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Evaluation of Gellan Gum as a Mini-Matrix for Sustained Release of Ephedrine Hydrochloride Granules

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Abstract: Gellan gum was evaluated for its swelling capacity and sustained release properties in varying pH media; 0.1 N hydrochloric acid (pH 1.2), simulated gastric juice (pH 1.5) and simulated intestinal fluid (pH 7.5). Granules were prepared by the conventional wet granulation method of massing and screening. Results obtained showed that the time for 50 ($t_{50\%}$) and 70% drug release ($t_{70\%}$) were higher for gellan gum than sodium carboxymethylcellulose. *In vitro* sustained release of ephedrine hydrochloride from granules in hard gelatin capsules was achieved over eight hours in all dissolution media. The matrix forming capacity of the polymer was concentration dependent and comparable to that of sodium carboxymethylcellulose. Maximum sustaining effect of gellan gum was achieved in the acidic media. The release kinetics of ephedrine hydrochloride from granules containing gellan gum was generally a mixture of first order and fickian diffusion. Gellan gum is suitable for the sustained-release formulation of ephedrine granules without the additional step of tablet formation.

Key words: Gellan gum, swelling kinetics, ephedrine hydrochloride, sustained release

INTRODUCTION

The fluctuating drug concentrations in blood and tissue caused by conventional dosage forms may lead to an insufficient drug concentration in blood and thus excessive use of drug may be required. Various oral dosage forms able to control the rate of drug delivery into the systemic circulation have been prepared and studied in this regard (Emeje *et al*., 2006). Inspite of recent technological advances in the fabrication of oral controlled-release dosage forms, particular attention has been paid to the regulation of the drug release rate by means of monolithic devices, whereby prior dispersion of the drug in a polymer matrix is carried out (Emeje *et al*., 2006). Gellan gum is an anionic extracellular polymer produced through the fermentation of glucose in the presence of trace elements, under controlled conditions by the bacterium *Sphingomonas elodea* (Rath and Schmidt, 2001). X-ray diffraction analysis shows that gellan gum exists as a half staggered, parallel, double helix which is stabilized by hydrogen bonds involving the hydroxymethyl groups of one chain and both carboxylate and glyceryl groups of the other (Fukada *et al*., 2002). Gellan gum has been useful in the food industry as a stabilizing agent and most of it is pharmaceutical application has been as an *in situ* gel in sustained release ophthalmics (Shrikant and Pandit, 2003; Ramaiah *et al*., 2007).

One of the major challenges in designing oral controlled-release drug delivery system is to retain the dosage form in the vicinity of the absorption site for the lifetime of drug delivery. Several

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approaches have recently been developed to extend gastrointestinal transit time. The hydrodynamically balanced gastrointestinal drug delivery system, in either capsule or tablet form, is designed to prolong the GI residence time in an area of the GI tract to minimize the amount of drug reaching its absorption site in the solution state and hence, ready for absorption. It is prepared by incorporating a high level (20-75% w/w) of one or more gel forming hydrocolloids such as hydroxyethyl cellulose, hydroxypropylmethyl cellulose and sodium-carboxymethyl cellulose into the formulation and then compressing these granules into tablets or encapsulating into capsules (Shrikant and Pandit, 2003; Emeje *et al*., 2005). Formulation of these devices must comply with several criteria such as possessing sufficient structure to form a cohesive gel barrier, maintaining an overall specific gravity lower than that of the gastric contents (1.004-1.010) and potentiality of dissolving slowly enough to serve as drug reservoir. When a hydrophilic polymers hydrate, it swells to form gel through which water-soluble drugs diffuse. The process of water transport into hydrophilic polymer matrices and the corresponding dimensional changes that occur in the form of volume increase as characterized by polymer swelling kinetics have a major influence on the profile of drug release from the matrices (Emeje *et al*., 2005; Roberts *et al*., 2007). It has been a challenge trying to retard the release of highly water-soluble drugs from hydrophilic matrices. In a recent study, Skinner *et al*. (2001) used Natrosol 250 (HEC), a hydrophilic polymer to sustain the release a highly water soluble drug for over 8 h.

The objective of the present study was to study the diffusion behavior of Ephedrine hydrochloride in the hydrated gels of gellan gum in order to predict the kinetics of drug release from controlled release capsules and thereby explain their ability to retard the release of drug. Indeed, diffusion of the drug through the swollen gelatinous polymer-drug-excipient mass is one of the most important determinant factor when a hydrophilic polymer is used as a drug carrier for the controlled release drug delivery formulation (Skinner *et al*., 2001; Emeje *et al*., 2006; Roberts *et al*., 2007).

