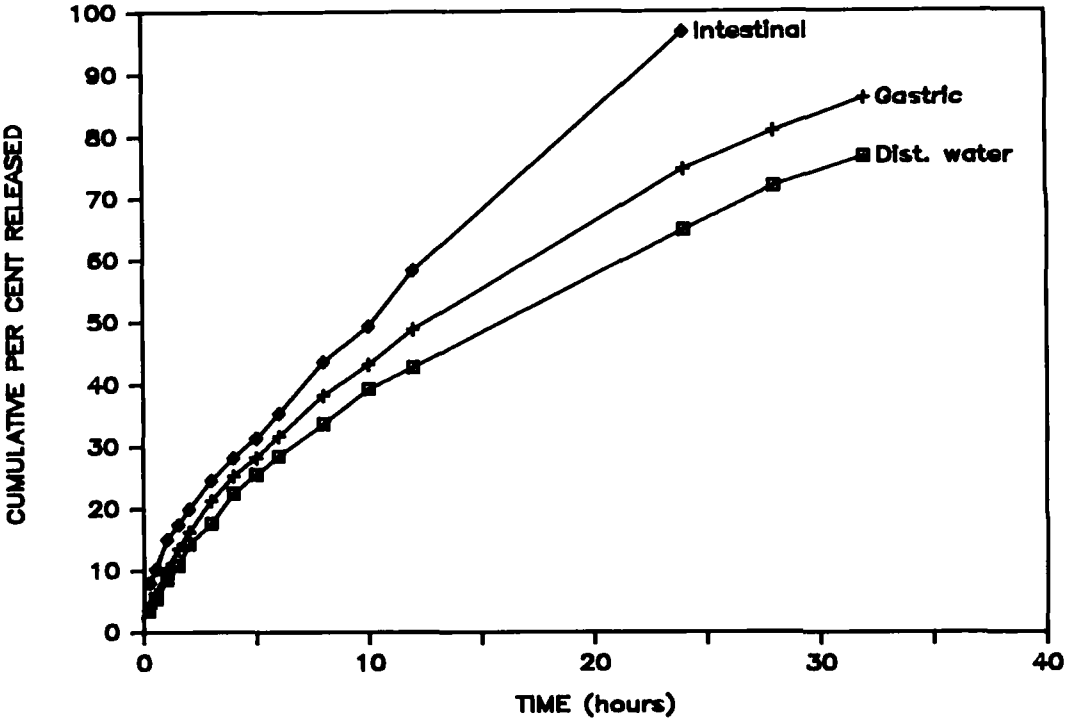

Figure 1

Release profiles of Theophylline from 20% HPMC - 80% Dried Molasses Matrix. Dissolution media were artificial intestinal fluid, artificial gastric fluid, and distilled water.

upon immersion in dissolution fluids, the tablets underwent rapid surface disintegration followed by the formation of a gel layer around the remaining matrix. A typical release profile of theophylline is shown in Figure 1. A visual inspection of the release profiles from all the formulations revealed a similar pattern. The drug release was observed to be greatest in intestinal fluid, least in distilled water, and

intermediate in gastric fluid. Overall, the duration of release ranged between 3 and 36 hours.

The following stages could be involved in the release process from this system:

1. Hydration/penetration of the matrix by the dissolution fluid
2. Gelation at the outer layer of the matrix
3. Dissolution of the drug in the gel
4. Diffusion of drug through the gel layer
5. Slow dissolution of the outermost gelled layer

Any or a combination of these could be a rate-limitating step in the process.

The diffusion of dissolution fluid through the gel is affected by the gel strength. The protective or barrier gel is in turn, controlled by the viscosity and concentration of the polymer used. Therefore, as expected, there was an inverse relationship between the HPMC concentration and the rate of release. As the level of HPMC was increased, the gel formed was firmer and more cohesive. This resulted in slower drug release.

On the other hand, an increase in the HPMC concentration would also increase the viscosity of the surrounding fluid, which would increase the gel-strength, and thus would slow the permeation rate

of both the dissolution fluid, and the drug through the gel layer.

For matrices of this type which contain insoluble or poorly soluble fillers, the effect of concentration is even more complex. For instance, if the level of insoluble filler is increased, the gel surface available for the dissolution fluid or drug permeation is decreased. Any further increase in the level of the insoluble filler would prevent the gel from both uniform hydration and/or swelling resulting in the formation of cracks in the tablet surface, and thus affecting the release characteristics. Therefore, for such matrix systems which contain insoluble ingredients, there may be an optimum level of a gel-forming substance for maximum effect. For this study, the best level of HPMC tested was 20%.

CONCLUSION

The fabrication of molasses matrix by incorporating HPMC gave a suitable matrix for controlled release study. Depending upon the concentration of HPMC, and the dissolution fluid used, duration of release ranged from 3 to 36 hours. The minimum HPMC requirement was 12.5%, while for practical purposes, the best level was 20%.

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REFERENCES

1. R.H. Blythe,. Drug Standards 26:1-7 (1958).
2. N.C. Chaudhary, and L. Saunders. J. Pharm. Pharmacol. 8:975-983 (1956).
3. S.C. Khanna and P. Speiser. J. Pharm. Sci. 58:1114-1117 (1969).
4. A. Asker, and C.H. Becker. J. Pharm. Sci. 55:90-94 (1966).
5. I.C. Robinson, and C.H. Becker. J. Pharm. Sci. 57:49-53 (1968).
6. D.R. Paul. In D.R. Paul and F.W. Harris (eds.), Controlled Release Polymeric Formulations. American Chemical Society Press. 1976. p. 1.
7. R. Langer, and J. Folkman. Nature 263:797-800 (1976).

8. S.D. Uko-Nne, and R.W. Mendes. Pharm. Tech. 6(11):104-108 (1982).

9. J.J. Orcutt, P.P. Kozak, Jr., S.A. Gillman and L.H. Cummins. Clinc. Chem. 23(3):599-601 (1977).

10. The United States Pharmacopeia XXI and National Formulary XVI. Mack Publishing Co. Easton, Pennsylvania. 1984. P. 1244.