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Research Article

Rheological Characterization and Drug Release Studies of Gum Exudates of *Terminalia catappa* Linn

Sadhis V. Kumar,[1] Dinakar Sasmal,[1,3] and Subodh C. Pal[2]

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Abstract. The present study was undertaken to evaluate the gum exudates of *Terminalia catappa* Linn. (TC gum) as a release retarding excipient in oral controlled drug delivery system. The rheological properties of TC gum were studied and different formulation techniques were used to evaluate the comparative drug release characteristics. The viscosity was found to be dependent on concentration and pH. Temperature up to 60°C did not show significant effect on viscosity. The rheological kinetics evaluated by power law, revealed the shear thinning behavior of the TC gum dispersion in water. Matrix tablets of TC gum were prepared with the model drug dextromethorphan hydrobromide (DH) by direct compression, wet granulation and solid dispersion techniques. The dissolution profiles of the matrix tablets were compared with the pure drug containing capsules using the USP Basket apparatus with 500 ml phosphate buffer of pH 6.8 as a dissolution medium. The drug release from the compressed tablets containing TC gum was comparatively sustained than pure drug containing capsules. Even though all the formulation techniques showed reduction of dissolution rate, aqueous wet granulation showed the maximum sustained release of more than 8 h. The release kinetics estimated by the power law revealed that the drug release mechanism involved in the dextromethorphan matrix is anomalous transport as indicated by the release exponent *n* values. Thus the study confirmed that the TC gum might be used in the controlled drug delivery system as a release-retarding polymer.

KEY WORDS: controlled release; dextromethorphan hydrobromide; gum exudates of *Terminalia catappa*; viscosity.

INTRODUCTION

Natural polymeric materials have been used in the pharmaceutical dosage forms and food products for many years. Natural polysaccharides and their derivatives represent a group of polymeric materials, which are widely used in controlled drug delivery system in recent years (1). Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release from the liquid penetration into the center of the matrix system (2). The semi synthetic polymers and synthetic polymers used for this purpose (3–6) in combination with various drugs have been protected by end number of patents, thus there is always a search for new polymers to circumvent these patents in the pharmaceutical field. As the nature possesses much more plant exudates and gums to be explored, the research in this field had yielded many useful gums like acacia, tragacanth and karaya for the controlled drug delivery system. Natural gums are often preferred over synthetic materials due to their non-toxicity, low cost and free availability. Natural gums have been modified to overcome certain drawbacks like uncontrolled rate of hydration, thickening, drop in viscosity on storage and microbial contamination (7). Various natural gums like agar gum, guar gum and gellan gum have been successfully used as polymer for the sustained release of drugs (8–10). Hence to encourage the research in the field of natural gums, we made an attempt to explore the utility of one of the gum exudates of plant origin *Terminalia catappa* Linn., as a release-retarding polymer in the oral controlled drug delivery system.

Terminalia catappa Linn. is a tree belongs to the family *Combretaceae*, broadly distributed on tropical and subtropical beaches. The leaves, trunk bark and fruits of the tree have been used as a folk medicine for antidiarrheic, antipyretic and haemostatic purposes in India, Philippines, Malaysia, and Indonesia (11). The leaves and the fruits of *T.catappa* were studied for treating various diseases (12,13). Even though the contents of leaves, seeds, and fruits of the plant had been reported by many researchers (14–16), the chemistry and contents of the gum exudates have not been reported yet. More Surprisingly the gum exudates of *T. catappa* have not been studied so far as a controlled release polymer in the pharmaceutical field even though many other plant gum exudates like gum acacia, gum karaya, and gum ghatti have been successfully established for the purpose (17–19). Hence the objective of this study was to investigate the application of

[1] Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, 835 215, India.
[2] Department of Pharmacognosy, College of Pharmacy, Nashik, 422 002, India.
[3] To whom correspondence should be addressed. (e-mail: sasmal_bit@yahoo.co.in)

the gum exudates of *T. catappa* as a natural release-retarding polymer in the oral controlled drug delivery system using dextromethorphan hydrobromide (DH) as a model drug. DH is a low molecular weight organic compound, sparingly soluble in water and has been used extensively as a cough suppressant in combination with several other drugs. By studying the rheological behavior and the drug release pattern from tablets prepared by different formulation techniques, it was possible to establish the utility of the gum exudates of *T. catappa* in controlled drug delivery system.

