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# Sustained-release from Layered Matrix System Comprising Rice Bran Wax and Sterculia Foetida Gum

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**Abstract:** Sustained release tablets of Diltiazem HCl were prepared by direct compression using purified rice bran wax and sterculia foetida gum (SFG) as a matrix forming material. The effective prolongation of drug release from hydrophobic rice bran wax coated with hydrophilic SFG matrices was achieved. Dissolution study of layered tablet investigate that drug release from both planer surfaces of tablet, lag time for drug release through barrier layer was apparently longer as the amount of barrier was increased. Least square fitting experimental dissolution data to the mathematical expressions (zero order, first order, Higuchi, Korsmeyer peppas and Hix. Crowell) was performed to study the drug release mechanism. Drug release from cylindrical portion and plane surfaces of tablet were described. Texture analysis (TA.2Xi) of the hydrophilic polymer supported the way in which the swelling and erosion of SFG gum was done. Swelling and erosion of exposed hydrophilic layer and increase in surface area per unit time were explained. The objective of this work was to design and evaluate three-layered matrix tablets containing a highly soluble drug, Diltiazem HCl (DIZ), embedded in hydrophobic rice bran wax (RBW) matrix middle layer and Sterculia foetida gum (SFG), as hydrophilic barrier layers press coated to the faces of tablet core to aim to achieve constant rate release.
**Keywords:** Diltiazem HCl; Rice bran wax; Sterculia foetida gum; Aspect ratio,; zero-order release.

## Introduction

The multilayered tablet according to present scenario belongs to the group of tablet which contains active substance embedded in to core tablet and coated on both faces of core tablet controlling the release of active substance[1]. Various barrier compositions at symmetric and asymmetric level were tested and reported, using different polymer type according to their technological behavior and modulation efficiency were investigated[2]. The utilization of Rice Bran wax as a matrix forming material in core layer tablet as a hydrophobic polymer is an alternative for carnauba and other waxes used in earlier technology for highly soluble drugs [3]. The linear release kinetic of highly soluble drugs was achieved by application of sterculia foetida gum barrier layers[4,5].

Present scenario of sustained release formulation indicates the researcher have become increasingly interested in utilization of biopolymers in sustained release dosage forms[6,7,8]. The sustained release tablet were prepared by direct compression keeping the rice bran with drug as a central core layer and coated with SFG barriers [9,10,11,12]. The drug release from such layered matrices follows swelling as well as erosion mechanism. Due to their rapid hydration and polymer chain disentanglement hydrophilic polymer predominantly follows both swelling and erosion while hydrophobic polymer only through erosion mechanism[13].

The encouragement for advanced investigation and utilization of rice bran wax in combination with sterculia foetida gum came from the actuality that these biopolymers is not only naturally abundant, but also satisfactorily biocompatible, biodegradable and nontoxic. The potential application of SFG and RBW as a release retardant polymer in oral formulation and other delivery systems are reported. The utilization of RBW and SFG was claimed as diluents for controlled release formulation, tablet coating, ocular inserts and many more formulations.

RBW obtained from species of oryza sativa produced from rice bran oil industries by extraction processes. It consists of chiefly melissyl cerotate.

The Pinari tree, Sterculia foetida, found in South India, has been well documented for the utility of its various parts gummy exudates of this tree has not been reported to be exploited as hydrophilic barrier layer in tri-layered matrix system. Sterculia foetida gum is obtained from gummy exudates of stem bark of *Sterculia foetida* of the family Sterculiaceae. The SFG is chemically characterised by high acetyl content, a high proportion of D- galactouronic acid and the presence of residues of L - rhamnose, D-galactose and a ketohexose. Earlier it was reported from our laboratory that SFG is a potential hydrophilic matrix career for controlled delivery of freely soluble drug such as diltiazem hydrochloride.

