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### Ophthalmic Minitablet with Natural Polymer: Sterculia Foetida Gum

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#### Abstract

Numerous novel ophthalmic drug delivery systems have been developed to achieve a higher bioavailability of drugs. Some of these may be in situ gelling systems, microspheres, nanoparticles, liposomes and ocular inserts. The natural polymers include botanical polysaccharides (guar gum, locust bean), microbial polymer polysaccharides (dextran), algal polysaccharides (sodium alginate, carrageenan) and animal polysaccharides (sodium hyaluronate). Natural gums & their derivatives have been used as gel forming agents in the form of matrices. Natural gums are frequently preferred to synthetic materials due to their safety, economy and availability. One such natural material would be Sterculia foetida gum (SFG). The ocular use of this formulation as matrix minitabulet (MT) was considered in the present work to possibly improve the bioavailability of ocular drugs.

**Key words:** Sterculia foetida gum, Ocular minitabulets, CR excipient, Hydrophilic matrix, Swelling

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#### Introduction

Most of ophthalmic drugs are administered topically in the form of eye drops, a dosage form consisting of buffered, isotonic, aqueous solution or suspensions of the drug. The research currently focuses on controlled drug delivery systems (CDDS). Ophthalmic CDDS have been mainly prepared as gels, ointments, liposomes, micro and nanoparticles, microspheres and ocular minitabulets (MT) or films or inserts [1,3,15].

The ophthalmic MTs are defined as sterile preparations, whose size and shape are specially designed for ocular application. They are composed of polymer(s) with drug(s) in the form of matrix MT or coated MT. The objective of MT are to increase ocular bioavailability, to extend the duration of drug action, to reduce the number of instillations, to minimize systemic

side effects, to administer accurate dose and to reduce the wide fluctuations in ocular drug concentrations [1,4,13-15].

Hydrophilic matrices (HM) for the past two decades have been popular in the formulation of CR solid dosage forms. A HM usually consists of one or more active ingredients with one or more gel forming agents. Synthetic polymers, Natural gums & their derivatives have been used as the gel forming agents in the matrices. Natural gums are frequently preferred to synthetic materials due to their safety, economy and availability. One such natural material would be *Sterculia foetida* gum (SFG). SFG is obtained from dried gummy exudates of stem bark of *Sterculia foetida* of the family Sterculiaceae. It is partially acetylated polymer of galactose, rhamnose and glucouranic acid. The charged nature of sugar units and their structural arrangements account for its physical properties such as hydration and formation of gel. Since no work has been reported pertaining to this gum in the ophthalmic use, the objective of this work was to evaluate the suitability of SFG as CR matrix former for the same [2, 5-10, 16-17].

### **Materials and Methods**

*Sterculia foetida* gum (SFG), Diclofenac sodium (DS), Carbopol 974, Microcrystalline cellulose, Spray dried lactose, Magnesium stearate

#### **Preparation of minitabets:**

SFG, carbopol 974, spray dried lactose and DS were mixed properly. The powder mixture was compressed into minitabets using single punch compression machine equipped with flat round tooling ( $\Phi$  4mm) specially developed in the lab. Each MT was prepared by weighing out 15 mg of the mixture. Hardness was adjusted on the single punch press to a value of 3.1-3.2 kPa. The diameter and thickness were equal to 4mm and 0.9 mm respectively. They were packaged in polyethylene zip lock bags and thermally sealed. These were sterilized by gamma-ray irradiation (dose: 2.5 MRad) [13, 14].

#### **Evaluation of ocular irritation:**

The objective of this in vivo test was to establish whether the insert being investigated would be 'Irritant' for the rabbits.

The test protocol for ocular irritation was conducted on 6 rabbits after insertion of one single insert in one eye. Each animal was observed at 0.25,0.5,1,2,3,6,12,18,24,48,72 hrs. after insert deposition and scored by comparison with the control eye using a scale of Table as a basis for assessing eye injury after insert deposition. If at any single time of observation an "irritation" is found, using table criteria. After 72 hr. any irritation response persists, the eye is under examination on daily and evaluate score until complete disappearance of any eye irritation (all score = 0) [4, 5].

#### **Evaluation of expulsion:**

One ocular MT was inserted into the lateral conjunctival sulcus of one eye of each of the 6 rabbits. The rabbits were regularly observed over the period of complete release of drug [7, 9].

