# Sustained Release of a Water-Soluble Drug from Directly Compressed Okra Gum Matrix Tablets

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**Okra gum was evaluated as a controlled-release agent in modified release matrices in comparison with sodium carboxymethylcellulose (NaCMC) using aspirin as the model drug. Tablets were produced by direct compression and the *in vitro* drug release was assessed under conditions similar to those in the gastrointestinal system for a period of 6 hours. The hydration (swelling) and erosion rates of the okra gum matrix tablets were also studied. Okra gum matrices provided a controlled-release of aspirin and the release rates followed time-independent kinetics. The addition of the tablet excipients, lactose and Avicel, altered the dissolution profile and release kinetics. Okra gum compared favourably with NaCMC and a combination of okra gum and NaCMC resulted in near zero-order release of aspirin from the matrix tablets. The results indicate that okra gum is suitable for the sustained release of water soluble drugs.**

**Keywords:** Okra gum, aspirin, matrix tablet, sustained-release

## INTRODUCTION

Hydrophilic polymers have the ability to hydrate and form a gel layer which is essential to sustain and control drug release from matrices. The thickness of the hydrated gel layer determines the diffusion path of the drug molecules through the polymeric mass into the dissolution medium [1-2]. A number of natural and modified polysaccharides such as xanthan, guar and karaya gums, alginates and carrageenan have been shown to be useful as controlled release agents due to their hydrophilic properties. They have proven to be choice materials for hydrophilic drug delivery due to their non-toxic nature and relatively low cost [3-4].

The oral route is usually preferred for drug administration due to safety considerations and patient compliance [5]. The tablet should preferably be produced by direct compression of a mixture of ingredients without the need for any preliminary or subsequent processes such as granulation or coating.

Okra gum is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid [6]. The gum has been investigated as a binding agent in tablets and has been shown to produce tablets with good hardness, friability and drug release profiles [7]. It has been used as a stabilizer, thickener, swelling agent and binder in the food and pharmaceutical industries. Its desirable properties have encouraged a more extensive assessment of the gum as a hydrophilic controlled release delivery system.

The aim of this study was to evaluate the gum extracted from the pods of *Hibiscus esculentus* (commonly known as okra) in *in vitro* sustained release formulations containing the water-soluble drug, acetylsalicylic acid.

## MATERIALS AND METHODS

### *Materials:*

Aspirin was supplied by Sigma Chemical Company, St. Louis, Mo, USA. Lactose and Magnesium stearate were obtained from BDH Chemicals Ltd, Poole, UK, while sodium carboxymethylcellulose (NaCMC) was obtained from Shanghai Chemicals, Shanghai, China. Microcrystalline cellulose was received as Avicel PH 102 from FMC International, FMC Corp, Princeton, NJ, USA. Okra gum was obtained from *Hibiscus esculentus* that was purchased from the local market. The description of extraction and purification of okra gum has been described by Tavakoli et *al.* [7]. The particle size range of 50-75 μ was used to prepare the tablets.

### Preparation of matrix tablets

Okra gum matrix tablets weighing 400 mg were prepared by direct compression of the polymer

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at a compression force of 1 ton maintained for 30 seconds using a Carver laboratory press (Model C, USA) equipped with a 10 mm flat-faced punch and die set. The dies and punches were lubricated with a 1 % dispersion of magnesium stearate in ethanol. The breaking load, friability and disintegration times of the tablets were determined using the hardness tester (Veego, India), friabilator (Veego, Model VFT1D, India) and disintegration tester (Veego, India) respectively.

### Drug formulation

The effect of drug concentration on okra gum matrix tablets was studied using tablets containing 40 % w/w acetylsalicylic acid while the effects of excipients was studied on matrix tablets containing Avicel and lactose.

### Drug release testing

*In vitro* drug release studies from the prepared matrix tablets were conducted for a period of 6 hours at 37 ºC in a dissolution basket equipped with a magnetic stirrer apparatus rotating at 100 revolutions per minute. The sample holder was immersed in 500 ml of medium and a sink condition was followed for the whole duration of the test. The media used were 0.1N HCl pH 1.2 for the first 2 h followed by Sorensen's phosphate buffer pH 7.4 for 4 h to simulate the gastrointestinal environment. The amounts of aspirin released were determined using a UV spectrophotometer (Unico, UV 2102 pc) at a wavelength of 278 nm. The concentration of drug dissolved in the medium at specified time periods was plotted as percent release versus time.

