



MODELING OF DRUG-DIFFUSION KINETICS OF AMOXICILLIN TRIHYDRATE FROM BUCCAL TABLETS

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ABSTRACT

The aim of the current investigation is to study the kinetics of drug release pattern from buccal swellable, controlled release tablets of amoxicillin trihydrate. Buccal tablets were prepared with modified gum karaya in 5-20% concentration. Drug release from the formulated amoxicillin trihydrate loaded buccal tablets followed Zero order kinetics resulting in regulated and controlled release for a given time from all the batches. Swelling index increased with increase in concentration of modified gum karaya. The drug release mechanism was confirmed by Korsmeyer-Peppas exponential equation. It was also observed that among the four batches, the tablets with 5-15% modified gum karaya obeyed Fickian diffusion mechanism, whereas the other (20%) showed the relaxation mechanism. Further for proper clarification the data were fitted to Kopcha mathematical model. This finding is supported by evaluation of the ratios of the exponents A/B (i.e., diffusional factor A and erosional factor B) derived from the Kopcha model, which were greater than 1 in all cases. A/B were found to be much higher (35-40) in the tablets with 5-15% of modified gum karaya suggesting that drug release from the buccal tablets is primarily controlled by a Fickian diffusion process. In the buccal tablets with 20% of modified gum karaya A/B was found to be quite less (24) than the previous batches. Due to the high water affinity of the gum there will be a greater rate of polymer swelling, which is reflected in the drug diffusion mechanism.

KEYWORDS: Swelling index, Release Kinetics, Kopcha mathematical model, Fickian diffusion



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INTRODUCTION

In recent years the basic approach to design the dosage forms is to reduce the frequency of dosing by controlling the drug release. Controlled delivery systems can maintain uniform drug levels, reduce dose, side effects, and increase the safety margin. A wide variety of polymer matrix systems are nowadays used in the field of oral controlled drug delivery to obtain a desirable drug release profile¹. The oral mucosa is the mucous membrane lining the inside of the mouth and consists of stratified squamous epithelium termed oral epithelium and an underlying connective tissue termed lamina propria. The oral mucosae in general are somewhat leaky epithelia, intermediate between that of the epidermis and intestinal mucosa. It is estimated that permeability of buccal mucosa is 4-4000 times greater than that of the skin². Buccal mucosa is relatively permeable, with rich blood supply, which makes it an excellent site for absorption. It also bypasses first pass metabolism and enzymatic degradation. Buccal Drug Delivery means administration of drug through buccal mucosal linings and it refers to the pharmacological route of administration by which drugs diffuse into the blood through tissues of the buccal vestibule, the area inside the mouth between the lining of cheek (the buccal mucosa) and the teeth / gums³. Certain medications are designed to be given buccally (as opposed to orally or sublingually). Buccal (as opposed to oral) administration usually results in a more rapid onset of action, since the medication can be absorbed directly through the mucosal membrane. The buccal formulations need to be adhered to the buccal cavity. Hence a bioadhesive material should be included in the formulation. That bioadhesive material is responsible for maintaining the bond strength to hold it properly. The concept of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is confirmed by the diffusion theory⁴. The bond strength increases with the increase in the degree of the penetration. This penetration is dependent on the concentration gradients and the diffusion coefficients. Buccal