MATERIALS AND METHODS

Materials

Dextromethorphan hydrobromide was obtained as a gift sample from Blue Cross Laboratories ltd (Nashik, India). The authentic gum exudates of *Terminalia catappa* was purchased from the local vendor and the particle size of the gum determined by sieve analysis was 60 to 250 μm. Sodium hydroxide and Potassium dihydrogen phosphate were purchased from Merck (Mumbai. India). Ethanol was obtained from Qualigens fine chemicals (Mumbai. India).

Methods

Rheological Characterization

Rheological analyses were performed in triplicate using a Brookfield digital rheometer (Model DV-III, Brookfield, Middleboro, MA) equipped with a spindle number LV2 at different speeds.

The following tests were carried out:

• *Concentration*: The effects of concentration on viscosity were studied after 6 hours of dispersing the gum in water in a concentration from 1% to 3% wt/wt at temperature 25±0.5°C.

• *Time*: The test was performed to see the changes in the TC gum dispersion with the time at a constant temperature. The 2% wt/wt TC gum dispersion was allowed to stand without disturbance at 25±0.5°C and viscosity was measured at 1, 6, 12, 18, 24 and 36 h intervals at temperature 25±0.5°C.

• *pH*: The effect of pH on viscosity was studied by adjusting the pH of 2% wt/wt TC gum dispersion with 1 N Hydrochloric acid and 1 N Sodium hydroxide and viscosity was measured after 6 hours of pH adjustment. The temperature of the gum dispersion was maintained at 25±0.5°C. The pH range studied was 1.5 to 8.0.

• *Temperature*: The test was performed to study the TC gum behavior in a range of temperatures. The viscosity was measured with 2% wt/wt TC gum dispersion in water with temperature varying from 25–60±0.5°C. All viscosity measurements were carried out after keeping the dispersion in particular temperature for 6 hours.

• *Rheological Kinetics:* Systems that exhibit non-Newtonian flow behavior frequently are represented as power law fluids such that the apparent viscosity of the material changes as shear stress is applied to it. The shearing behavior of a fluid is represented by a straight line in a log-log shear rate/shear-stress plot, and it is possible to have a good approximation of the shearing properties of fluids (20). The flow characteristic of the TC gum dispersion in water with respect to the effects of spindle speed was analyzed using the "Power law".

$$\tau_w = \kappa\gamma^n \quad (1)$$

Where τ_w and γ correspond to the wall shear stress and shear rate respectively and k and n are the consistency and power law index respectively. A power law index of $n=1$ represents Newtonian flow, $n<1$ represents shear thinning (pseudoplastic) and $n>1$ represents shear thickening (dilatant) behavior (21).

Preparation of Solid Mixtures

Solid mixtures containing DH and TC gum were prepared by different formulation techniques described below. The abbreviations used to describe the different techniques and their gum to drug ratios are given in Table I.

• *Physical Mixing Technique:* The required quantities of DH and TC gum were weighed accurately, sifted through a mesh no. 60 and mixed thoroughly in a mortar and pestle.

• *Aqueous and Non-aqueous Wet Granulation Techniques:* For aqueous wet granulation, the required quantities of DH and TC gum were weighed accurately, mixed in a mortar and then the mixture was kneaded with sufficient quantity of purified water for 10 min. The resultant wet mass was dried at 40°C, pulverized and sifted through a mesh no. 20. For non-aqueous wet granulation, the process was repeated similarly by using ethanol instead of water.