### Data Analysis

The dissolution data were fitted in the Korsmeyer equation [8] which is often used to describe drug release behaviour from polymeric systems:

$$M_t/M\infty = Kt^n \quad (1)$$

Where $M_t/M\infty$ is the fraction of drug released at time t, k is the kinetic constant (with unit $t^{-n}$) incorporating the properties of the polymeric system and the drug and n is the release exponent, which indicates the mechanism of release. This equation can be used to analyze the first 60 % of a release curve where the release is linearly related to $t^n$ regardless of the geometric shape. According to the known criteria of release kinetics from swellable systems, zero-order (Case II), non-Fickian (anomalous) kinetics and Fickian (Case 1) release are represented by $n = 1.0$, $0.5 < n < 1.0$, and $n = 0.5$ respectively [4, 8], $n > 1.0$ for Supercase II type of release. However, different kinetic models (zero-order and Higuchi's equations) were equally applied to interpret the release rate from the matrix system in order to determine the best fit with higher correlation for all the formulations [9]. Higuchi's model, which describes the release of drugs from insoluble matrices as a square root of time-dependent process based on Fickian diffusion [10], is given by:

$$W = Kt^{1/2} \quad (2)$$

Where W is percent drug release at time t and k is the release constant.

## RESULTS AND DISCUSSION

Okra gum matrix tablets produced at a compression force of 1 ton had a very high hardness value and low friability and compared favourably with tablets produced with NaCMC in hardness having a hardness value of 13 Kgf, friability of 0.79 % and disintegration time of 42 minutes. The results agree with those from earlier work by Tavakoli *et al.* [7]. One of the requirements for a tablet is that its strength should be sufficiently high to withstand the different conditions in the distribution chain from producer to patient. Higuchi observed the great influence of the compression force employed in the tabletting process on the apparent density, porosity, hardness, disintegration time and average primary particle size of compressed tablets [10]. Drug release from polymeric matrices occurs when a matrix is placed in contact with a compatible solvent and progressive swelling of the polymer particles occurs leading to considerable structural changes. These include a change of the mobility of the macromolecular chains, macromolecular relaxations and changes of the porous structure including alteration of the shape and size distribution of the pores. These changes will influence the porosity and

tortuosity of the polymer during swelling and diffusional release [8].

The release profiles of aspirin from okra gum and NaCMC matrix tablets are shown in Figure 2. The drug was released in a controlled manner over 6 h. The increase in the dissolution rate of tablets containing 40 % w/w aspirin in okra gum may be due to the weakening of the matrix lattice due to the high concentration of the water-soluble drug, which provides a diffusion pathway for the disintegration of the matrix.

The release parameters derived from the Korsmeyer equation are presented in Table 1. The high values of the coefficient of linear regression confirm that the data treatment may be used successfully for okra gum matrices.
Aspirin in okra gum showed an anomalous transport mechanism (n = 0.62) while in NaCMC it exhibited a Supercase II release mechanism (n = 1.11). It has been shown that factors such as the presence of monovalent cations like potassium and sodium tend to reduce swelling and increase the rate of drug release from the matrix tablet [12]. This may be the reason behind the higher release rates observed with NaCMC matrices when compared to okra gum matrices. The lower release rate of aspirin in 0.1N HCl was due to the low solubility of the drug in the diffusion layer because of the low pH of the medium [13]. The dissolution data were further characterized by fitting them into the Higuchi's square root of time (diffusion) model, and the zero-order model, in order to determine the best fit for the release. The release parameters seemed to fit more into the Korsmeyer's and the zero-order models.

The results of the release profiles of okra gum matrix tablets containing the excipients lactose and Avicel are shown in Figure 1. The results showed that the addition of the directly compressible excipients slightly altered the release rate from the okra gum matrix tablets. Lactose increased the rate of release of the drug as compared to Avicel. Generally, okra gum when in contact with the dissolution medium absorbs water, swells and becomes a hydrated gel. At the same time, lactose being freely water soluble will dissolve and provide a pathway for diffusion of the drug and erosion of the matrix leading to a fast release of the drug from the matrix tablet.

Lactose caused a decrease in the tortuosity of the diffusion path of the drug and this accounted for the faster release. Although Avicel is insoluble in water, it promotes the disintegration of the matrix making it easier to erode [14]. The release parameters presented in Table 1 showed that lactose had a higher release profile for aspirin in okra gum matrix tablets compared to Avicel. Lactose showed a Fickian release mechanism in 0.1N HCl (n = 0.40), while Avicel showed a non-Fickian (anomalous) release mechanism (n = 0.67). The slower release observed with Avicel may be as a result of its insolubility in water combined with the insolubility of aspirin in the diffusion layer of 0.1N HCl.

The release mechanism of aspirin from matrix tablets containing Avicel followed time-independent, zero-order release kinetics with $r^2$ = 0.991 for the zero-order model. Directly compressible excipients can alter the mechanical properties of the tablet and modify the release rate of drugs besides being used to alter the tablet bulk. This effect will result in a decrease in release rate which is normally observed as the drug concentration in the tablet decreases.

