Indonesian J. Pharm. Vol. 24 No. 1 : 30 – 34
ISSN-p : 0126-1037

Research Article

DESIGN, DEVELOPMENT AND *IN VITRO* EVALUATION OF CAFFEINE LOADED NATURAL GUM MATRIX TABLET

Nidhi Jain*, Divya Kumar, Neha Gulati, Upendra Nagaich

Dept. of Pharmaceutics, School of Pharmacy, Bharat Institute of Technology., By-Pass Road, Partapur, Meerut-250103, Uttar Pradesh, India

Submitted: 18-10-2012
Revised: 30-10-2012
Accepted: 21-11-2012

*Corresponding author
Nidhi Jain

Email :
jain.nidhi2505@gmail.com

ABSTRACT

The present research work was carried out to develop sustained release tablets of caffeine using natural matrix former (tragacanth) and different filling polymers like hydroxyl propyl methyl cellulose (HPMC K15M) and ethyl cellulose (EC). Caffeine was used as model drug. The polymers and tragacanth gum were incorporated in varying ratios into a matrix system using wet granulation technique. All the lubricated formulations were compressed into tablets and evaluated for various physicochemical properties such as thickness, hardness, friability, weight variation, drug content and *in vitro* drug release studies. From the investigation it was observed that increase in the amount of gum tragacanth (from F1 to F5) led to reduced friability, increased hardness and retarded drug release. Different filling polymers also sustained the drug release. The *in vitro* drug release data were fitted in various release kinetics models to understand the mechanism of drug release. All solid matrix formulations were found to follow Higuchi kinetics, indicating the diffusional release of drug from the matrix type system. The Formulation F5 containing highest amount of gum tragacanth have shown promising results. The findings of the current investigation clearly indicate the potential of tragacanth gum to be used as release retardant and natural matrix material in sustained release formulations.

Key words: Sustained release, Matrix tablets, Tragacanth, Caffeine.

INTRODUCTION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, and flexibility in the design of its dosage form. Developing oral sustained release tablets for highly water-soluble drugs has always been a challenge to pharmaceutical technologists. Most of these highly water-soluble drugs, if not formulated well, may readily release the drug at a faster rate and are likely to produce toxic effects when administered orally (Baloglu, 2010, Vijay *et al*., 2012). Introduction of matrix tablets as sustained release has given a new breakthrough for Novel drug delivery system. It excludes complex production procedure such as coating, pelletization during manufacturing and release the drug in a controlled manner for extended period of time (Pal *et al*., 2007, Sudha *et al.,* 2010).

Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets. As the fluid or media penetrates the matrix tablet, the polymer swells and drug diffuses from the system at a rate determined by nature and composition of polymer (Shoaib *et al*., 2010). A water swellable gum from natural origin such as tragacanth prolong drug release due to its rapid hydration, good compression and gelling characteristic along with its ease of use, availability and low toxicity. So tragacanth could be used as a tablet adjuvant especially for sustained release tablets (Rowe *et al.,* 2009, Owen, 2003).

Caffeine, a highly water-soluble drug, which is used as a CNS stimulant, mild diuretic, and respiratory stimulant, has been selected as a model drug. Hence in the present study, an attempt has been made to develop sustained release matrix tablets of caffeine using natural matrix former (tragacanth) and various polymers

such as hydroxyl propyl methyl cellulose (HPMC K15M), and ethyl cellulose (EC) by the conventional wet granulation method and to evaluate the effect of formulation variables (Tragacanth concentration) on drug release.

METHODOLOGY

Materials

Caffeine was obtained as a gift sample from (Sun Pharmaceuticals Ind. Ltd., India), Tragacanth, Ethyl Cellulose (EC), Hydroxy Propyl Methyl and Cellulose (HPMC K15M), Lactose, Talc, Starch and Magnesium Stearate were purchased from Central Drug House (CDH), New Delhi. All other solvents and chemicals were of analytical grade.

Method of preparation

Caffeine matrix tablets were prepared by wet granulation method. Matrix forming polymers and lactose were weighed, sieved and mixed thoroughly. The powder blend was moistened with the required amount of 1% starch mucilage and granulated using #10 mesh screen. The granules were dried at 45°C for 30 min. The dried granules (granules containing 10-12% moisture) were then passed through #22 mesh screen, mixed with magnesium stearate and talc. Finally granules were compressed into tablet using a flat-faced punch in a single punch tablet compression machine (KI-150, Khera Instruments Ltd, New Delhi, India). The composition of various formulations is shown in table I.