tablet dissolves or erodes slowly when held between the cheek and gum, permitting direct absorption of the active ingredient through the oral mucosa. It is usually a small, flat tablet intended to be inserted in the buccal pouch, where the active ingredient is absorbed directly through the oral mucosa. Amoxicillin trihydrate is a β -lactam antibiotic agent which is chemically 7-[2-amino-2-(4-hydroxyphenyl) -acetyl] amino-3, 3-dimethyl-6-oxo -2-thia-5-azabicyclo [3.2.0] heptane -4-carboxylic acid. Amoxicillin trihydrate acts by inhibiting the cross-linkage between the linear peptidoglycan polymer chains on the cell wall of gram positive bacteria such as *Streptococcus* spp., *Staphylococcus* spp. and *Enterococcus* spp. and gram-negative organisms such as *Haemophilus*, *Neisseria*, *Escherichia*, *Proteus* and *Salmonella* spp. Amoxicillin in trihydrate form is available in capsules, chewable and dispersible tablets, syrup and paediatric suspension, for oral use and as sodium salt for intravenous administration⁵. Gum Karaya is an extract of *Sterculia* trees. It is used as a thickener, emulsifier and laxative in foods, and as a bio adhesive⁶. The majority of commercial karaya gum is obtained from *Sterculia urens*. Karaya gum is a complex, partially acetylated polysaccharide obtained as a calcium and magnesium salt. The polysaccharide component of karaya has a high molecular weight and is composed of galacturonic acid, beta-D-galactose, glucuronic acid, L-rhamnose, and other residues. Karaya gum is the least soluble of the commercial plant exudates, but it absorbs water rapidly and swells to form viscous colloidal solutions even at low concentrations (1%). When used in higher concentrations in water (up to 4%), karaya forms gels or pastes. Unlike other gums, karaya swells in 60% alcohol, but remains insoluble in other organic solvents. Karaya may absorb water up to 100 times its weight. Because the gum is partially acetylated, it may release acetic acid during storage. The gum karaya has been modified for the study. It has been observed that by heating the viscosity of gum karaya is reduced but swelling ability remained same.

Here an approach has been made to prepare buccal tablets of Amoxicillin trihydrate with modified gum karaya in different concentration and to study the drug release kinetics from those buccal tablets in phosphate buffer pH 6.8.

2. MATERIALS AND METHODS

2.1 Materials

Amoxicillin trihydrate was a gift from Unimerk Remedies, Birganj, Nepal. Gum karaya powder # 150 was obtained as gift sample from Nutriroma, Hyderabad, India. All other materials used were of analytical reagent grade.

2.2 Methods and Methodology

2.2.1. Preparation of modified gum karaya

The Modified Gum Karaya (MGK) used in this study was prepared by the method reported by Murali Mohan Babu et al ⁷. Briefly, powdered gum was placed in a porcelain bowl and subjected to heating using a sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling properties similar to GKs, but viscosity was decreased as a function of temperature and time period of heating⁷. However, it was observed that GK samples were charred when heated at 130°C. In the preparation of MGK, no further change in viscosity of GK was observed by heating it at 120°C for more than 2 hours. Hence, these conditions of heating at 120°C for 2 hours were selected to prepare MGK. The prepared MGK was finally sieved (100 mesh) and stored in an airtight container at 25°C.

2.2.1 Preparation of Buccal tablets

Buccal tablets were prepared by wet granulation method. All the powders were passed through 80 mesh sieve. Required quantity of drug and excipients were mixed thoroughly. Mixture was then granulated using Modified Gum Karaya paste. Granules were dried at 40°C for about 15 min. After drying, talc and magnesium stearate were finally added as glidant and lubricant respectively. The mixture was then compressed into tablets using an 8 mm, round-shaped flat punch in a single-stroke

using 10 station rotary machines (Karnavati Engg. Pvt. Ltd., India). The tablets were prepared with different concentrations of Modified Gum Karaya (Table-1).

2.2.2 Swelling Index

The buccal tablets were weighed (W1) and placed separately in petri dishes containing 25 ml of Phosphate buffer (pH-6.8) and allowed to swell at 37± 0.5°C. The dishes were stored at room temperature. After 4 h the tablets were removed and the excess water on their surface was carefully removed using filter paper. Percent swelling was calculated in terms of water uptake and presented as percentage of water uptake ⁸. The swollen tablets were weighed (W2) and the percentage of swelling was calculated by the following formula. Swelling index = (W2 - W1)/W1*100

2.2.3 Surface pH Study

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo ⁹. As an acidic or alkaline pH may irritate the buccal mucosa, the surface pH was kept as close to neutral as possible. For determination of surface pH the buccal tablets were allowed to swell for 2 h on the surface of an agar plate. Then the surface pH was determined by touching the electrode of a pH meter (Toshniwal Instruments, Ajmer, Rajasthan, India) in the excess phosphate buffer (pH-6.8) present at the surface of the tablets. A mean of three readings was recorded ¹⁰.