• *Solid Dispersion Technique:* DH was dissolved in 70% *v/v* ethanol to obtain a clear solution. TC gum was added to the solution and dispersed well. The solvent was evaporated at reduced pressure at 60°C with constant mixing. The resultant residue was dried under vacuum for 3 h and stored overnight in a desiccator. Finally, the mass obtained was pulverized and sifted through a mesh no. 20.

Preparation of Tablets

Solid mixtures prepared were mixed well with magnesium stearate (1.0% wt/wt). Powder weighing the equivalent of 30 mg of DH was compressed into tablets using an 8.0 mm flat faced punch with sufficient hardness on a 8-station

Table I. Abbreviations Used for Solid Mixtures of Dextromethorphan Hydrobromide and TC Gum

Factor	Process Variable	Drug/ TC Gum Ratio	Abbreviation
Method of preparation	Physical mixture	1:3	PM1
	Physical mixture	1:6	PM2
	Aqueous wet granulation	1:6	AG
	Non aqueous wet granulation	1:6	NG
	Solid dispersion	1:6	SD

tabletting machine (Cadmach. India). The compression force applied was 15–20 KN in all the cases. Pure DH 30 mg was filled into the hard gelatin capsules size 2 for the comparison of dissolution studies.

In Vitro Dissolution Rate Studies

Dissolution studies were carried out using the USP basket method in a dissolution tester (TDT-08L. Electrolab. India). The dissolution medium used was 500 ml phosphate buffer of pH 6.8 maintained at 37±0.5°C by the constant temperature water bath. The rate of stirring was 100±2 rpm. Tablets of solid mixtures prepared above containing 30 mg of DH and the capsules containing pure DH were used. Five milliliters of sample was withdrawn at each time point and the same amount was replaced with the fresh medium. The sample was filtered through a 0.45 μm syringe filter and assayed spectrophotometrically for DH at 278 nm (Shimadzu UV-1601, Japan).

Drug Release Kinetics

In order to investigate the mechanism of drug release, experimental data within the interval of $0.1 \leq M_t/M_\infty 0.6$ were fitted to the following semi-empirical equation widely called as power law (22).

$$M_t/M_\infty = \kappa t^n \quad (2)$$

Where M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant incorporating structural and geometric characteristics of the device, and n is the release exponent, indicative of the mechanism of drug release (23). The logarithm of fractional release was plotted against the logarithm of time to derive the values for n and k for each formulation. The slope of the line is n while log k is the intercept.

Statistical Analysis

To compare the means of all release data and to assess statistical significance between them, an unpaired two-tailed t-test was used. Results are quoted as significant where $p<0.001$.

RESULTS AND DISCUSSION

Rheological Characterization

The viscosity of the TC gum in water was directly proportional to the concentration of the gum as indicated by the viscosity data given in Fig. 1. The viscosity increased as the concentration of the gum increased and formed a gel above the concentration of 3.0% wt/wt in water. The gum dispersion at 3.0% wt/wt concentration was pourable whereas at 4.0% wt/wt concentration, it formed an unpourable thick gel. It exhibited maximum viscosity at 24 h interval as shown in Fig. 2 and there was no significant further increase in viscosity after 24 h. The pH of the freshly prepared 2% wt/wt of the gum dispersion was 4.3–4.4. The TC gum dispersion