Evaluation of tablets

Thickness and hardness

Randomly selected 6 tablets were subjected to thickness measurement by using Vernier Caliper. Average values were calculated and presented in millimeters. Hardness of 6 tablets from each formulation was determined using Monsanto hardness tester (Cadmach, Ahmedabad, India). The reading was noted in kg/cm^2 which indicates the pressure required to break the tablets (Sathiyaraj *et al.*, 2011*)*.

Weight variation

Weight variation study was carried out as per Indian Pharmacopoea. Twenty tablets were randomly selected from each formulation and weighed individually. The average weight was calculated. By comparing the individual weights to the average weight, tablet weight variation was determined. Not more than two of the individual weights should deviate from the average weight by more than 5% (Indian Pharmacopoea, 2007; Negi *et al.*, 2011).

Friability

For each formulation, pre-weighed tablet samples (6 tablets) were placed in the Roche friabilator (Veego, Mumbai, India) which was then operated for 100 revolutions (25 rpm, 4 min). The tablets were reweighed to check lose in weight. The friability (F) was calculated using the formula:

$$F = (1- W / W_0) \times 100$$

Where, W_0 is the initial weight and W is the final weight of the tablets.

Drug content

For determination of drug content 10 tablets from each formulation were weighed individually, crushed and diluted to 100 mL with sufficient amount of phosphate buffer of pH 7.4. Then aliquot of the filtrate was diluted suitably and analyzed using UV visible spectrophotometer (UV 1601, Shimadzu, Japan) at 273 nm against blank.

In vitro release study

The drug release from the prepared matrix tablets were studied using six station USP apparatus Type II (DS 8000 LAB INDIA) at 100 rpm speed. The test was performed using 900 ml phosphate buffer (pH-7.4), maintained at $37 \pm 0.5°$ C. At predetermined time intervals, an aliquot was withdrawn and replenished with fresh medium. After filtration and appropriate dilution, the sample solutions were analyzed using UV spectrophotometer (UV 1601, Shimadzu, Japan) at 273 nm against an appropriate blank. The amount of drug present in the samples was calculated. All trials were conducted in triplicate and the average reading was noted.

Drug release kinetics

Data obtained from *in vitro* release study was fitted into various kinetic equations. The kinetic models used were *zero order* (Eq. 1) as cumulative amount of drug release *vs.* time, *first order* (Eq. 2) as log cumulative percentage of

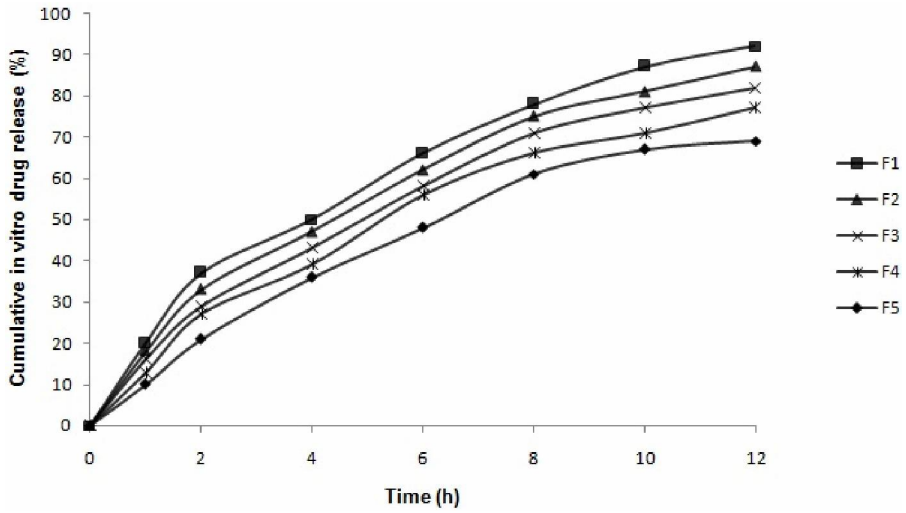

Figure 1. In vitro drug release profile of Caffeine Matrix Formulations (F1-F5)

Table I. Composition of caffeine matrix tablets

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**
Caffeine	100	100	100	100	100
Tragacanth	30	45	60	75	90
HPMC K15M	80	80	80	80	80
Ethyl Cellulose	80	80	80	80	80
Lactose	90	75	60	45	30
Talc	12	12	12	12	12
Magnesium Stearate	8	8	8	8	8

drug remaining *vs.* time, *Higuchi* (Eq. 3) model as cumulative percentage of drug release *vs.* square root of time, *and Korsmeyer and Peppas* as log cumulative percent drug release *vs.* log of time (Eq. 4)

Zero-Order Kinetics:

$Q_t = K_0 t$ **(1)**

where K_0 is the zero-order rate constant expressed in units of concentration/time, t is the time in h, and Q_t is the amount of drug release in time t; graph of concentration *vs.* time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis (Dash *et al.*, 2010).