MATERIALS AND METHODS

Materials

Materials used include: Gellan gum (Kelco USA), Maize starch, Lactose, Ephedrine hydrochloride (BDH Ltd., poole, England), Magnesium stearate (Amend Drugs and Chemicals, Irvington, New Jersey, USA), sodium carboxymethylcellulose (Aqualon USA). All other chemicals used were of analytical grade.

Methods

Preparation of Ephedrine Hydrochloride Granules

Five batches of ephedrine hydrochloride granules were prepared by wet granulation method, using either gellan gum or sodium carboxymethylcellulose at concentrations of 20 and 30% w/w. The wet mass was screened through a 1.7 mm sieve, dried at 60°C for 3 h in a hot air oven (Salvis, Switzerland). The dried granules were rescreened through the same sieve to break the agglomerates. Two fifty milligram of granules of each batch were weighed accurately and filled in a capsule shell of size 1. The filled capsules were kept in airtight containers and kept in a dessicator. The composition of each capsule is shown in Table 1.

Moisture Sorption Profile Ephedrine Hydrochloride Granules

One gram sample from each batch was accurately weighed out into a foiled dish, placed in desiccators at 85 and 100% RH over a period of forty days. The weight gained by the exposed samples was recorded and the amount of water sopped was calculated from the weight difference. The average moisture per day was evaluated and the percentage moisture content calculated. A plot of percentage moisture content versus relative humidity was used to evaluate the stability of ephedrine hydrochloride granules to moisture at different polymer matrix concentrations.

Table 1: Composition of matrix capsules containing ephedrine HCl granules

Parameters	Control	Gellan gum 20%	Gellan gum 30%	Sodium CMC 20%	Sodium CMC 30%
Ephedrine HCl (mg)	60.0	60.0	60.0	60.0	60.0
Gellan gum (mg)	-	50.0	75.0	-	-
NaCMC (mg)	-	-	-	50.0	75.0
Mg stearate (mg)	2.5	2.5	2.5	2.5	2.5
Lactose qs	250.0	250.0	250.0	250.0	250.0

Na CMC: Sodium carboxymethylcellulose; CMC: Carboxymethylcellulose

Weight Uniformity Test

Twenty capsules randomly selected from each batch of ephedrine hydrochloride were weighed individually and collectively using analytical balance. Mean weight, standard deviation and coefficient of weight variations were calculated according to the BP (1995) uniformity of weight method.

Dissolution Profile

The dissolution profile of each batch of ephedrine hydrochloride capsule was studied in triplicate using the USP basket method and 1000 mL of 0.1 N hydrochloric acid maintained at 37±1°C at a speed of 100±1 rpm. The dissolution sample (5 mL) was withdrawn at 30 min interval, replaced with an equal volume of fresh dissolution medium. The concentration of the drug was determined spectrophotometrically using Ultraspec III UV/visible spectrophotometer (Pharmacia LKB Model) at a wavelength of 257 nm.

Effect of pH on the Release of Ephedrine Hydrochloride from Capsules

The effect of pH on the release of ephedrine hydrochloride from granules prepared with 30% w/w gellan gum at three pH levels were investigated in 1000 mL of 0.1 N hydrochloric acid (0.1 N HCl), Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) without enzymes (USP, 1995) having pH values of 1.2, 1.5 and 7.5, respectively. Samples were withdrawn and analyzed spectrophotometrically at various wavelengths, 277, 235 and 230 nm corresponding to λ max of the drug in 0.1 N HCl, SGF and SIF, respectively.

Analysis of Drug Release Data

Data generated from drug release were subjected to two common release models (First order release equation and Korsenmeyer equations, (Eq. 1 and 2) in order to establish the drug release kinetics and hence drug release mechanisms. The criterion for selecting the most appropriate mode was based on the best line of fit (USP, 1995; Ofoefule, 2002).

$$\ln (a- x) = \text{In } a - k\, t \quad (1)$$

$$Mt/M\alpha = k.\, t^{n} \quad (2)$$

Where,

$Mt/M\alpha$ is fractional release; n, diffusion coefficient; K, is dissolution rate constant; a - x, amount of drug after time t, a, matrix-drug load.

Statistical Analysis

The data obtained were analyzed using Microsoft Excel software (SSPS) which included mean, standard deviation, variances and ANOVA (F-test) at $p<0.05$ level of significance.