#### **Water uptake and swelling behavior [6, 10]**

**Bottle method:** the bottle used for this purpose was based on NF-XIV recommendation. The size was 3 cm diameter x 4 cm height. The bottle was attached to the end of paddle drive in

the dissolution jar. The jar having adequate quantity of water was used as secondary water bath for the bottle. The medium in the bottle was 5, 10 and 15 ml of SLF maintained at  $32 \pm 0.5^{\circ}\text{C}$ . A piece of glass slide with the stuck minitabket was placed in the bottle and allowed to show swelling and erosion. The slide was taken out for the estimation of swelling and erosion at fixed intervals for 6 hrs using microscopy and photography as mentioned earlier.

A MT of known diameter was instilled in the cul-de-sac of the eye with all due care precautions and formalities. To measure the changes in diameter of the tablet in the eye photographically, the distance between object and camera was kept constant. The diameter of original minitabket was used as reference to assess subsequent changes. Digital camera information when coupled with computer could indicate precise changes due to swelling and erosion. The study was conducted at suitable intervals for 6 hrs.

#### ***In vitro* evaluation:**

In this study, the rotating glass vial (NF XIV) was used. The MT was accurately weighed, and transferred to glass vial with rubber closure containing 3ml isotonic phosphate buffer solution pH 7.4, placed in water bath at  $32 \pm 0.5^{\circ}\text{C}$  rotated at 25 rpm.

The aliquots measuring 0.5ml each were withdrawn at 15, 30, and 60 minutes, followed by hourly intervals thereafter for the next eight hours. Each aliquot withdrawal was followed by replenishment with 0.5 ml of medium at the same temperature. The samples were diluted with methanol. The UV absorbance of the withdrawn samples was measured at 280.2 nm on a Shimadzu UV-DEC 1601 Spectrophotometer against an appropriate blank.

Drug release studies with MT containing DS were performed in rotating glass vial (NF XIV) with 3ml isotonic phosphate buffer solution pH 7.4. The vials were placed in water bath at  $32 \pm 0.5^{\circ}\text{C}$  and rotated at 25, 50 and 100 rpm. DS was determined by using UV-Spectrophotometer at 280.2nm.

#### ***In vivo* evaluation:**

New Zealand albino rabbits, 2.5–3.0 kg. (Raj Biotech, Pune) were used. They were treated as prescribed in the publication 'Guide for the care and use of laboratory animals' (NIH Publication No 92–93, revised 1985). The animals were housed in standard cages, in a light controlled room at  $19 \pm 1^{\circ}\text{C}$  and  $50 \pm 5\%$  relative humidity, with no restriction of food or water. During the experiments, the rabbits were placed in restraining boxes, where they could move their eyes and heads freely. All experiments were carried out under veterinary supervision, and the protocols were approved by the Institutional Animal Ethics Committee (IAEC) of the Veterinary Nuclear Medicine Center, Bombay Veterinary College, Parel, Mumbai-12.

Unanaesthetised rabbits (n=6, 2-3 kg.) were kept in a prone position on wooden frame. One MT was carefully instilled into the lower conjunctival sac of one eye of the rabbit. The other eye was available as control. The precorneal drug release was evaluated [7-9].

#### **Tear sampling (Lacrimal uptake)**

The basic problem of the drug levels determination in lacrimal fluid results from the collection methods. Two procedures are classically reported. Direct method using capillary tubes requires stimulation of tear secretion. The error in concentrations determination is difficultly controlled and the values are drastically reduced. On the contrary, indirect method is preferable. This one is carried out with absorbent materials like blotting paper strips. Its principal advantages are the following:

1. Small uptake
2. Satisfactory tolerance
3. Easy to use
4. No preliminary stimulation

Nevertheless, previous tests are necessary to verify the total recovery of the drug molecule in the solution before the analytical procedure. Several materials were tested in order to study the drug recovery and the eventual interference on the analytical procedure:

1. Schirmer strips (Faure, Annonay, France)
2. Whatman paper U 92000 455000 (Waters, Saint Quentin en Yvelines, France)
3. Millipore filter AP 20 (Water)

Simulation tests were performed using strips (5mm/30mm) impregnated with 3  $\mu$ l of drug solution. Then, the strips were disposed in glass tubes with required extractive solvent and submitted to supersonic waves for specified duration.

