

USE OF NATURAL GUMS IN FORMULATION OF CONTROL RELEASED THEOPHYLLINE TABLET

*CLEMMENT JACKSON, MUSILIU ADEDOKUN AND EKAETTE AKPABIO

Department of Pharmaceutics and pharmaceutical Technology, Faculty of Pharmacy, University of Uyo, Nigeria.
Email: clementjackson1@yahoo.com

Received: 29 Dec 2010, Revised and Accepted: 11 Sep 2011

ABSTRACT

Matrix tablets were prepared using blends of xanthan gum (XG) and Guar gum (GG). Theophylline was used as the model drug. Theophylline controlled release (CR) powder mixtures were prepared and evaluated for the angle of repose, bulk density, tapped density, compressibility index and hausners ratio. All the formulation showed good flow properties. The compressed tablets were evaluated for the hardness, uniformity of weight, friability, drug content and *in vitro* dissolution studies. All the formulations showed compliance with pharmacopial standards. Formulations XG₁GG₁ and XG₃GG₁ followed non-fickian transport mechanism via diffusion and erosion while XG₁GG₃ followed fickian diffusion. The results revealed that increased xanthan gum: guar gum ratio retarded and controlled the release of drug from the matrices. Xanthan gum has a higher retarding ability than guar gum. Among all the formulations XG₃GG₁ (i.e. polymer ratio3:1) showed prolong release when compare to other formulations.

Keywords: Guar gum, Xanthan gum, Matrix tablets, Theophylline.

INTRODUCTION

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within therapeutic range over prolonged periods¹. Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers². Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form and ease of scale-up and process validation³.

Theophylline is a methylxanthine derivative and it is very effective in the chronic treatment of bronchial asthma and bronchospastic reaction. Its therapeutic concentration range is narrow from 10 to 20 g/ml while toxicity usually appears at concentration above 20 g/ml⁴. Since theophylline has narrow therapeutic index, it can be used as a controlled release product to protect asthma patients from frequent attacks and to prevent toxic side effects⁵.

Developing oral controlled-release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentrations when administered orally.⁶

Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Guar gum is a natural nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae). In pharmaceuticals, Guar gum is used in solid dosage forms as a binder and disintegrant.⁷ Xanthan gum is another natural, biosynthetic, edible gum and an extracellular polysaccharide produced by the bacterium *Xanthomonas campestris*. Xanthan gum consists of

glucose, mannose, and glucuronic acid⁸ and is used in different foods as thickener and stabilizer.⁹

The objective of this study was to develop matrix controlled-release tablets of theophylline using natural gums (xanthan and guar gum) as suitable hydrophilic matrix systems to deliver the drug continuously with set limits of dissolution profile.

MATERIALS AND METHODS

Theophylline, Guar gum and xanthan gum were all purchased from Sigma Aldrich, USA. Lactose monohydrate and magnesium stearate were procured from BDH, England. All other chemicals used were of analytical grade.

Preparation of controlled release matrix tablets

The polymers (Guar gum, Xanthan gum) were included in the formulation in various combination ratios 1:1 (XG₁GG₁), 1:3 (XG₁GG₃) and 3:1 (XG₃GG₁). The drug was geometrically blended with sufficient quantity of lactose and the various polymers as stated in the formulae in Table 1, using pestle and mortar. Mixing was maintained for 10 minutes and the powder mixtures stored in well-closed specimen bottles.

Direct compression method was used. Before each compression, the die (12 mm in diameter) and flat faced punches were lubricated with a 1 % w/v dispersion of magnesium stearate in chloroform. Compression was achieved using a single punch tableting machine (THP Shanghai, Tianxiang and Chentai Pharmaceutical Machinery Co.Ltd. China) fitted with flat-faced punches and compressed to a target weight of 500 ± 10 mg. Each drug compacts were stored in airtight specimen bottles and allowed to equilibrate 24 hours before further evaluations.

Table 1: Composition of Theophylline CR matrix tablets

Ingredient	XG ₁ GG ₁	XG ₁ GG ₃	XG ₃ GG ₁
Drug (mg)	100	100	100
X.G (mg)	100	50	150
G.G (mg)	100	150	50
Lactose (mg)	200	200	200

Key: XG = Xanthan gum, GG = Guar gum

Evaluation of powder mixtures

The powder mixtures were evaluated for angle of repose^{10,11}, bulk density¹², tapped density¹², compressibility index and hausner ratio¹³ for micromeritic properties.