The release profile of aspirin was evaluated in 0.1N HCl since instability will occur in aqueous medium (phosphate buffer). The dissolution rate of an oral dosage form containing a weak electrolyte drug will be influenced by the solubility of the drug and hence the pH in the diffusion layer surrounding each dissolving drug particle. The slow release of aspirin from the polymer was due to the low solubility exhibited by the drug in the diffusion layer since unionized aspirin, with an aqueous solubility of 33 g/L, is practically insoluble. Aspirin has a pKa of 3.48 and hence its dissolution rate in gastric fluid (pH 1-3) will be relatively low. The pH in the diffusion layer is not necessarily equal to the pH in the bulk of the gastrointestinal fluids [13]. In fact, incomplete dissolution of aspirin in the stomach is responsible for its gastrointestinal side effects and hence the need for enteric coating.

**Result of Swelling Studies**

When a polymer is placed in contact with a compatible solvent, the solvent penetrates the polymer forming a swollen gel phase in the wetted region [15].

**Table 1: Release parameters from matrices containing aspirin (ASA)**

| Matrix tablet composition | Release Parameters | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Korsmeyer's model | | | Higuchi's model | | | Zero-order | |
| | Release exponent (n) | Kinetic constant (K) | Corr. Coeff. ($r^2$) | Intercept (%) | Slope (%/$M^{1/2}$) | Corr. Coeff. ($r^2$) | Slope (K) | Corr. Coeff. ($r^2$) |
| 2:3 Drug: Okra | 0.62 | 0.15 | 0.981 | -0.81 | 0.34 | 0.982 | 0.013 | 0.999 |
| 2:3 Drug: NaCMC | 1.11 | 0.044 | 1.00 | -8.30 | 1.62 | 0.994 | 0.08 | 0.985 |
| 1:2:1 Drug :okra: lactose | 0.40 | 0.59 | 0.999 | 1.02 | 0.27 | 0.992 | 0.011 | 0.958 |
| 1:2:1 Drug:okra:avicel | 0.67 | 0.099 | 0.991 | -1.23 | 0.34 | 0.964 | 0.013 | 0.991 |

The formation of the gel phase is accompanied by sharply reduced mechanical strength and increased permeability in the swollen region. The surface polymer when exposed to aqueous liquid hydrates to form a viscous gel layer [16]. The gel layer forms a diffusional barrier that retards further water uptake and release of dissolved drug. The extent of polymer swelling and the hydration of the microstructure formed within the gel layer vary in accordance with polymer interaction with the hydrating media [17].

Okra gum underwent hydration when placed in contact with the test media. It has a pH of about 6.5 and is soluble at near neutral pH. Due to its low solubility, it was difficult to hydrate in 0.1N HCl. The result of water uptake and swelling of okra gum matrix is shown in Figure 2.