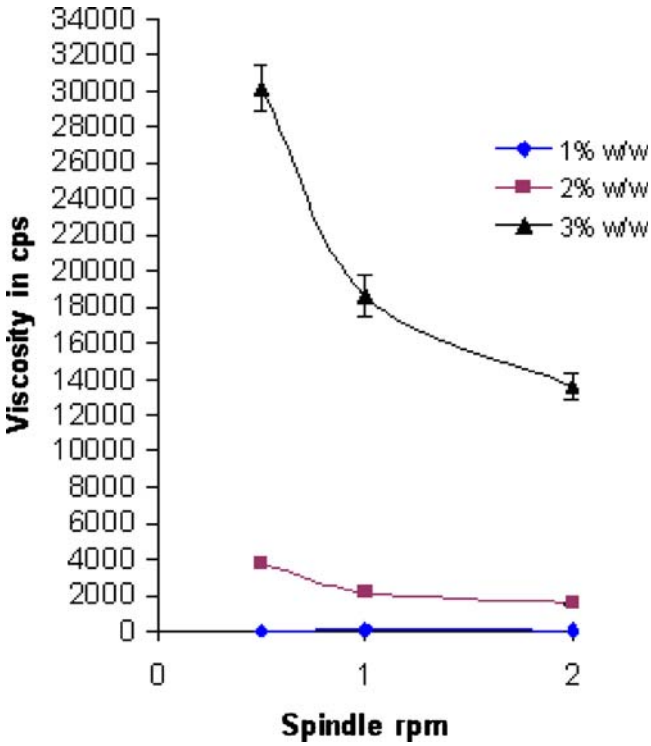

Fig. 1. Effects of concentration on viscosity of TC gum dispersion in water at different rpm of spindle. Error bars are standard deviations for at least three determinations

exhibited the pH dependent viscosity. It had low viscosity in acidic pH and the viscosity was gradually increased as alkalinity of the medium was increased as indicated in Fig. 3. Temperature up to 60°C did not show significant effect on the viscosity as shown in Fig. 4, that indicates the thermal stability of the gum in normal working temperatures. The effect of shear rate as a function of spindle rpm was evaluated with the 3% and 2% wt/wt TC gum dispersion in water by

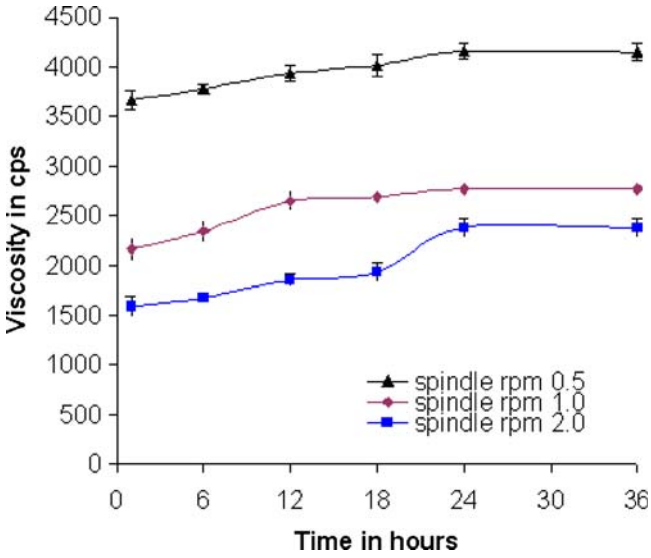

Fig. 2. Effects of duration on viscosity of 2% *w/w* TC gum dispersion in water at different rpm of spindle. Error bars are standard deviations for at least three determinations