RESULTS AND DISCUSSION

Moisture Sorption Profile of Ephedrine Hydrochloride Granules

The moisture sorption profile of the granules show a concentration dependent increase in moisture uptake. Moisture sorption was also found to increase with increase in RH. At 20% w/w, gellan gum absorbed less moisture than Na CMC, while at 30% use level, the reverse was the case, suggesting that gellan gum at lower concentrations (20%) is more stable than at higher concentration (30%) w/w. Gellan gum, stored at low relative humidity will maximize stability.

In vitro Release Studies

In vitro sustained release of all batches of ephedrine hydrochloride capsules studied was achieved over eight hours in all dissolution media and the matrix capacity of the gum was concentration dependent as increase in the concentration of gellan gum from 20 to 30% w/w led to an enhanced retardation of drug release (Table 2). Most commonly, the results of dissolution tests are expressed in terms of the time required to release some percentage of labeled amount of the drug from the dosage form. This approach is reported to be particularly useful for quality control purposes once the dissolution characteristic of a drug and dosage form is understood (Ofoefule, 2002b). The dissolution of ephedrine hydrochloride from the capsules was evaluated using the above concept. The time taken for 50 and 70% of the drug to be released (t_{50} and $t_{70\%}$, respectively) was adopted to characterize the release of the drug from the capsules. These parameters which are shown in Table 3 indicate fastest dissolution of the drug from capsules containing 0% gum (control) followed by those containing 20% w/w Na CMC. The drug release was in the order: control > 30% Na CMC > 20% Na CMC > 20% gellan gum > 30% gellan gum. The dissolution results show that the polymer content affected drug release in a manner that was related to its concentration. The results also show that release from capsules containing 30% gellan gum was highly retarded (Fig. 1 and 2). This is consistent with the report of (Ofoefule and Chukwu, 1994). Some earlier studies (James *et al*., 1997; El-Gazayerly, 2003; Sinha *et al*., 2005) showed varying effects of concentration on drug release. In one of the studies

Table 2: Linear regression of ephedrine HCl release using korsenmeyer and first order kinetic equations

	Drug release mechanism			
	Kosenmayers		First order kinetics	
Matrix conc.	n	K	n	K
Control in 0.1 N HCl	0.246	0.196	46.238	0.0096
20% Gellan in 0.1 N HCl	0.394	0.070	82.528	0.0078
30% Gellan in 0.1 N HCl	0.412	0.052	70.226	0.0048
20% SCMC in 0.1 N HCl	0.378	0.079	62.173	0.0053
30% SCMC in 0.1 N HCl	0.293	0.139	50.304	0.0051
30% Gellan in SIF	0.211	0.218	59.470	0.0062
30% Gellan in SGF	0.378	0.079	67.499	0.0059

SGF and SIF: Simulated gastric and intestinal fluids, respectively; n: Release, exponent; k: Dissociation constant; a: Amount of drug

Table 3: Dissolution parameters of ephedrine hydrochloride in 0.1 N HCl

Binder conc. (%)	$T_{50\%}$ (min)	$T_{70\%}$ (min)
Control	70	115
Gellan gum 20%	170	285
Gellan gum 30%	270	360
Sodium CMC 20%	140	273
Sodium CMC 30%	110	245