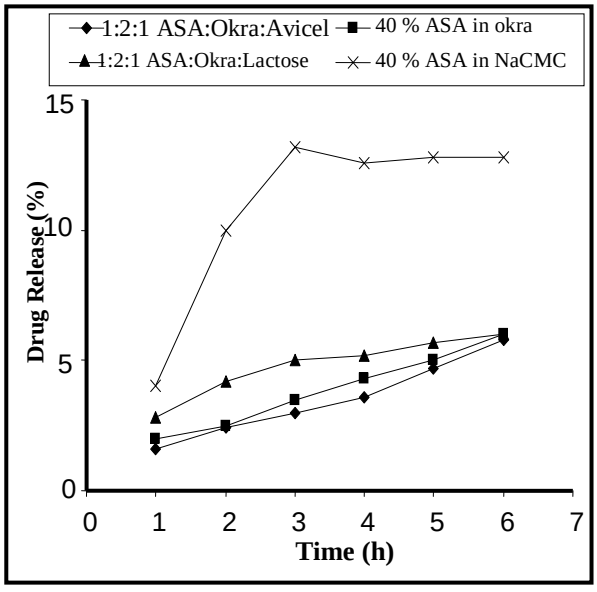


**Figure 1: Release Profile of aspirin from okra gum and NaCMC matrices (in 0.1 N HCl, pH 1.2)**

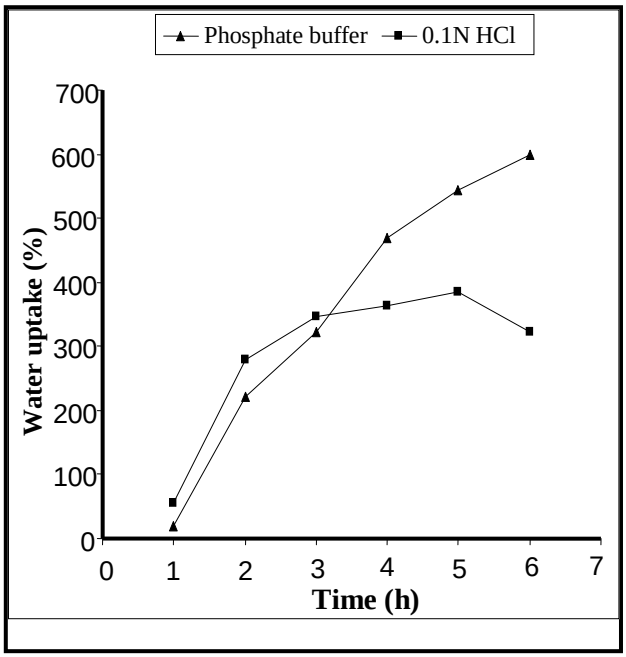


**Figure 2: Percentage water uptake by okra gum matrix in 0.1 N HCl and phosphate buffer, as a function of time.**

Rapid swelling and erosion were observed at pH 7.4. The maximum liquid uptake at pH 1.2 was observed after about 4 h and then gradually decreased, while that in the phosphate buffer at pH 7.4 continued after 6 hours. Although the matrix swelled in both solutions almost instantaneously forming a viscous gel mass, the matrix in 0.1N HCl had a smaller swollen mass. However, the release mechanism of a drug would depend on the dosage form selected, the pH, the nature of the drug and the polymer used [12].

## Matrix Erosion

The result of okra gum matrix erosion studies presented in Figure 3 showed that the matrix underwent erosion during the dissolution

process. Okra gum underwent greater erosion in phosphate buffer pH 7.4 compared to 0.1N HCl at pH 1.2. Due to the slow erosion of the matrix in 0.1N HCl, drug release is expected to be slower from the matrix in this medium. However, the rate of drug release also depends on its solubility.

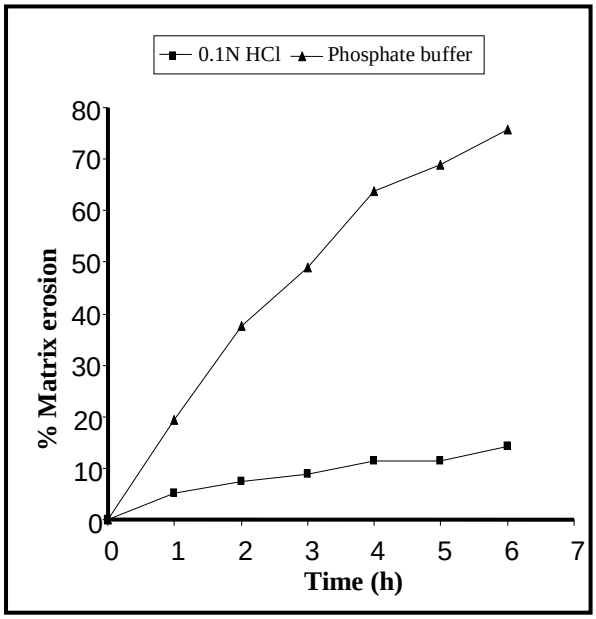


**Figure 3: Result of erosion studies of okra gum matrix tablets**

Therefore drug release is controlled by both diffusion and erosion phenomena. Erosion dominates as the solubility of drug in water decreases and vice versa [4]. The weight loss of the okra gum matrices increased progressively with the erosion time as shown in Figure 3. The percentage weight loss was linear in the phosphate buffer for the first 4 hours. The change to non-linearity may be due to the disintegration of the polymer after excessive water uptake. The rate of erosion of okra gum matrix tablets was much higher in phosphate buffer as compared to 0.1N HCl. This indicates that the viscous gel layer around the polymer in the 0.1N HCl medium at pH 1.2 was more durable and more resistant to erosion than that formed in the phosphate buffer. The erosion in phosphate buffer increased the drug dissolution rate thereby compensating for the higher swelling index of okra gum at pH 7.4 thus leading to gradual weight loss.

## CONCLUSION

Okra gum controlled the release of aspirin from a matrix system. It compared well with the release from NaCMC matrices. Aspirin in okra gum matrices showed a Case I (diffusion) controlled release but approached Case II release from NaCMC matrices. A characteristic of Case II mechanisms is that the rate of interface movement is constant, so that the amount released is directly proportional to time. The release rate can further be controlled by using a combination of okra gum and other polymers and by using suitable diluents like lactose and Avicel. This study suggests that okra gum may be useful in the formulation of aspirin matrix tablets.

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