Evaluation of tablets

The formulated tablets were evaluated for thickness and diameter (using a vernier caliper), hardness test (using Monsanto hardness tester)¹⁴ and friability (using Roche friabilator)¹⁵. For weight

variation test¹⁶, 20 tablets of each formulation were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation. The results were expressed in table-3. For content uniformity test¹⁷, ten tablets were powdered in a mortar. The powder equivalent to 100mg of theophylline was weighed and transferred to 100ml volumetric flask. It was dissolved in pH 7.4. From this appropriate dilution were made and the absorbance was analyzed at 277nm using UV spectrophotometer.

In-vitro release studies

Drug release studies were carried out using USP dissolution rate apparatus (Apparatus 1, 100rpm, 37°C) for the first 2h in pH 1.2 simulated gastric fluids (SGF) without enzymes (500ml). Then the dissolution medium was changed to pH 7.4 simulated intestinal fluid (SIF) without enzymes (500ml) and tested for drug release for the remaining 6h. 5ml aliquots of the dissolution medium were withdrawn at hourly intervals up to at least 8h. The withdrawn amount was replaced with an equal volume of fresh dissolution medium kept at 37°C. The withdrawn samples were suitably diluted with pH 7.4 and analyzed at 277nm using pH 7.4 as blank in a Shimadzu UV Spectrophotometer (Shimadzu, Japan). For each dissolution profile, the release data was analyzed after three repeats.

Drug release kinetics

To analyze the mechanism of drug release rate kinetics, the results of invitro release profile were plotted in various kinetic models like zero order, first order, Higuchi model and korsmeyer – peppas¹⁸.

Results and Discussion

The powder mixtures of all the formulations were evaluated for angle of repose, bulk density, tapped density, and compressibility index and hausner ratio. The angle of repose was found to be 33 – 34°. It indicates that powder mixtures have a good flow property. The bulk density and tapped density was found to be in the range of 0.395- 0.415 gm/cc and 0.435 - 0.462 gm/cc respectively. The compressibility and hausner ratio was found to be 8.2 to 13.42 and 1.10 to 1.16 indicating good flow character of the powder mixtures (table-2). All the results are within the prescribed limits¹⁴.

The hardness of the tablets for all the formulations was in the range of 5-7 kg/cm². The uniformity weight of 20 tablets of all the formulations was within 5% deviation. The friability of all the formulation was less than 1%. Drug content of all the formulations were found to be in the range of 96 to 99 % (table-3). All the results are within the prescribed limits¹⁴.

Table 2: Evaluation of theophylline controlled release matrix powder mix

Parameters	Formulation		
	XG ₁ GG ₁	XG ₁ GG ₃	XG ₃ GG ₁
Angle of repose (0)	33°± 0.65	34°± 0.70	33°± 0.59
Bulk density (gm/cc)	0.415 ±0.01	0.395± 0.01	0.400± 0.01
Tapped density (gm/cc)	0.452 0.01±	0.435± 0.01	0.462± 0.01
Compressibility	8.2± 1.74	9.2± 1.66	13.42± 1.27
Hausner ratio	1.10± 0.04	1.10± 0.02	1.16± 0.02

Table 3: Evaluation of Theophylline controlled release matrix tablets

Parameters	Formulation		
	XG ₁ GG ₁	XG ₁ GG ₃	XG ₃ GG ₁
Hardness (kg/cm ²)	5.01± 0.23	5.03± 0.18	5.95± 0.12
Uniformity Weight (mg)	499± 6.2	501.6± 5.5	500.2± 3.9
Fraibility	0.25± 0.05	0.23± 0.07	0.30± 0.09
Drug content (%)	96.7± 0.20	97.5± 1.40	97.8± 1.35
Thickness (mm)	4.1± 0.01	4.2± 0.03	4.1± 0.04
Diameter (mm)	12.6± 0.00	12.5± 0.02	12.6± 0.03

* All values are expressed as mean ± SD, n=5

The results of the *invitro* release study for all the formulations are shown in figure-1.

At the end of 8th hours the cumulative percentage drug release for the formulations XG₁GG₁, XG₁GG₃ and XG₃GG₁ were found to be 95, 98 and 60 respectively. Among the three formulations, XG₃GG₁ showed prolonged drug release. The controlled drug release may also be due to increased proportion of polymer¹⁹.

The release rate kinetic data for all formulations is shown in table-4. When the data were plotted according to zero order, the formulations showed a high linearity with regression co-efficient values (R²) between 0.9523 – 0.9942. It showed that the drug release followed zero order¹⁹. Diffusion is related to transport of drug from the matrix tablets into the dissolution medium and is concentration dependent. This is explained by

Higuchi's equation. When the data were plotted according to Higuchi's equations, the regression co-efficient values (R²) were between 0.896 – 0.9940.