## Materials and Methods

### Materials

Diltiazem Hydrochloride (DIZ) was a gift sample from Themis Laboratories, Mumbai, India and Sterculia foetida gum (SFG) (Medicinal natural products research laboratory, University Institute of Chemical Technology, Mumbai, India) were received as gift samples. Rice Bran Wax obtained as a gift sample from Godrej Soap Industries Ltd. Mumbai, India. Lactose IP, Microcrystalline cellulose (Avicel PH 101), Talc and Magnesium stearate (VG) received from Evoniks research lab. All other chemicals and solvents were of analytical grade and used without further purification.

### Preparation of Diltiazem hydrochloride matrix tablet with rice bran wax

Four different batches of tablets were prepared and referred to as A, B, C and D. DIZ HCl (36%w/w), RBW (58%w/w, 38%w/w, 18%w/w and 10%w/w respectively.), lactose monohydrate (04w/w, 24%w/w, 44%w/w and 52%w/w respectively.), magnesium stearate (0.5%w/w) and talc (1.5%w/w) respectively. The compositions of all four batches are shown in table I These materials were shifted through # 80 and blended together in bin blender.

### Preparation of Diltiazem hydrochloride matrix tablet with Sterculia foetida gum

Three different batches of tablets were prepared and referred to as A, B and C. DIZ HCl (36%w/w), SFG (49%w/w), lactose monohydrate (13%w/w), magnesium stearate (0.5%w/w) and talc (1.5%w/w) constituted formulation A and microcrystalline cellulose PH 101 (13%w/w) in place of lactose monohydrate was used in the formulation B. These materials were shifted through # 80 and blended together in bin blender. Formulation C containing drug, SFG (62%w/w), magnesium stearate and talc were prepared under identical condition as shown in table II.

**Table I: Composition of Diltiazem hydrochloride core matrix tablet containing 10%w/w, 18%w/w, 38%w/w and 58%w/w of rice bran wax.**

| Component | Diltiazem HCl (%w/w) | RBW (%w/w) | Lactose (%w/w) | Magnesium stearate (%w/w) | Talc (%w/w) |
|---|---|---|---|---|---|
| PRBW A | 36 | 10 | 52 | 1.5 | 0.5 |
| PRBW B | 36 | 18 | 44 | 1.5 | 0.5 |
| PRBW C | 36 | 38 | 24 | 1.5 | 0.5 |
| PRBW D | 36 | 58 | 04 | 1.5 | 0.5 |

**Table II: Composition of Diltiazem hydrochloride matrix tablet containing 49%w/w and 62%w/w sterculia foetida gum sterculia foetida gum**

| Component | Diltiazem HCl (%w/w) | SFG (%w/w) | Lactose (%w/w) | MCC (%w/w) | Magnesium Stearate (%w/w) | Talc (%w/w) |
|---|---|---|---|---|---|---|
| SFG A | 36 | 49 | 13 | 00 | 0.5 | 1.5 |
| SFG B | 36 | 49 | 00 | 13 | 0.5 | 1.5 |
| SFG C | 36 | 62 | 00 | 00 | 0.5 | 1.5 |

**Compression of tablets**

Diltiazem hydrochloride, Rice bran wax, microcrystalline cellulose and lactose were shifted through # 40 mesh. Sterculia foetida gum was shifted through # 80 mesh to obtain the ultimate fines. Active (API) and all ecxipients were blended together in bin blender (Karnavati, India). Tablets were prepared by direct compression (DC) through such a compression force that a predetermined hardness (5-6 kg/cm$^2$) was achieved with a rotary tablet press (Jaguar, India) using 9.5mm diameter circular beveled punches.

**Preparation of Diltiazem hydrochloride Triple layer matrix tablet** [14,15,16,17]

The preparation of three-layered matrix tablets involved the following steps:

1) Preparation of hydrophobic (wax) composition with DIZ HCl/Active core.
2) Preparation of hydrophilic composition.
3) Compression of hydrophilic layer on both faces of the matrix/Barrier layers.