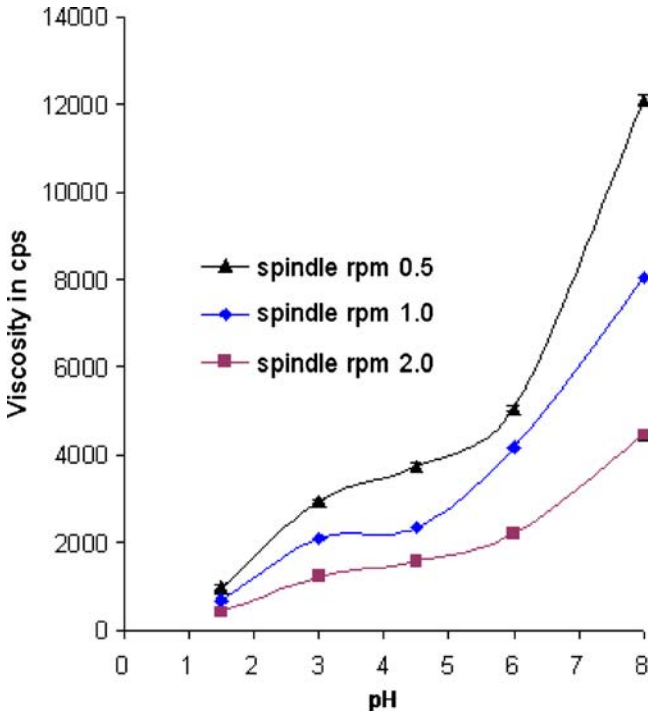

Fig. 3. Effects of pH on viscosity of 2% *w/w* TC gum dispersion in water at different rpm of spindle. Error bars are standard deviations for at least three determinations

Eq. 1 and the results are shown in Table II. The *n* value is found to be less than 1, proving its shear thinning property. Rheological characterization of the swollen gum yielded much insight about the gel nature of the TC gum. The concentration dependent and pH dependent viscosity of TC gum will be helpful in achieving the desired release profile of the drug delivery system and releasing the drug at a desired site.

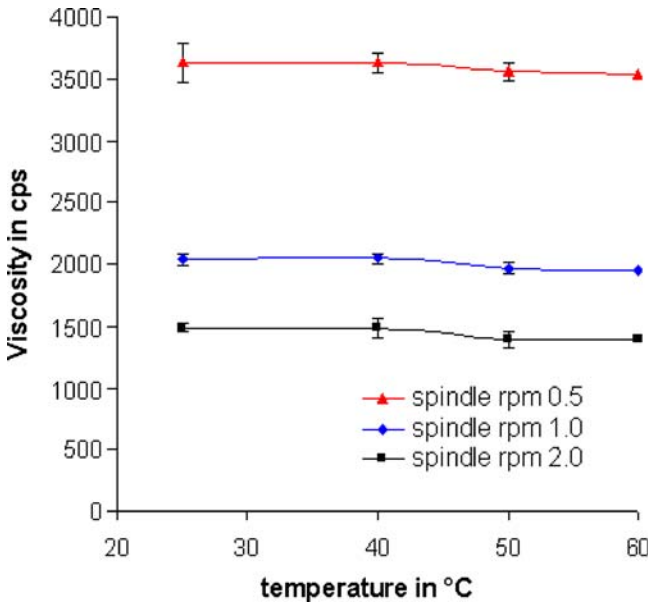

Fig. 4. Effects of temperature on viscosity of 2% *w/w* TC gum suspension in water at different rpm of spindle. Error bars are standard deviations for at least three determinations

Table II. Rheological Characteristics of the TC Gum Dispersion in Water

	Power Law		
	Behavior	Coefficient of Correlation (r^2)	Exponent (n)
Concentration, 3% wt/wt	Shear thinning	0.985	0.576
Concentration, 2% wt/wt	Shear thinning	0.976	0.629

In Vitro Dissolution Rate Studies

In vitro dissolution profiles of DH from matrix tablets in comparison with pure drug indicates that the rate of release of DH was retarded by the presence of the carrier, TC gum. Figure 5 compares the mean percent release of DH from pure drug containing capsules and tablets prepared from the solid mixtures (PM1, PM2) containing different proportions of TC gum, in phosphate buffer of pH 6.8. Release rate of DH from the tablets was significantly reduced ($p<0.001$) than that for the pure drug in both the cases. But increasing the TC gum concentration up to 85% had significant decrease ($p<0.001$) of release rate of DH than 75% concentration in physical mixtures. Figure 6 compares the mean percent release of DH from tablets prepared from the solid mixtures (AG, NG, SD). The drug release was sustained upto 8 h in case of non-aqueous and solid dispersion, whereas in case of aqueous, the release was sustained for more than 8 h. Even though the release of DH from the matrices was sustained in all the formulation techniques, the aqueous wet granulation exhibited more sustained drug release property than solid dispersion