2.2.4. Drug Content Analysis

A buccal tablet was taken in 100 mL phosphate buffer pH 6.8 in a volumetric flask, and the mixture was stirred for 48 h at room temperature using a magnetic stirrer (Remi Equipments, Mumbai, India). The drug content analysis for Amoxicillin trihydrate was done by UV method at 273 nm. Initially, the time of analysis of the method was standardized by taking formulation with measured amount of drug in phosphate buffer pH-6.8 and determination of amount of drug released with the duration ¹¹.

2.2.5 *In vitro* drug release study (Dissolution Study)

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the buccal tablet. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release was performed at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, with a rotation speed of 50 rpm. In this study sinker was used to retain the tablet at the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through What man filter paper and analyzed after appropriate dilution by UV spectrophotometer (UV – 1800 Shimadzu) at 273 nm¹².

2.2.6 Kinetics of Drug Release

To investigate the drug release kinetics from buccal tablets of Amoxicillin trihydrate the release data obtained from dissolution studies were fitted to various kinetic equations. The kinetics models used were Zero order equation ($Q_t = Q_0 - K_0t$), First order equation ($\ln Q_t = \ln Q_0 - K_0t$), Higuchi's equation ($Q_t = K_h t^{1/2}$), Korsmeyer –Peppas ($Mt / M^{\infty} = Kt^n$) and Kopcha kinetics ($Q_t = At^{1/2} + Bt$). [Q_0 is the initial amount of drug in the solution ($Q_0 = 0$), K_0 is the zero order release constant, Q_t = amount of drug released at time t , K_h is the Higuchi constant, where Mt / M^{∞} is a fraction of drug released at time t , k is the release rate constant and n is the release exponent, A = diffusional constant and B = erosion constant].

2.2.7 Statistics

Data were assessed by one-way ANOVA followed by Tukey HSD Test using Vassar Stats software (USA). $P < 0.01$ has been considered as statistically significant.

RESULTS AND DISCUSSION

The present study was intended to develop buccal tablets containing Amoxicillin trihydrate. After screening with several combinations of various polymers and evaluating the different physico-chemical parameters and *in vitro* drug release, the best polymeric composition

achieved has been reported in this study. The buccal tablets showed satisfactory physico-mechanical properties (Table 1). Among the four formulations drug content was found above 98% and the low values of standard deviation indicates content uniformity of the tablets. The surface pH obtained in this study was within the limits and showed hardly any variation from time to time which omits the chances of irritation in the buccal mucosa upon application. Swelling depends on the polymer concentration and the water absorption capacity of the polymers¹³. The swelling results were expressed in terms of percentage water uptake at 37°C ¹⁴. The swelling indices were found to be within 17 -120 %. For MGK4 the value was 120 % and for MGK1 it was 17%. The swelling ability increases with increase in percentage of Modified Gum Karaya. The highest hydration (swelling) was observed with the formulation MGK4 (Fig.1). Flexibility of polymer chain from individual polymer is important for interpenetration and entanglement, and in presence of water molecules, polymers become cross linked and the mobility of individual polymer chain decreases and swelling occurs with the time¹⁵. The release profile and kinetics of drug release are important because they correlate the *in vitro* and *in vivo* drug responses by comparing results of pharmacokinetics and dissolution profile patterns¹⁶. Hence, the cumulative drug release results of the formulations were fitted into various mathematical models (Table 2). The drug release pattern of formulations shows linearity. Therefore it was ascertained that the drug release from these formulation could follow either zero or near zero order kinetics (Fig. 2). These formulations released the same amount of drug per unit of time irrespective of the drug concentration. Further, to understand the drug release mechanism, the data were fitted to Korsmeyer-Peppas exponential equation, $Mt/M^{\infty} = Kt^n$, where Mt/M^{∞} is the fractional drug release into the dissolution medium, K is a constant which incorporates the properties of the macromolecular polymeric system and drug and n is the diffusional exponent, which characterizes the drug transport mechanism. When $n = 0.5$, it indicates quasi-Fickian diffusion