By using korsmeyer model, the mechanism of drug release was determined. If n < 0.45, it is fickian diffusion and if n= 0.45 – 0.89, it is non-fickian diffusion transport²⁰. The results of all the formulations showed that the n values for XG₁GG₁, XG₁GG₃ and XG₃GG₁ were 0.50, 0.39 and 0.64 respectively. It proved that formulations XG₁GG₁ and XG₃GG₁ followed non-fickian transport mechanism²⁰ both diffusion and erosion²¹ while XG₁GG₃ followed fickian diffusion.

The results revealed that increased xanthan gum: guar gum ratio retarded and controlled the release of drug from the matrices. Xanthan gum has a higher retarding ability than guar gum.

Table 3: Maximum cumulative release of SAG-formulated Metronidazole tablets

Batch	T ₅₀ (hrs)	T ₇₀ (hrs)	C _{max} (%)
XG ₁ GG ₁	2.5	4.3	95.00
XG ₁ GG ₃	1.3	4.0	98.00
XG ₃ GG ₁	6.7	-	60.00

Table 4: Kinetics and mechanism of release for formulated theophylline matrix tablets

formulation,	Zero - order	First - order	Higuchi	Korsmeyer(n)
XG ₁ GG ₁	0.9866	0.9338	0.994	0.9884 (0.50)
XG ₁ GG ₃	0.9942	0.8699	0.988	0.9755 (0.39)
XG ₃ GG ₁	0.9523	0.9033	0.896	0.9270 (0.64)

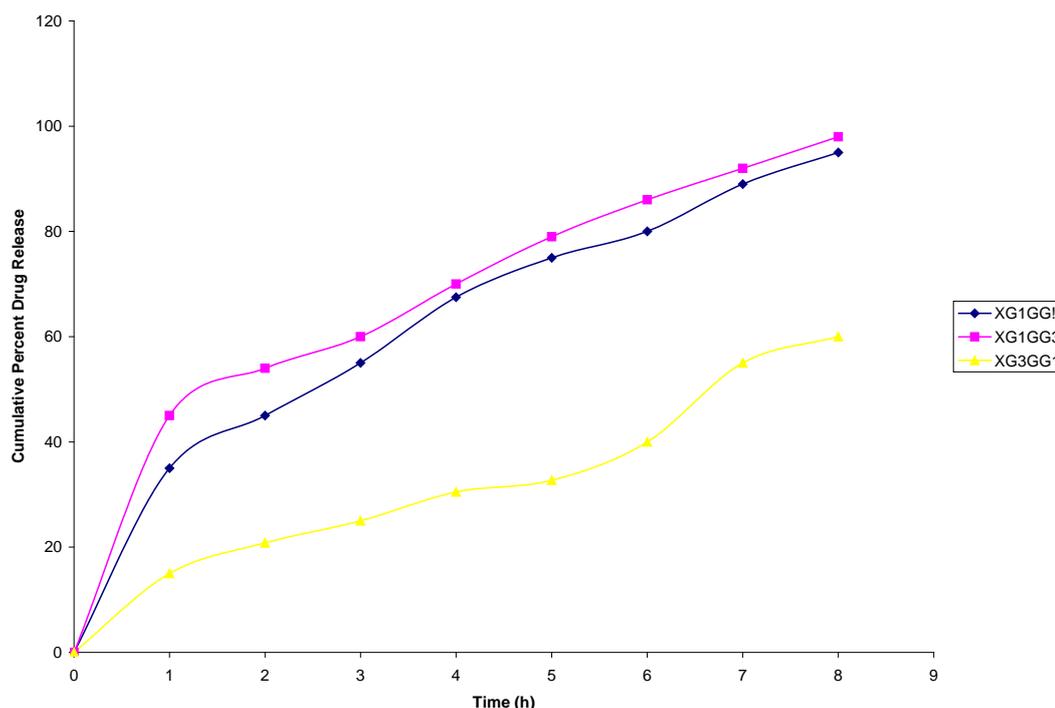


Fig. 1: Release profile of Theophylline tablet batches containing Guar Gum and Xanthan Gum

CONCLUSION

Polymers are frequently used in drug delivery systems. By polymer combinations, formulators may be able to develop sustained release drug dosage forms with better performance than is shown by the individual polymer combinations. Various polymers blends have been studied in order to achieve their desired release kinetics²². The presence of more than one polymer may result in spatial configuration, but it is also possible that a polymer additive may become part of a gel network²³

Matrix tablets were prepared using blends of Xanthan gum (XG) and Guar gum (GG). Theophylline was used as model drug. The ability of the prepared matrices to control drug release in the gastrointestinal tract (GIT) was evaluated. For this, drug release studies were carried out. The overall rate of release of drug was higher with increased guar gum concentration. These results indicate that Xanthan gum has higher drug retarding ability than Guar gum. Optimum release was observed with formulation (XG₃GG₁)

Results of the present study confirmed that the polymer ratio plays a major role in drug release.