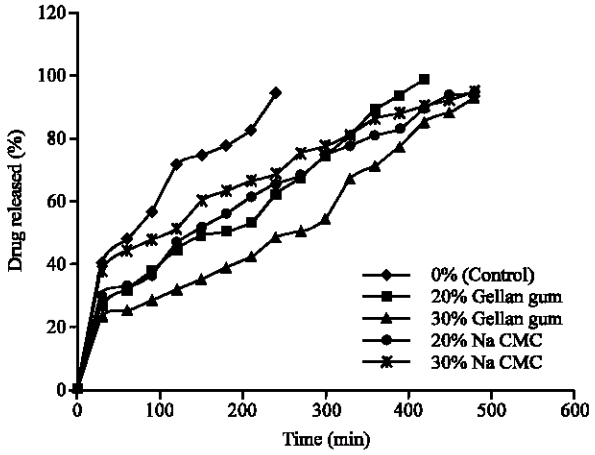

Fig. 1: Dissolution profile of ephedrine HCl in 0.1 N HCl

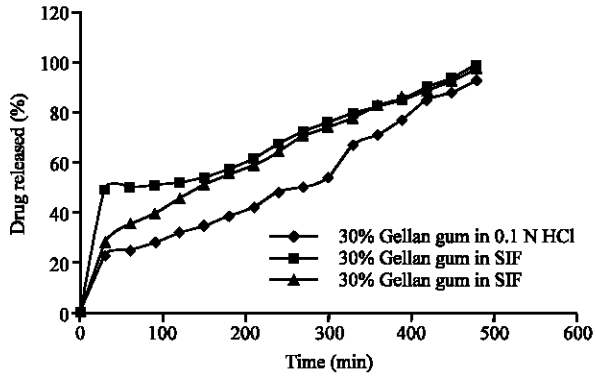

Fig. 2: Dissolution profile of ephedrine HCl in the three dissolution media (0.1 N HCl, SGF and SIF)

(El-Gazayerly, 2003), Pentoxifylline-controlled release tablets were prepared using xanthan gum. The effects of p olymer concentration, rotation speed, ionic strength and pH of the dissolution medium on the release of the water-soluble pentoxifylline were studied. The release rate decreased with increasing polymer concentration in the tablet, which was reflected in the increase in the mean dissolution time. The initial decrease in drug release rate on increasing the concentration of xanthan gum was explained on the basis that a higher binder concentration led to an increase in hardness of the tablet, while the porosity and capillary pore sizes were reduced. This in-turn reduced the wicking of water into the tablet and consequently the swelling and drug release rates are slowed. In the other study, the effect of different concentrations of Eudragit RLPO or RSPO (10, 20, 30 and 40% wt./wt. of drug) on release rate of AZT was studied. The authors reported that drug release was slower from tablets containing Eudragit RLPO or RSPO as compared with that from conventional tablets. They also observed that, No significant difference in release rate was observed between tablets containing either 10 or 20% of Eudragit RLPO or RSPO. However drug release decreased significantly when 30% of either Eudragit preparation was used individually in tablet formulation. Further increase in concentration of Eudragits did not significantly affect the release rate. Drug diffusion in a hydrated matrix involves the transport of a drug molecule through swollen polymer gel across a porous membrane of capsules shell into a bulk medium where perfect sink conditions prevail. Subsequently,

Table 4: Effect of pH on dissolution parameters of ephedrine hydrochloride

Dissolution media	$T_{50\%}$ (min)	$T_{70\%}$ (min)
SIF	60	255
SGF	142	265
0.1 N HCl	270	355

SGF and SIF: simulated gastric and intestinal fluids, respectively

drug diffusion rate means the rate of transfer of a drug from swollen gel into an external medium. The diffusion of ephedrine HCl through the hydrated matrix gel was affected by the concentration of the polymers, with gellan gum having a more pronounced effect than Na CMC at equivalent concentrations. This suggests that, gellan gum made a stronger barrier by forming a thicker layer of gel throughout the active materials. Consequently, erosion of matrix gel was inhibited and drug release was delayed.

Effect of pH on Release of Ephedrine Hydrochloride from Gellan Gum Mini-Matrix

Although sustained release of ephedrine hydrochloride was achieved with gellan gum in the different dissolution media, a distinct pH dependency of drug release was observed (Table 4). Drug release from capsules containing 30% w/w gellan gum as shown by the t_{50} and t_{70} values (Table 3) suggest that gellan gum was more effective in sustaining drug release than Na CMC. The results also show that at the acidic pH of 1.2 (0.1 N HCl), the retardant effect of gellan gum was more pronounced than at the SGF and SIF. The order of increase in retardation was 0.1 N HCl > SGF > SIF. This difference could be attributed to the differential solubility of gellan gum at these pH.

Drug Release Mechanism

The curvilinear nature of the cumulative percentage drug release versus timeplots above suggests that none of the products followed zero order release kinetics. The dissolution data from all the batches were fitted into first order equation and the linear relationship observed indicated that the drug release was matrix-drug load dependent, this observation is consistent with that of Wu *et al*. (2002), where *in vitro* and *in vivo* release of potassium chloride from polyglycolyd glycerides matrices was explained to be dependent on matrix-drug load. It also showed that similar release kinetics existed at different pH levels.

Based on Korsenmeyer model (Korsenmeyer *et al*., 1983), drug release data from different batches followed Fickian diffusion at all pH levels ($n \leq 0.5$, Table 4) implying that the main release mechanism through the swollen aggregated mini matrices is diffusion. The dissociation constant of the formulations shows that, the capsules containing 30% w/w gellan gum had the least values from both kinetic models (Table 4). This implies that capsules containing 30% gellan gum is more effective in controlling the release of ephedrine HCl than Na CMC at the same concentration. This corroborates the drug release study. On the whole, release of drug from all the batches is observed to be a combination of first order and fickian diffusion.