## Results and Discussion

### Ocular irritation and expulsion:

The method usually consists in grading the severity of ocular lesions based on several criteria (see in table). The objective of the test, developed in this work, is to determine clearly whether the insert being investigated is an "irritant" or a "non-irritant", based on the physiological effects of the physiological effects of the tested insert formulation. Six rabbits are used for each trial. The choice of six rabbits was originally based on judgment rather than on strict scientific reasons, but there exist a general agreement that six rabbits are adequate for drawing reliable conclusions on ocular irritancy. This assumption has been confirmed by the experience accumulated during the past decade.

The physiological reactions have been divided into four distinct types: discharge, iris, conjunctival chemosis and conjunctival redness. In fact, scoring for all these parameters may not be necessary to determine if a tested insert is an "irritant" or a "non-irritant". The most important parameters to be scored are those that establish specific ocular injury and the determination of the critical period of time susceptible of inducing ocular irritation.

A rabbit is considered as positive for eye irritancy if any score reaches or exceeds the criterion for a positive response of the eye as follows: discharge: 2, iris: 1, conjunctival chemosis: 2, and conjunctival redness: 2. The choice of these limit values is based on the following reasoning.

- Discharge is often considered as a non-specific phenomenon when solutions are tested. In the case of ophthalmic solid devices, this criterion reflects the reaction and discomfort caused by the introduction of a (semi)solid foreign body in the inferior fornix or the presence of an insoluble body. Discharge is therefore used as a scoring system, and is indicative of irritation when its score is equal or higher than 2.
- Iris abnormalities indicative of anterior segment inflammation and reactions that affect the iris are potentially sight threatening. Thus, any iritis reaction is score indicative of ocular injury.
- Conjunctival chemosis is a debated irritation criterion: This parameter is often considered as an individual reaction. In the case of ophthalmic inserts, the conjunctival chemosis reflects the development of irritation due to the presence of a solid device in the eye. An insert with score lower than 2 is considered as non-irritant.

- Conjunctival redness is indicative of injury or irritation. Frequently the degree of redness is the highest in the area immediately surrounding the site of injury. It is such a sensitive indication that mild degrees of redness (scoring equal to 1) may occur in situations of stress even without specific injury. Redness may therefore be used in a scoring system as an irritancy parameter, when the score is 2 or higher.

Scoring is assigned at predetermined times and especially during the first hours, corresponding to a time of high sensitivity. Just after deposition, the ophthalmic insert can possibly induce the feeling of a foreign body or a cutting sensation associated with the movements of the device: The insert may travel in the inferior fornix or from the lower to the upper fornix. These reactions are indirectly observed during the eye irritancy evaluation. But the insert can also fall out of the eye and this last observation has never been investigated even though it corresponds to an important factor for the success of an ocular insert therapy. This study proposes a simple test to evaluate the so-called expelled insert.