First-Order Kinetics:

$\text{Log } Q = \text{Log } Q_0 - kt/2.303$ **(2)**

where Q_o is the initial concentration of drug, k is the first-order rate constant, and t is the time (Arora *et al.*, 2011).

Higuchi Kinetics:

$Q = kt^{1/2}$ **(3)**

where k is the release rate constant and t is the time in h. Hence, the drug release rate is proportional to the square root of time (Arora *et al.*, 2011, Higuchi, 1963).

Korsmeyer and Peppas Model:

$M_t/M_\infty = Kt^n$ **(4)**

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 characteristic of the device, and n is the diffusional exponent indicative of the release mechanism. For a cylindrical-shaped matrix, if the exponent $n = 0.45$ indicates Fickian release (case I), >0.45 but <0.89 indicates non-Fickian (anomalous) release, 0.89 indicates case II (zero order) release, and >0.89 indicates super case II type of release (Higuchi, 1963, Korsmeyer,. 1983).

Table II. Physical characterization of Caffeine matrix tablets

Physical Parameters	F1	F2	F3	F4	F5
Thickness (mm)	3.58±0.40	3.64±0.46	3.62±0.33	3.52±0.47	3.69±0.38
Hardness (kg/cm²)	6.4±0.8	6.8±0.6	6.7±0.3	7.1±0.7	7.4±0.5
Weight Variation (%)	±2.5	±1.9	±2	±2.9	±2.6
Friability (%)	0.46±0.04	0.42±0.08	0.44±0.07	0.39±0.04	0.34±0.05
Drug Content (%)	98.7±0.16	98.51±0.2	99.44±0.13	98.24±0.21	99.35±0.27

Table III. Release kinetics data for caffeine matrix tablets

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	K	R^2	K	R^2	K	R^2	n	R^2
F1	7.296	0.934	0.110	0.543	27.93	0.993	0.826	0.628
F2	6.960	0.937	0.110	0.559	26.57	0.991	0.797	0.646
F3	6.685	0.944	0.111	0.581	25.37	0.987	0.762	0.669
F4	6.312	0.943	0.112	0.601	23.92	0.983	0.719	0.698
F5	5.923	0.950	0.114	0.643	22.26	0.974	0.648	0.748

RESULTS AND DISCUSSION

Physical characterization

The physical evaluation tests such as thickness, weight variation, hardness, friability, and content uniformity of five formulations (F1-F5) were within the recommended limits. The results are shown in table II. The thickness value ranged from 3.58±0.40 to 3.69±0.3 mm. As a measure of mechanical strength, these formulations exhibited satisfactory hardness of 6.4±0.8 to 7.4±0.5 kg/cm² and the same fact was further supported by friability of less than 1%. The percent weight variation of tablets ranged from ±2.5 to ±2.6 % for all the formulations which complied with the monograph specification limit of ±5%. The percentage drug content of different tablet formulations were varied from 98.7±0.16 to 99.35±0.27 (within the standard limits of 90.00 - 110.00 %) indicating the uniformity in drug content.

In vitro release study

The *in vitro* drug release from the tablets is depicted in fig.1. As shown by in vitro dissolution data, the increase in amount of gum tragacanth (from F1-F5) progressively retarded the drug release. The lowest gum concentration (F1) showed faster release 92.8% in 12 h and the highest gum concentration (F5) released only 69% drug after 12 h. Tragacanth gum swells rapidly 10 times of its own weight to produce viscous colloidal gel on contact with aqueous media which may be useful in sustained delivery of highly water soluble drug. So when the level of the gum was increased, the time taken for its swelling in the media was increased due the high viscous gel strength. Therefore the diffusion of the drug from matrix was retarded to its maximum and the drug release was slowed down.