**Preparation of active core**

The drug Diltiazem, Purified Rice bran wax and lactose were blended together in geometric proportion by using bin blender. The materials were shifted through # 80. These blends were ready for core compression.

**Preparation of hydrophilic composition**

The sterculia foetida gum and lactose were shifted through # 80 mesh. Both the SFG and lactose were blended in geometric proportion and again shifted through #80 mesh to obtain uniform hydrophilic composition.

**Application of barrier layers**

The volume of die cavity (9.5mm, round) was adjusted equivalent to the weight of three-layered matrix tablets e.g. in case of batches RBWA, RBWB and RBWC could be 330mg. Then the pre-weighted amount of SFG powder equivalent to bottom layer (40 mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up, and 250mg of the mixture of the core layer formulation was placed over the bottom layer of SFG powder (40 mg) in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre-weighted (40mg) amount of SFG powder equivalent to top layer and compressed with the full force on rotary tablets press to obtain three-layered matrix tablets. Three-layered matrix tablets of each composition were compressed and tested for their friability, hardness, drug content and drug release characteristics with a suitable number of tablets for each test. Compositions of each batch were given in table III.

**Determination of aspect ratio** [18, 19]

**Aspect ratio:** It is the ratio between the horizontal maximum and the vertical maximum distance of the objective. For the spherical or cubical object the aspect ratio is 1, whereas for those elongated in the X or Y direction the ratio is higher or lower than 1, respectively. For cylindrical objects like tablets, it is diameter to thickness ratio.

The purpose of determination of aspect ratio of triple layered tablet is to correlate the dissolution profile of core tablets and layered tablets where core is coated with barrier layers. It is easy to understand from aspect ratio, how drug releases are maintained from core layer by application of the barrier layers. Different area of

core is exposed to the dissolution media as a function of swelling and subsequent erosion mechanism of barrier layers as time proceeds as shown in table IV.

Two different aspect ratio considered during experimentation as shown in Fig I and II

**Aspect ratio 1** = radius of tablet /Thickness of tablet

**Aspect ratio 2** = Area of two faces of tablet/Area of side

Area of the top face of tablet = Area of the Circle ($\pi r^2$)

Area of the side of tablet = Area of the Cylinder ($2\pi rh$)

Total area of tablet = Area of Cylinder + Area of both faces of tablet
$= 2\pi rh + 2\pi r^2 = 2\pi r (r + h)$

Aspect ratio 2 changes with time as a function of the swelling and erosion mechanism of the top and bottom layers. The change in diameters of this surface was considered for determination of aspect ratio 2 as time progressed.
However the determination of aspect ratio of tablets would play a vital role in formulation optimization to modulate the release profile by adjusting particular aspect ratio.

**Aspect ratio determination of triple layered tablet:**

1. Initially the diameter and thickness of the triple layered tablet was measured. Then tablet was subjected to the dissolution study (dynamic method). In this the tablet was stuck to a glass slid (1× 1") with the help of cyanoacrylic adhesive.
2. The tablets were kept in the dissolution jar having 900ml of distilled water at $37^0$c and paddle speed was maintained at 50 rpm.
3. Change in diameter and thickness of tablets were noted at each hour interval up to 12hr.
4. The change in diameter of tablet were taken by keeping the ruler in close proximity with horizontal position of upper barrier layer of the tablet and this is supported by photographs as shown in fig (axial View).
5. Whereas change in thickness of tablet were taken by keeping the ruler right angle to the tablet in vertical position.
6. The accuracy of measurements of change in diameter and thickness of tablet were confirmed by referring computer grooming scale.