ACKNOWLEDGEMENT

The authors are very much thankful to the members of Staff of God's Glory Computers Institute, Uyo, Nigeria.

REFERENCES

- Pandit JK, Singh S and Muthu MS. Controlled release formulation in neurology practice. Annual of Ind Academy of Neurology .2006; 207 – 216.
- Yeole PG, Galgatte, Babla IB and Nkhat D. Design and evaluation of xanthan gum – based sustained release matrix tablets of diclofenac sodium. Ind J Pharm Sci 2006; 68: 185-189.
- Manthena VS Varma, Aditya M. Kaushal, Alka Garg and Sanjay Garg. Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am J Drug Deliv 2004; 2:43-57.
- Evelyn Ojoe, Edna Mitie Miyachi, Telma Mary Kaneko, Maria Valéria Rolbes Velasco and Vladi Olga Consiglieri. Influence of cellulose polymers type on in vitro controlled release tablets containing theophylline. Brazilian J Pharm Sci 2007; 43: 571-579.
- Prafulla Kumar Nandi. Invitro evaluation of theophylline – SR tablets. The Eastern Pharmacist oct-1997; 149-150
- Krishnaiah YSR, Karthikeyan RS, Satyanarayana V. A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. Int J Pharm. 2002;241:353-366.
- Krishnaiah YS, Karthikeyan RS, Gouri Sankar V, Satyanarayana V. Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride. J Control Release. 2002; 81:45-56.

8. Pai VB, Khan SA. Gelation and rheology of xanthan/enzyme-modified guar blends. *Carbohydrate Polym.* 2002;49:207-216.
9. Castro IA, Tirapegui J, Benedicto ML. Effects of diet supplementation with 3 soluble polysaccharides on serum lipid levels of hypercholesterolemic rats. *Food Chem.* 2003;80:323-330.
10. Carr RL. Evaluating flow properties of solids. *Chem Eng* 1965; 72: 163 – 168.
11. Cooper J and Gunn C. Powder flow and compaction. In: Carter S.J, Tutorial Pharmacy, CBS publishers, New Delhi, 1986; 211 – 233.
12. Shah D, Shah Y and Rampradhan M. Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross – linked polyvinyl alcohol. *Drug Dev Ind Pharm* 1977; 23: 567 – 574.
13. United States of Pharmacopeia-National Formulary. USP 30 – NF 25. The United States Pharmacopeial Convention, Rockville, MD, 2007, Vol. 1, 226.
14. Rippe E. Compression of solid and compressed dosage forms. In: Encyclopedia of pharmaceutical technology, Swarbrick, J.Marcel Dekker. Inc., New York, 1990; 149-166.
15. Pharmacopoeia of India. Ministry of health and family welfare. Govt. of India, Controller of publications, New Delhi, 1996; vol.II., 736; A-80-83, 147 and 169.
16. Leon Lachman, Herhert A, Liberman and Joseph L Karnig. The theory and practice of industrial pharmacy. 3rd ed. Lea and Febigen, Philadelphia, 1986; 430-456.
17. Pharmacopoeia of India. Ministry of health and family welfare. Govt. of India, Controller of publications, New Delhi, 2007; vol.II, 1795.
18. Hamid A. Merchant, Harris M. Shoaib, Jaweria Tazeen and Rabia I. Yousuf. Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxy propyl methylcellulose: A technical note. *AAPS PharmSciTech* 2006; 7: E1 – E6.
19. Sundaramoorthy K, Kavimani S, Vetrichelvam T, Manna PK and Venkappayya D. Formulation and evaluation of extended release dosage form of metformin hydrochloride using combined hydrophobic and hydrophilic matrix tablets. *Ind J Pharm Edu Res* 2008; 42: 232-242.
20. Schwarz BJ, Simonelli AP and Higuchi WI. Drug release from wax matrix analysis of data of order of kinetic release and diffusion controlled model. *J Pharm Sci* 1998; 57: 274-277.
21. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm* 1983; 15: 25-35.
22. Emeje MO. Effect of Molecular size and some Hydrophobic polymers on the sustained release performance of a gel forming polymer:M.Pharm Dissertation, University of Nigeria, Nsukka. 2005
23. Merchant, H. A ; Shoiab H. M ; Tazeen J ; and Yousuf R. I. A once daily Tablet formulation and *in vitro* release evaluation of cefpodoxime using Hydroxypropylmethylcellulose: a technical note: *AAPS Pharm. SciTech* 2006; 7 (3) article 78.