mechanism. For $n > 0.5$, an anomalous non-Fickian diffusion and the special case of $n = 1$ that has gained importance due to its potential application in the development of swelling controlled drug delivery systems with zero-order. Further for proper clarification the data were fitted to Kopcha mathematical model. This finding is supported by evaluation of the ratios of the exponents A/B (i.e., diffusional factor A and erosional factor B) derived from the Kopcha model¹⁷ which were greater than 1 in all cases. The data in Table 2 clearly show that the value of A is far greater than that for B, suggesting that drug release from the buccal tablets is primarily controlled by a Fickian diffusion process. The swollen layer in the buccal tablets behaves like a complete matrix

structure and controlled the drug release; the swelling of the polymers varied the entanglement of polymeric pathways to control the diffusion of the drugs from the formulations¹⁸. Drug release from the swellable matrix tablet is based on the glassy-rubbery transition of the polymer, which is due to the penetration of the water into the matrix system. This may result in a greater rate of polymer swelling and an increase in gel thickness resulting in a drastic decrease in the rate of drug release¹⁹. Hence the main factor in controlling the drug release is the interaction between the water, drug and concentration of polymer. Hence it can be well said that with increase in polymer concentration, drug release is significantly decreased.

Table 1
Physicochemical evaluation of buccal tablets

Formulation	Modified gum karaya (%)	Weight variation (mg) \pm SD	Drug content (%) \pm SD	Surface pH \pm SD
MGK1	5	120 \pm 0.5	97.22 \pm 0.5	6.7 \pm 0.1
MGK2	10	119 \pm 0.6	98.46 \pm 0.4	6.8 \pm 0.1
MGK3	15	120 \pm 1.0	98.15 \pm 0.5	6.7 \pm 0.1
MGK4	20	119 \pm 1.0	98.50 \pm 0.3	6.7 \pm 0.1

Table 2
Kinetic-data of drug release from buccal tablets

Batch	Zero Order Kinetics	1 st Order Kinetics	Higuchi Kinetics	Korsmeyer-Peppas Kinetics		Kopcha'S Kinetics			
	R ²	R ²	R ²	R ²	n	R ²	A	B	A/B
MGK1	0.934	0.9097	0.8413	0.7719	0.4	0.9304	4.478	0.127	35.12
MGK2	0.8722	0.8528	0.7674	0.702	0.44	0.9068	3.327	0.081	40.92
MGK3	0.8254	0.8007	0.7086	0.6564	0.39	0.9232	3.041	0.089	33.87
MGK4	0.9794	0.9764	0.9384	0.8704	0.18	0.9757	5.991	0.248	24.12