CONCLUSIONS

It may be concluded from the present study that slow and controlled release of ephedrine HCl from gellan gum over a period of 8 h was obtained from matrix capsules formulated using 20-30% w/w polymer concentration. It was observed that ephedrine HCl followed both first order and fickian release mechanisms. Drug release was slower in acidic than alkaline pH, the rate and extent of which depends on the concentration of the polymer. On the whole, Gellan gum was found to be more effective than Na CMC in modulating drug release, it is therefore a promising sustained release matrix former for a water-soluble drug such as ephedrine hydrochloride.

REFERENCES

British Pharmacopoeia, 1995. Her Majesty's Stationary Office Press, London.

El-Gazayerly, O.N., 2003. Release of pentoxifylline from xanthan gum matrix tablets. Drug Dev. Ind. Pharmacy, 29: 241-246.

Emeje, M.O., O.O. Kunle and S.I. Ofoefule, 2005. The effect of molecular size of CMC on the rates of hydration, matrix erosion and drug release from its matrix. Drug Delivery Tech., 3: 56-61.

Emeje, M.O., O.O. Kunle and S.I. Ofoefule, 2006. Effect of the molecular size of carboxymethylcellulose and some polymers on the sustained release of theophylline from a hydrophilic matrix. Acta Pharm., 56: 325-335.

Fukada, H., A. Takahashi, S. Kitamura, Y. Yuguchi, H. Urakawa and K. Kajiwara, 2002. Thermodynamics and structural aspect of the gelling process in the gellan gum/metal salt aqueous solutions. J. Thermal Anal. Calorimetry, 70: 797-806.

Korsenmeyer, R.W., R. Gurny, E.M. Doelker, P. Buri and N.A. Peppas, 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm., 15: 25-35.

James, E., G. Singh, L. Larny and P. Vinod, 1997. Method to compare the dissolution profile and a rational for wide dissolution specification for metoprolol tartrate tablets. J. Pharm. Sci., 86: 690-700.

Ofoefule, S.I. and A. Chukwu, 1994. The binding properties of *Treculia africana* gum in sodium salicylate tablets. STP Pharm. Sci., 4: 394-398.

Ofoefule, S.I., 2002a. A Textbook of Pharmaceutical Technology and Industrial Pharmacy. Samakin Nigeria Ent. Lagos.

Ofoefule, S.I., 2002b. Tablet Dosage Forms III. Pharmacopoeial Tests. In: A Textbook of Pharmaceutical Technology and Industrial Pharmacy, Vol 1. Ofoefule, S.I. (Ed.), Samakin Nig. Ent., pp: 58-63.

Ramaiah, S., T.M. Pramodkuma and V. Ravi, 2007. Studies on biopolymers for ophthalmic drug delivery. J. Macromol. Sci. Part A., 44: 229-234.

Rath, P. and D. Schmidt, 2001. Gellan gum as a suitable gelling agent in microbiological media for PCR applications. J. Med. Microbiol., 50: 108-109.

Roberts, M., M. Cespi, J.L. Ford, A. Dyas, J. Downing, L.G. Martini and P.J. Crowley, 2007. Influence of ethanol on aspirin release from hypromellose matrices. Int. J. Pharm., 332: 31-37.

Shrikant, J.B. and J.K. Pandit, 2003. *In vitro* and *in vivo* evaluation of the Gelrite gellan gum-based ocular delivery system for indomethacin. Acta, 53: 251-261.

Sinha, V.R., B.R. Mittalb and R. Kumria, 2005. *In vivo* evaluation of time and site of disintegration of polysaccharide tablet prepared for colon-specific drug delivery. Int. J. Pharm., 289: 79-85.

Skinner, G.W., W.W. Harcum and T. Diirig, 2001. Versatility of Natrosol® hydroxyethyl cellulose in controlled release matrix. System-Pharmaceut. Tech. Report. Hercules, PTR 017.

United States Pharmacopoeia, 1995. XXIII Edn., The USP Convention Inc., Roackville, MD, pp: 1790-1794.

Wu, P.C., M.J. Tsai, Y.B. Huang, J.S. Chang and H.Y. Tsai, 2002. *In vitro* and *in vivo* evaluation of potassium chloride formulation prepared with standard polyglycolyd glycerides matrices. Int. J. Pharm., 243: 119-124.