**Fig. 1 Radial view of tablets**

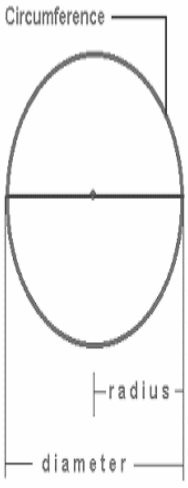


**Fig 2 Axial view of tablets**

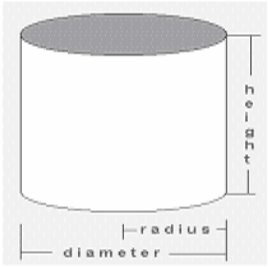



**Table III: Composition of triple layer matrix tablets containing rice bran wax as a core and sterculia foetida gum in press coated barrier layers.**

| | Three - layered tablet formulations (RBW) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **INGREDIENTS** | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** | **I** |
| | | | | **Middle Layer** | | | | | |
| Diltiazem Hydrochloride (%w/w) | 36 | 36 | 36 | 36 | 36 | 36 | 36 | 36 | 36 |
| Rice Bran Wax (%w/w) | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 |
| Lactose (%w/w) | 24 | 24 | 24 | 24 | 24 | 24 | 24 | 24 | 24 |
| Mg Stearate. (%w/w) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Talc (%w/w) | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Total weight (mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| | | | | **Barrier layer (on each side)** | | | | | |
| Sterculia foetida Gum (%w/w) | 75 | 85 | 98 | 75 | 85 | 98 | 75 | 85 | 98 |
| Lactose (%w/w) | 23 | 13 | 00 | 23 | 13 | 00 | 23 | 13 | 00 |
| Mg. Stearate (%w/w) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Talc (%w/w) | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Total weight (mg) | 40 | 40 | 40 | 80 | 80 | 80 | 120 | 120 | 120 |

**Table IV: Different aspect ratios created at constant interval and release profile.**

| Time | Aspect Ratio 2 | Newly exposed area ($mm/cm^3$) | Total area ($mm/cm^3$) |
|---|---|---|---|
| 15 min. | 0.5 | 17.34 | 34.40 |
| 30 min. | 0.96 | 33.02 | 51.64 |
| 45 min. | 1.40 | 48.12 | 67.32 |
| 60 min. | 1.79 | 74.54 | 82.42 |
| 75 min. | 2.1 | 85.92 | 95.96 |
| 90 min. | 2.5 | 96.58 | 108.84 |
| 105 min. | 2.8 | 105.82 | 120.22 |
| 120 min. | 3 | 116.5 | 130.68 |
| 135 min. | 3.3. | 130.33 | 140.12 |
| 150 min. | 3.8 | 132.26 | 150.86 |
| 165 min. | 3.86 | 134.16 | 164.68 |
| 180 min. | 3.9 | 135.98 | 166.56 |
| 195 min. | 3.96 | 137.8 | 168.46 |
| 210 min. | 4.01 | 138.4 | 170.28 |
| 225 min. | 4.09 | 140.5 | 172.1 |
| 240 min. | 4.12 | 140.99 | 174.7 |

**In vitro dissolution testing**

The release of drug from matrix tablets was measured utilizing USP apparatus 2 (paddle method) at 37 ± 0.5 $^0$C using 900ml of dissolution medium at 50 rpm and distilled water as a dissolution medium. After predetermined time intervals, 5ml aliquot were taken out and replaced with same volume with same media, filtered through PVDF filter (0.45µm) and analyzed by using an ultraviolet spectrophotometer (Shimadzu UV-DEC1601) at 237 nm for DIZ. Each formulation was tested in triplicate and a mean of these measurements was reported.

**Texture analysis of SFG** [20, 21]

Texture analysis study of the swollen tablets of SFG was done by exposing the tablet in dissolution medium 900 ml at 37$^0$c (Distilled water) using USP 26 apparatus 2 (paddle) at 50 rpm. To avoid random sticking of tablets to dissolution jar, the tablet was stuck initially to a piece of glass slide (about1" × 1") with the help of a cynoacrylic adhesive. Once the treatment in jar start, tablets with the glass slide were removed from the dissolution jar after each hour and texture analysis was carried out. Texture analysis was performed using TA.2Xi texture analyzer equipped with 500gm load and texture expert software. The force-displacement vs. time profiles associated with

the penetration of cylindrical stainless steel probe of 2mm dia in to the swollen matrices were monitored at data acquisition rate of 250 points per second. Probe approached the sample at pretest speed of 2mm/s. Once a trigger force of 0.7gm was detected (at contact of probe with tablet) probe was advanced in to the sample at the test speed of 0.2mm/s until the maximum force at the glassy core boundary was reached.