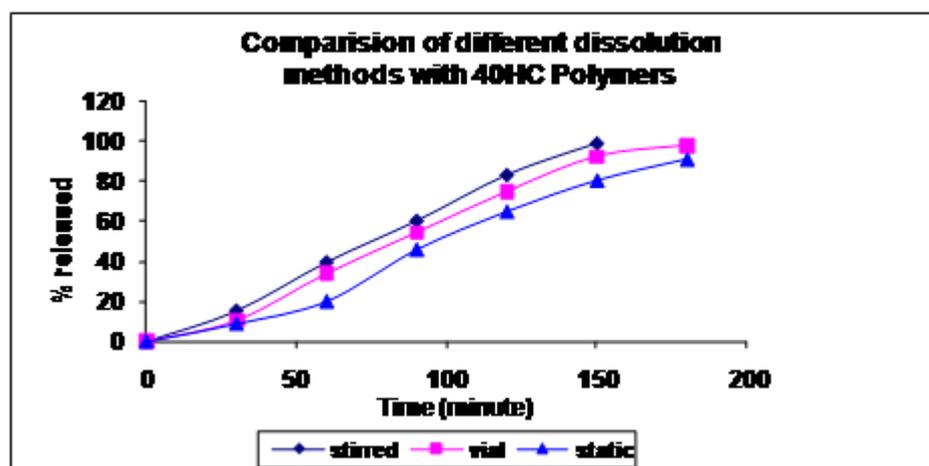
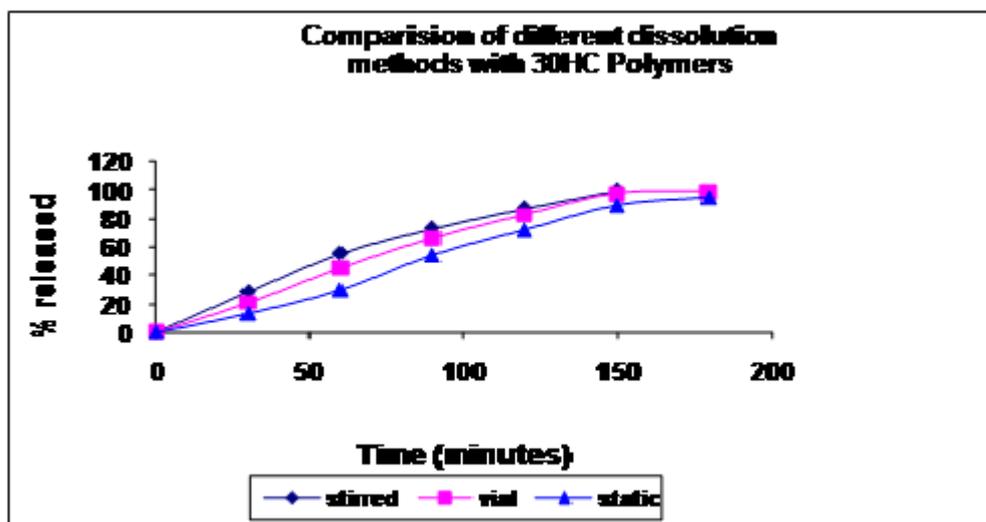
The common behavior of formulation was that, after instillation of the MT into the inferior lateral conjunctival sulcus, lacrimation occurred within a short time (about 1min). However, lachrymal fluid uptake by MT immediately followed, resulting in their softening to produce outer surface gelling. This supported the MT on the mucus membrane of eye. The result showed that the MT was well accepted due to less irritation and absence of expulsion.

Ocular Observation	Score
Cornea	
Opacity: Degree of density (area most dense taken for reading). No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible.	*1
Easily discernible translucent area, details of iris slightly obscured	*2
Nacrous area, no details or iris visible, size of pupil barely discernible	*3
Opaque cornea, iris not discernible through the opacity	*4
Iris	
Normal	0
Markedly deepened rugae, congestion, swelling moderate circum corneal hyperemia or injection, any of these or combination of any thereof, iris still reacting to light 9 sluggish reaction is positive)	*1
No reaction to light, hemorrhage, gross destruction (any or all of these)	*2
Conjunctivae	
<b>Redness</b> (refers to palpebral and bulbar conjunctivae, excluding cornea and iris).	
Blood vessels normal	0
Some blood vessels definitely hyperemic ( injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	*2
Diffuse beefy red	*3
<b>Chemosis</b> ( refers to lids and/or nictitating membranes)	
No swelling	0
Any swelling above normal ( includes nictitating membranes)	1
Obvious swelling with partial eversion of lids	*2
Swelling with lids about half closed	*3
Swelling with lids more than half closed	*4
<b>Conjunctival discharge</b>	
No charge	0
Any amount of discharge different from normal	1
Discharge with moistening of the lids and hairs adjacent to lids	2
Discharge with considerable moistening around the eyes	3

\* Starred figures indicate positive grades.