Drug release kinetics

The kinetics and mechanism of drug release was determined using zero-order, first-order, Higuchi's square root equation and further analysis was performed using Korsemeyer-Peppas equation. All formulations were found to be followed Higuchi's square root equation (Eq. 3) as the plot showed high linearity (R^2= 0.974 to 0.993) as shown in table III. This equation indicates that the amount of drug release is proportional to the square root of time for the diffusional release of a drug from the matrix type system. The calculated 'n' values from power law equation (Korsemeyer-Peppas equation) for drug release profiles were between 0.648-0.826, suggest that drug release mechanism from matrix formulations followed Non-Fickian (anomalous) transport mechanism**,** which indicates that the drug release rate is controlled by coupled diffusion and erosion.

CONCLUSION

The present study showed that the water swellable natural gum like Tragacanth could be used as a matrix material to design sustained release formulations of water-soluble drug with desired quality and release characteristics. It was found that higher the proportion of gum tragacanth, higher the hardness value, and prolonged is the drug release when compared to the drug release observed with lower proportion of gum. Formulation F5 containing highest amount of gum tragacanth have shown promising results. The significant reduction in the release of drug provided by tragacanth gum could make it a potential natural material for its application in other pharmaceutical dosage forms.

ACKNOWLEDGEMENT

The authors are thankful to Sun Pharmaceuticals Ind. Ltd. (India) for providing the caffeine as a gift sample. We are also thankful to the Board of Trustees, Bharat Institute of Technology, Meerut, India for providing necessary facilities to carry out this work.

REFERENCES

Arora G., Malik K., Singh I., Arora S. and Rana V., 2011, Formulation and evaluation of controlled release matrix mucoadhesive tablets of domperidone using Salvia plebeian gum, *J Adv Pharm Tech Res*, 2(3), 163-9.

Baloglu E., 2010, A Design and Evaluation of Layered Matrix Tablet Formulations of Metoprolol Tartrate, *AAPS Pharm Sci Tech*, 11(2), 563-573.

Dash S., Murthy PN., Nath L. and Chowdhury P., 2010, Kinetic modeling on drug release from controlled drug delivery systems, *Acta Pol Pharm*, 67 (3), 217-223.

Higuchi T., 1963, Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, *J Pharm Sci*, **52**, 1145-1149.

Indian Pharmacopoeia 2007. Ministry of Health and Family Welfare. Government of India.

Korsmeyer RW., Gurny R., Peppas NA., *et al.*, 1983, Mechanisms of solute release from porous hydrophilic polymers, *Int J Pharm*, **15**, 25-35.

Negi JS., Trivedi A., Khanduri P., *et al.*, 2011, Effect of Bioadhesion on initial in vitro buoyancy of effervescent floating matrix tablets of ciprofloxacin HCl, *J. Adv. Pharm. Tech. Res*, **2**, 121-127.

Owen SC., 2003, Handbook of Pharmaceutical Excipients, *The Pharmaceutical Press and The American Pharmaceutical Association,* pp.654-656

Pal TP., Mandal U., Gowda V., *et al.* 2007, Formulation and Optimization of Sustain release matrix tablets of Metformin Hcl 500 mg using Response Surface Methodology, *Yakugaku Zasshi*, **127** (8), 1281-1290.

Rowe RC., Sheshkey PJ. and Quinn ME., 2009, *Handbook of pharmaceutical excipients*, 6th ed, London: RPS Publication, pp.143.

Sathiyaraj S., Devi RD., Hari and VBN. 2011, Lornoxicam gastroretentive floating matrix tablets: Design and in vitro evaluation, *J Adv Pharm Tech Res*, **2** (3), 156-62.

Shoaib MH., Yousuf RI., and Zaheer K, 2010, Development and Evaluation of Hydrophilic Colloid Matrix of Famotidine Tablets, *AAPS Pharm Sci Tech*, **11**(2), 708-718.

Sudha BS., Sridhar BK., and Srinatha A., 2010, Modulation of Tramadol Release from a Hydrophobic Matrix: Implications of Formulations and Processing Variables, *AAPS Pharm Sci Tech*, **11**(1), 433-440.

Vijay J., Sahadevan JT., Prabhakaran R., *et al.*, 2012, Formulation and Evaluation of Cephalexin Extended-release Matrix Tablets Using Hydroxy Propyl Methyl Cellulose as Rate-controlling Polymer, *J Young Pharm*, **4**(1), 3-12.