**Kinetic treatment**

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first order, Higuchi equations. The above models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems Where, *Mt* is the amount of drug release at time *t*; *M* is the amount of drug release after infinite time; *k* is a release rate constant incorporating structural and

geometric characteristics of the tablet; and *n* is the diffusional exponent indicative of the mechanism of drug release.

## Results

**In vitro drug release studies from sterculia foetida gum matrix tablets:**

Out of three formulations prepared from hydrophilic wax material formulation SFGA (13% of lactose & 49% of SFG) showed 80% of drug release within 8hr. Formulation SFGB and SFGC (13% MCC & 49% SFG and 0% MCC & 62% SFG respectively) showed 70% and 60% of drug release within 8 hr.

**Texture analysis of sterculia foetida gum matrix tablets:**

TA of lactose containing formulation was performed scientifically according to procedure described in previous section. TA result showed the different penetration values against the gel resistance developed at different interval. The displacement values obtained after 1hr, 2hr, 3hr and 4hr would be of 1.960, 2.984, 1.106 and 0.570 respectively.

***In vitro* drug release from rice ban wax (RBW) hydrophobic matrix tablets.**

The formulation containing least quantity of wax (10%) and excess of lactose (52%) (PRBWA) showed complete release within 3hr. whereas the formulation containing least quantity of lactose (04%) and excess of wax (58%) (PRBWD) showed 80% of drug release within 10 hr. regarding intermediate concentration of wax (18% & 38%) and lactose (44% & 24%) containing formulations showed more than 80% of drug release within 5hrs & 8hrs respectively. Moreover the formulation containing higher concentration of wax (38%) & 24% of lactose (PRBWC) out of intermediate concentration containing formulations gave us 90% of drug release within 8hr.

***In vitro* drug release from layered matrix tablets (Rice bran wax + Sterculia foetida gum**

As discussed earlier intermediate concentrations containing formulation PRBWC coated on both faces with hydrophilic composition barriers with three different concentration levels of sterculia foetida gum i.e. 75%,85% and 98% and 40mg of barriers (RBWA, RBWB & RBWC respectively) showed 99.90%, 90.0% and 85.0% of drug release within 10hr respectively. However the formulations RBWD, RBWE and RBWF showed 100.0%, 95.0% and 90.0% drug release within 10hr, 11hr and 12hr respectively. The increase in amount of barriers with same extent of steculia foetida gum in formulation RBWG, RBWH and RBWI (120mg each) extend the release profile up to 12hr, 13hr and 14hr respectively. The formulation RBWC & RBWD and formulation RBWF & RBWG showed approximately same extent of release.

**Surface erosion and change in surface aspect ratio**

As earlier stated in the TA study sterculia foetida gum undergo swelling and erosion with hydrophilic excipient as time proceeds. The triple-layered formulation (RBWH) showed increase in newly exposed area and total tablet area as time proceeds and ultimately aspect ratio 2.