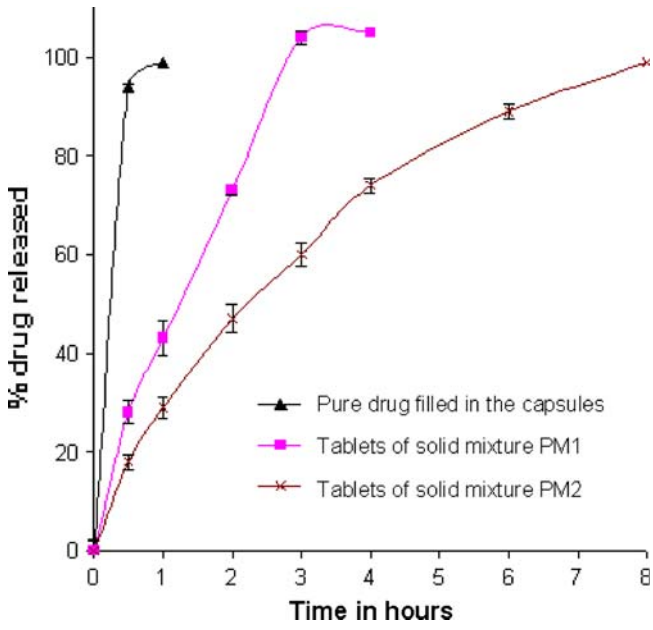

Fig. 5. Comparative *in vitro* dissolution profiles of dextromethorphan hydrobromide filled in the capsules, with tablets of solid mixtures PM1 and PM2. Error bars are standard deviations for at least three determinations

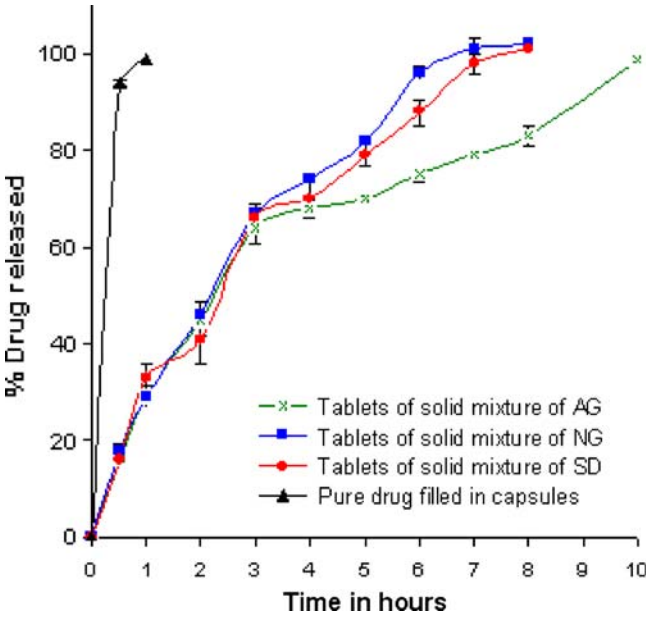

Fig. 6. Comparative *in vitro* dissolution profiles of dextromethorphan hydrobromide filled in the capsules, with tablets of solid mixtures AG, NG and SD. Error bars are standard deviations for at least three determinations

technique and non-aqueous wet granulation technique. The maximum reduction in release rate of DH from the tablets prepared by the aqueous wet granulation method may be attributed to the hydration and swelling of the TC gum during granulation, that resulted in lodging of the particles of the drug in the spaces of the swollen gum after drying. This phenomenon yielded stronger molecular binding of drug and gum and it took more time for the drug to diffuse out the matrix tablet. Whereas in the non aqueous and solid dispersion technique, the gum did not undergo the process of swelling during the preparation of mixture, thus resulted in the poor surface binding of gum and drug hence released the drug faster.