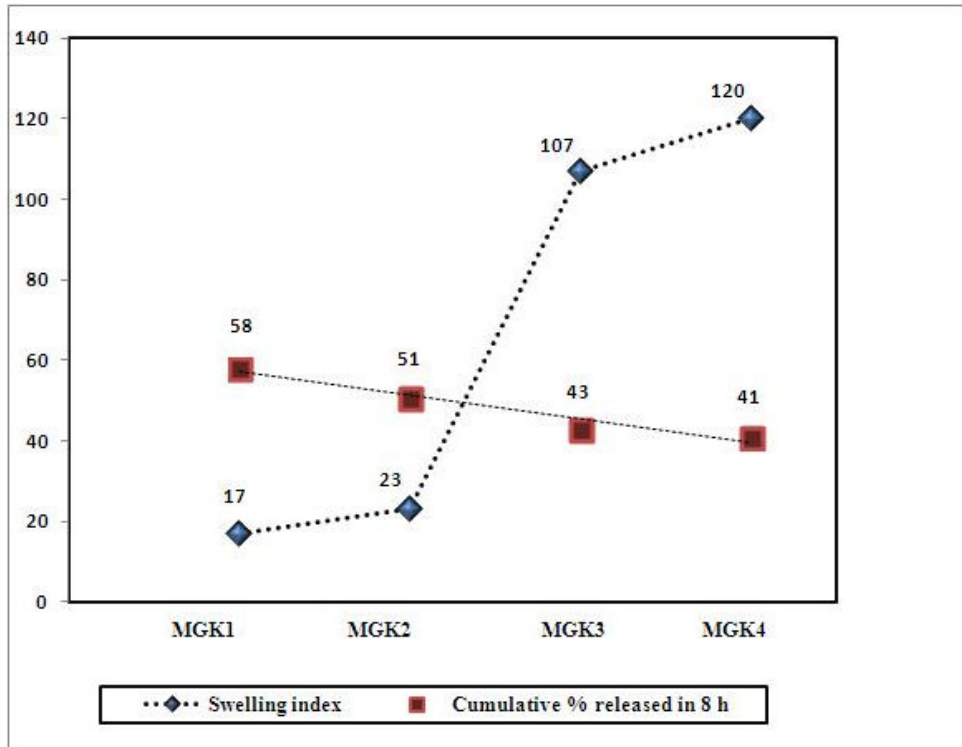


Figure 1
Drug release profile of Amoxicillin trihydrate from buccal tablets in phosphate buffer pH-6.8, (\pm SD, N=6)

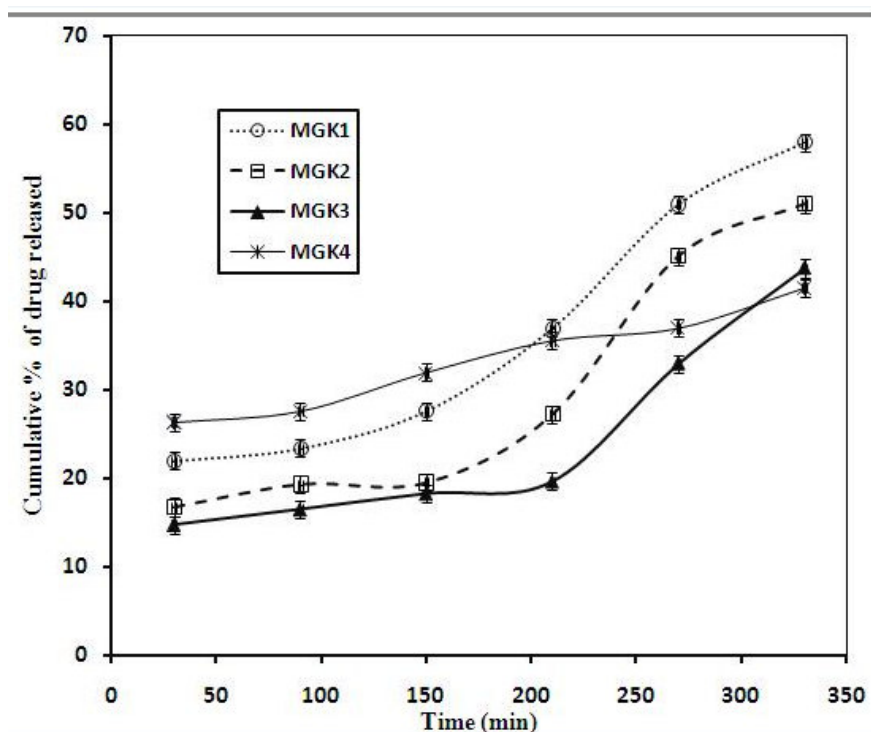


Figure 2
Correlation of swelling index and cumulative percent of drug release from buccal tablets in phosphate buffer pH-6.8 (\pm SD, N=6)

CONCLUSION

The prepared buccal tablets of Amoxicillin trihydrate can help to bypass extensive hepatic first-pass metabolism and improve bioavailability. A significant variation exists in the in vitro release pattern of Amoxicillin trihydrate from the buccal tablets in relation to change in concentration of modified gum karaya. The Korsmeyer-Peppas release exponent (n) of the formulations confirmed diffusion as the principal mechanism of drug

release from the prepared buccal tablets. It was further confirmed through Kopcha model. Evaluation of diffusion and erosion terms in the Kopcha model showed a predominance of diffusion relative to swelling or erosion throughout the entire test period.

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