## Discussion

**In vitro drug release studies from sterculia foetida gum matrix tablets**

For the purpose of developing formulation with different release rates, which could be evaluated *invitro* with the aim of establishing IVIVC, the effect of different excipients on drug release was studied by preparing matrix tablets containing 49% & 62% of SFG by direct compression. The release profiles for these formulations are depicted in Fig III from the figures it was observed that the release rate was greatly influenced by the matrix concentration: a direct relationship was noted between the amount of gum in the formulation and release rate of DIZ. i.e. 62% gum, a decrease in release rate of the drug was obtained because of increase in gel disentanglement. By reducing the concentration of SFG, the release rate was enhanced while the tablet properties were maintained. Also by comparing the release profiles of lactose containing formulation and MCC containing formulation it was noted that, the lactose containing formulation gave enhanced release than formulation containing MCC. It was concluded from the dissolution data that the release constant of lactose and MCC were 9.90 mg/hr & 8.10 mg/hr respectively. This was because of soluble nature of lactose improving the water penetration in to polymer matrices which was comparatively less in case of MCC known to be having swellable nature. These findings indicating that as the level of polymer in the formula was increased, the drug released from tablet was decreased. By virtue of the fact that increasing the concentration of polymer in a matrix system generally increases polymer chain entanglement in gels, which in turn result in a more concentrated gel and provide more tortuous and resistant barrier to diffusion which results in slower

release of DIZ from these matrices. At low polymer level, the rate of advancement of the swelling front into glassy polymer and the attrition of the rubbery state polymer might have been nearly equal, resulting in more diffusion for the drug until the entire drug was released from the tablets. According to dissolution kinetic data obtained from the SFG-lactose, SFG-MCC & SFG containing formulations gave zero-order release kinetic ($r^2$ = 0.9999, $r^2$= 0.9992 & $r^2$= 0.9998 respectively) as shown in Table V. The release exponents *n* were 0.7699, 0.8501 and 0.7889 respectively.

An exponent value of 0.89 is indicative of case II transport or typical Zero-order release. By keeping view on these formulations according to regression coefficients and diffusion coefficients, which appeared to indicate a coupling of the diffusion and erosion mechanism is so called anomalous diffusion and might indicate the drug release controlled by more than one processes.

**Texture analysis of sterculia foetida gum matrix tablets:**

Results indicated that there was initial high probe displacement due to greater hydration rate as noted in readings 0 to1h. Fig IV shows initial sharp increase in displacement with decrease in displacement at latter hydration stage because of inclusion of water soluble excipients in to the formulation containing highly soluble drug. This might have been attributed to gradual swelling as well as erosion of tablet matrix over the time. Lactose is water soluble excipient and helps more water to penetrate in to polymer, creating excessive osmotic force and polymer chain relaxation. Therefore leading to a decrease in tortuosity and/or increase in the matrix porosity.

Sterculia foetida gum containing water-soluble excipients demonstrated good swelling and erosion properties as these excipients are certainly capable of altering water penetration and hence mechanism of drug release. The role of gel layer and its rate of growth are central and fundamental to define various fronts and understand the operating release mechanism. The texture analysis (TA) method used for studying the dynamics of front movements offers new opportunities to understand the nature of the solute transport better in these systems when excipients of different solubilities are used. In case of lactose containing formulation the initial increase in probe displacement value (1hr=1.960mm & 2hr=2.984mm) indicated the soluble nature of lactose assisting to increase the hydration rate of polymer. As the time progressed, decrease in probe displacement value (3hr=1.106mm & 4hr=0.570mm) indicated the erosion mechanism favored at latter stage. The TA would provide additional operational tool to formulation scientists, allowing them to select optimal and easy to adapt methodology for dosage form development and assessment. Moreover introduction of sterculia foetida gum as a novel natural hydrophilic polymer in controlled release formulations and various interpretations presented might be useful for the pharmaceutical scientists who are busy with designing of hydrophilic matrix systems.

The aim of this study was to scrutinize the release profile of DIZ by inclusion of water soluble excipients in SFG matrix. The information generated would assist in further work when SFG would be used as barrier through which the DIZ would be expected to diffuse.