Drug Release Kinetics

In the case of a cylinder (i.e. tablets), Fickian diffusion is defined by $n=0.45$, case II transport by $n=0.89$ and anomalous transport by $0.45<n<0.89$. Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport (Non Fickian) refers to the summation of both diffusion and dissolution controlled drug release. The correct values of exponent n for the different geometrices have been derived (24,25) as listed in Table III. The kinetic values observed for the dextromethrophan hydrobromide matrix tablets were listed in the Table IV. The release kinetic of dextromethorphan hydrobromide from the TC gum matrices was found to be anomalous transport as n values are between 0.45 and 0.89. The goodness of fit was evaluated by the correlation coefficient values as given in Table IV. All the matrices prepared by the different formulation techniques showed better fit to the equation, as the r^2 values are more than 0.95. It is clear from Eq. 2, that when the exponent n takes a value of 0.89, the drug release rate is independent of time. This case corresponds to zero order release kinetics. Here the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate-controlling step. Water acts as a plasticizer and decreases the glass transition temperature (T_g) of the polymer. Once the T_g equals the temperature of the system, the polymer chains undergo the transfer from glassy to the rubbery state, with increasing mobility of the macromolecules and volume expansion. Thus the Eq. 2 has two distinct physical realistic meanings in the two special cases of $n=0.45$ (indicating diffusion-controlled drug release) and $n=0.89$ (indicating swelling-controlled drug release). Hence values of n between 0.45 and 0.89 can be regarded as an indicator for the superposition of both phenomena (anomalous transport).

Table III. Exponent n of the Power Law and Drug Release Mechanisms from Polymeric Controlled Delivery Systems of Different Geometry

Exponent (n)			
Thin Film	Cylinder	Sphere	Drug release Mechanisms
0.5	0.45	0.43	Fickian diffusion
$0.5<n<1.0$	$0.45<n<0.89$	$0.43<n<0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

Table IV. Parameters of Power Law Equation for the Release Curves of Dextromethorphan Hydrobromide Matrices Prepared by Different Formulation Techniques

Matrix Composition	Kinetic Constant (k)	Coefficient of Correlation (r^2)	Release Exponent (n)
PM1	0.439	0.991	0.706
PM2	0.292	0.997	0.666
AG	0.279	0.993	0.745
NG	0.289	0.996	0.739
SD	0.285	0.944	0.719

CONCLUSION

In this study, the excellent swelling properties of TC gum in water and its ability to sustain the release of dextromethorphan hydrobromide from matrix tablet, has been demonstrated. Therefore the proposed tablet formulations with TC gum may ensure the utility of the TC gum in controlled drug delivery systems of sparingly water-soluble, low molecular weight drug substance.

REFERENCES

1. T. R. Bhardwaj, M. Kanwar, R. Lal, and A. Gupta. Natural gums and modified natural gums as sustained release carriers. *Drug Dev Ind Pharm.* **26**(10):1025–1038 (2000).
2. M. M. Talukdar, A. Michoel, P. Rombaut, and R. Kinget. Comparative study on xanthan gum and hydroxypropylmethylcellulose as matrices for controlled-release drug delivery. I. Compaction and *in vitro* drug release behavior. *Int J Pharm.* **129**:233–241 (1996).
3. S. Chirico, A. Dalmoro, G. Lamberti, G. Russo, and G. Titomanlio. Analysis and modeling of swelling and erosion