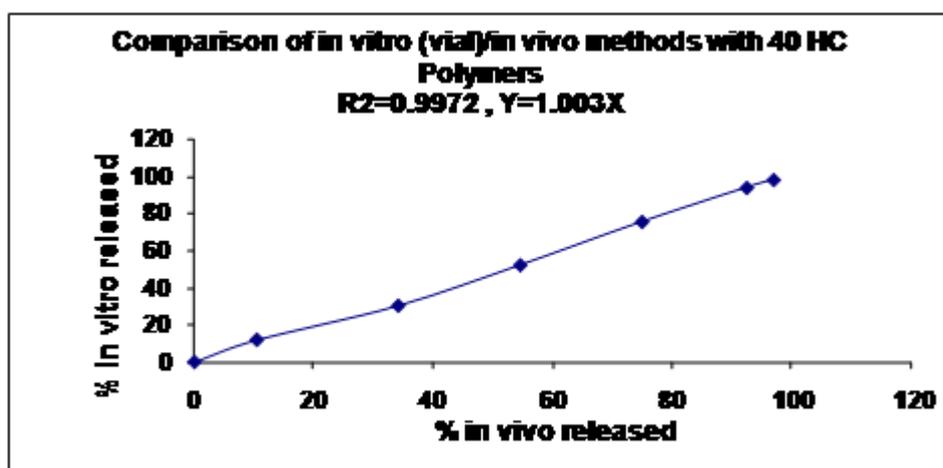
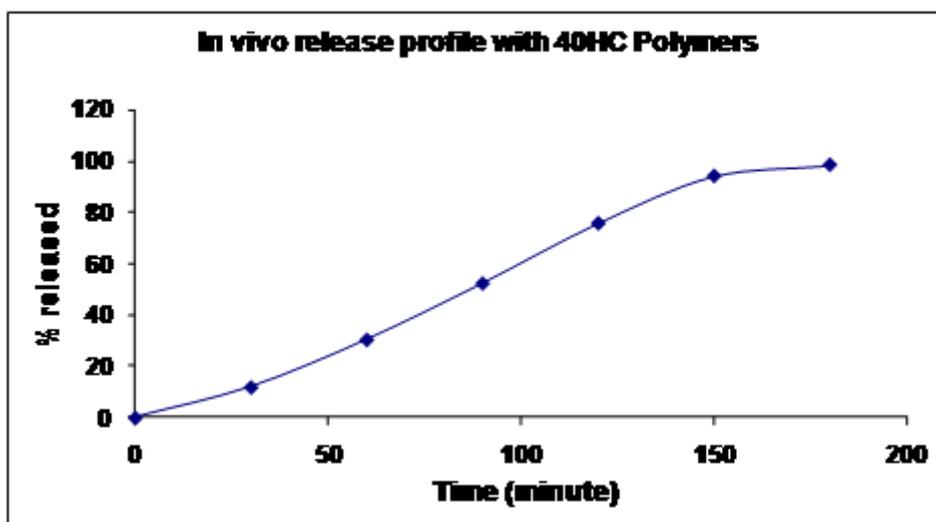
### Water uptake and swelling behavior

The swelling behavior of polymers in dry formulations has a remarkable impact on their adhesive properties, drug release and stability. In this case rapid water uptake by the polymer resulted in strong adhesion to the mucus membrane of the eye. This is possibly due to transient mucus dehydration, which favors interdiffusion process between the polymer and mucus layer.



### *In vitro* drug release:

Ocular MT constructed of SFG as matrix showed controlled drug release. Factors mainly influencing the release rate were the concentration of polymers, fillers, and rotational speed. A controlled release of drug over a period of more than 8 hrs was achieved. The drug release was characterized as non-fickian kinetic where  $n=0.85$  upto 60% release. In this case, drug diffusion through the swollen gel matrix was the governing step for the drug release and the swelling of the polymer caused the release kinetics shift to anomalous transport.



METHODS	EQUATION	R <sup>2</sup>
Stirred/In vivo	Y=1.0986X	0.9803
Vial/In vivo	Y=1.003X	0.9972
Static/In vivo	Y=0.8753X	0.9804

### ***In vivo* drug release:**

The release profiles demonstrated that MT could provide a sustained DS concentration in the cornea/tear film compartment for a prolonged period of time.

### **Conclusion**

The present study indicates that the ocular MT based on SFG can be considered as a promising new solid device for ocular drug delivery. In vivo study demonstrated that the MT can ensure a sustained drug release on the ocular surface for a prolonged period of time. Furthermore, SFG MT was well accepted because of absence of expulsion and less irritation.

Possible applications for SFG MT are the treatment and or prevention of inflammations and infections of the anterior part of the eye eg. after ophthalmic surgery. This new device would be beneficial since the current treatment of ocular inflammations and infections require very

frequent instillations of aqueous eye drops to maintain therapeutic drug levels. With placement of one ocular MT it might be feasible to maintain constant concentration of drugs for several hours and in particular, overnight. The dosage would be beneficial to elder, physically handicapped, mentally retarded and diseased patients like CVS and Asthma (by minimizing side effects of such drugs).

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