***In vitro* drug release from rice ban wax (RBW) hydrophobic matrix tablets.**

Developing formulation with different release rates, which could be evaluated *invitro* with the aim of establishing IVIVC. The effect of polymer level on drug release was studied by preparing waxy matrix tablets containing 10-58% of lactose by direct compression. The release profiles for these formulations are depicted in Fig V. It was observed that the release rate was greatly influenced by the matrix concentration. The direct relation between the amount of wax in the formulation and release rate of DIZ e.g. in case of 58 % wax, slowest release of the drug was obtained. By reducing the concentration of RBW, the release rate was enhanced while the tablet properties were maintained. These findings indicated that as the level of wax in the formula was increased, the drug release rate from tablet was decreased. This occurred because increasing the concentration of wax in a matrix system generally decreases erosion rate of wax, which in turn results in a more resistant barrier to diffusion, which results in decreased release of DIZ from these matrices. These experiments suggested that formulations with reasonably wide spread dissolution profiles might be obtained by varying the polymer level from 10 to 58 %. Also by comparing the release profile of formulations containing varying concentrations of lactose showed that the 24% lactose containing formulation gave improved release rate than formulation contain 04% of lactose, and it was concluded from the *invitro* dissolution data that the best fitted model for RBW A, RBW B, RBW C and RBW D formulations was First-order ($r^2$= 0.9993, $r^2$= 0.9932, $r^2$= 0.9998 and $r^2$= 0.9999 respectively) as shown in Table VI

For the preparation of multilayered tablets rice bran wax core containing 24% of lactose were selected (RBW C) as it gave > 90% of drug release with first-order release kinetics in 8hrs.
Rice bran wax matrix tablets gave first-order release profile (RBW C).This was required to be modified in to zero-order release in multilayered matrix tablet by selection of appropriate ratio of SFG & lactose. A suitable composition of hydrophilic layer could be developed containing 85% of SFG & 13% of lactose (batch RBW H) satisfying this requirement.

***In vitro* drug release from layered matrix tablets (Rice bran wax + Steculia foetida gum)**
In this system, the hydrophobic matrix tablet containing drug was laminated with swellable and erodible barrier on both the faces. Total drug release involves continuous diffusion from the lateral tablet surface as well as delayed diffusion from both the faces of tablets with changing surface area, diffusional path length and diffusion co-efficient as the

hydrophilic barrier layer hydrates, swells and erodes.
Fig VI, VII and VIII showed the *invitro* release profiles of three-layered matrices in this study. A zero-order release model (Table VII) empirically fits the data obtained from all nine formulations. The zero-order release could be qualitatively explained by assuming that the decreasing release rate from the lateral surface of the middle hydrophobic layer was balanced by delayed diffusion through the two laminated faces as a result of increasing polymer hydration/erosion of the hydrophilic polymer over the time. This was confirmed by the Peppa's exponent values ($n$) > 0.9 with regression coefficient $r^2$ close to 1 (Table VII). Functional modeling of this phenomenon is difficult because the release rate from the two laminated faces is dependent on several variable properties of the hydrophilic barrier layer, e.g. polymer concentration and amount (thickness) of the layer. These factors and their complex interplay determine the rate of both radial and axial hydration/swelling/erosion which in term affects the rate of additional release surface available, changing both the diffusional path length and the diffusion co-efficient over the time. This gained clarity through the studies on tablet aspect ratio and swelling-erosion (Table IV). When the barrier layer goes on increasing from 40mg in formulations like RBWA, RBWB and RBW C to 80mg in formulations RBWD, RBWE and RBWF to formulations RBWG, RBWH and RBWI, the release profile was get delayed from 9hr to 14hr. Release profile was extended because of increase in polymer tortuosity resulting in to increase in gelled path length and ultimately the more time required to the drug to diffuse out.