behavior for pure HPMC tablet. *J Control Rel.* **122**:181–188 (2007).
4. J. Mulhbacher, P. Ispas-Szabo, and M. A. Mateescu. Cross-linked high amylose starch derivatives for drug release II. Swelling properties and mechanistic study. *Int J Pharm.* **278**:231–238 (2004).
5. H. Onishi, T. Oosegi, Y. Machida, and J. W. McGinity. Eudragit coating of chitosan-prednisolone conjugate microsphere and *in vitro* evaluation of coated microspheres. *Drug Dev Ind Pharm.* **33**:848–854 (2007).
6. N. Wu, L. Wang, D. C. Tan, S. M. Moochhala, and Y. Yang. Mathematical modeling and *in vitro* study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. *J Control Rel.* **102**:569–581 (2005).
7. D. F. Durso. *Handbook of water soluble gums and resins,* 1st edn. McGraw Hill, New York, NY, 1980.
8. M. Nakano, Y. Nakamura, K. Takikawa, M. Kouketsu, and T. Arita. Sustained release of sulphamethizole from agar beads. *J Pharm Pharmacol*. **31**(12):869–872 (1979).
9. S. Altaf, K. Yu, J. Parasrampuria, and D. R. Friend. Guar gum-based sustained release diltiazem. *Pharm Res.* **15**:1196–1201 (1998).
10. S. A. Agnihotri, S. S. Jawalkar, and T. M. Aminabhavi. Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size and drug release. *Eur J Pharm Biopharm.* **63**:249–261 (2006).
11. T. C. Lin. Study on the tannins and related compounds in the fruit of *Terminalia catappa* L. *J Chi Med Pharm Res.* **14**:165–174 (1992).
12. P. S. Chen, J. H. Li, T. Y. Liu, and T. C. Lin. Folk medicine *Terminalia catappa* and its major tannin component, punicalagin, are effective against bleomycin-induced genotoxicity in Chinese hamster ovary cells. *Cancer Lett.* **152**:115–122 (2000).
13. A. N. Nagappa, P. A. Thakurdesai, N. Venkatrao, and S. Jiwan. Antidiabetic activity of *Terminalia catappa* L, fruits. *J Ethnopharmacol*. **88**(1):45–50 (2003).
14. T. Tanaka, G. I. Nonaka, and I. Nishioka. Tannins and related compounds. XLII. Isolation and characterization of four new hydrolysable tannins, terflavins A and B, ergallagin and tercatain from leaves of *Terminalia catappa* L. *Chem Pharm Bull.* **34**:1039–1049 (1986).
15. J. T. A. Oliveira, I. M. Vasconcelos, L. C. N. M. Bezerra, S. B. Silveira, A. C. O. Monteiro, and R. A. Moreira. Composition and nutritional properties of seeds from *Pachira aquatica* Aubl, *Sterculia striata* St Hil et Naud and *Terminalia catappa* Linn. *Food Chem.* **70**:185–191 (2000).
16. W. Dorsch and H. Wagner. New antiasthmatic drugs from traditional medicine. *Int. Arch Aller Appl Immun.* **94**:262–265 (1991).
17. A. R. Ray, V. Batra, A. Bhowmick, and B. K. Behra. Sustained release of ferrous sulfate from polymer-coated gum arabica pellets. *J Pharm Sci.* **83**:632–635 (1994).
18. D. L. Munday, and P. J. Cox. Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. *Int J Pharm*. **203**(1–2):179–192 (2000).
19. B. Daniel. Controlled release composition, *U.S. Patent No*. 6787156, 2004.
20. G. Bonacucina, S. Martelli, and G. F. Palmieri. Rheological, mucoadhesive and release properties of Carbopol gels in hydrophilic cosolvents. *Int J Pharm.* **282**:115–130 (2004).
21. A. Allahham, P. Stewart, J. Marriott, and D. Mainwaring. Factors affecting shear thickening behavior of a concentrated injectable suspension of levodopa. *J Pharm Sci*. **94**(11):2393–2402 (2005).
22. N. A. Peppas. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv.* **60**:110–111 (1985).
23. M. S. Reza, M. A. Quadir, and S. S. Haider. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. *J Pharm Pharmaceut Sci*. **6**(2):282–291 (2003).
24. P. L. Ritger and N. A. Peppas. A Simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J Control Rel.* **5**:23–36 (1987).
25. P. L. Ritger and N. A. Peppas. A Simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *J Control Rel.* **5**:37–42 (1987).