**Correlation between surface erosion and change in surface aspect ratio (aspect ratio 2)**
The triple layered tablets used in this study contained middle hydrophobic layer of rice bran wax and top and bottom layer of hydrophilic sterculia foetida gum. The aim of this study was to understand the surface erosion of top and bottom layer in triple-layer tablets to achieve the sustained release with zero-order. Table IV shows aspect ratios 2 made available at various time points during dissolution. To calculate the proposed second aspect ratio, it was necessary to consider areas of both the aspects of tablet i.e. cylindrical surface or sides and circular portion and face of the tablet. The change in diameter of circular portion (axial or top view) of the tablet and change in height of the cylindrical portion (radial or side view) of the tablet were measured with the help of a linear scale placed close to the portion of the tablet and measurement being finalized and confirmed by using grooming scale of the Picasa software. The study indicated that the erosion of sterculia foetida gum was facilitated in horizontal centric direction.
Fig. IX indicates steady rise in newly exposed area. The linear nature of the profile goes hand in hand with the dissolution profile of the tablets of the same batch (batch RBW H). This part of study supports existence of good correlation between the erosion of the hydrophilic layer and development of linearity in the release profile.
It could be concluded from this study that hydrophilic polymer press-coated on top and bottom of the core layer control the drug release from core layer by swelling and erosion mechanism by exposing different area of the core layer tablet. The application of the top and bottom layers on such tablet overcome the initial burst release and overall release profile got extended to more than 12hr. with improved linearity leading to zero order release kinetic.

**Statistical analysis**
**Required zero-order release rate constant for diltiazem hydrochloride formulation**
Calculations of required zero-order release rate would guide to work for better achievement of goals. As it was evident from the results of *in vitro* dissolution studies that Zero order release profile could be achieved with the laminated matrix tablet batches, it was decided to calculate a required zero order release rate constant for diltiazem hydrochloride formulation

to maintain therapeutically effective levels of drug in the circulation. Diltiazem hydrochloride daily dose for different conditions generally vary between 30-90 mg. The dose per tablet chosen in the present work was 90 mg. The required zero order release rate constant for 90 mg preparation was calculated based on the following equation.

$$\mathbf{K_{ro} = C_p V_d K_e}$$

Where $K_{ro}$ is the required zero order release rate constant, $K_e$ is the elimination rate constant, $V_d$ is volume of distribution, $C_p$ is effective plasma concentration to be maintained. The required zero-order release rate constant based on the mean pharmacokinetic parameters of the drug in humans, was found to be 7.5 mg/hr. Therefore, an ideal controlled release dosage form should release 90mg of the drug at constant rate, 7.5 mg/hr, during a predetermined 12 hours period. However, as the original aim of this work did not involve development of formulation with any particular release kinetic in mind, it was left to compare the zero order release rate constant of the developed formulations and determine whether any formulation met the criteria. Upon matching it was found that the batch RBW H showed the zero order release rate constant of 7.6 mg/hr which were near to the ideal value. Moreover, batch RBW H also showed $r^2$ values of 0.9999 & in the zero order kinetic treatment and the exponent *n* calculated from

Peppas treatment showed proximity to the value 1 (RBW H, n=0.9998 designated for zero order release. Hence, batch RBW H might be ranked as the best one among the other batches of diltiazem hydrochloride laminated matrix tablets prepared, as far as zero order release rate was concerned.

**Table V: In vitro dissolution Kinetics of DIZ HCl from sterculia foetida gum matrix formulations.**

| Formulations | Zero-order | First-order | Higuchi | Peppas | Peppas Diffusion exponent n | Peppas Kinetic Constant K |
|---|---|---|---|---|---|---|
| | $K_z$ ($r^2$) | $K_f$ ($r^2$) | $K_h$ ($r^2$) | $K_p$ ($r^2$) | | |
| **Lactose** | 9.90 (0.9999) | 0.1 (0.9245) | 26.17 (0.9816) | 18.13 (0.9988) | 0.7699 | 13.91 |
| **MCC** | 8.10 (0.9992) | 0.15 (0.9692) | 22.57 (0.9828) | 13.95 (0.9984) | 0.8501 | 9.95 |
| **Plain Polymer** | 7.51 (0.9998) | 0.1 (0.9845) | 18.64 (0.9016) | 9.90 (0.9995) | 0.7889 | 9.85 |

**Note:** Zero-order release rate constant ($K_z$), First-order release rate constant ($K_f$), Higuchi release rate constant ($K_p$), and $r^2$ is respective regression coefficient.

**Table VI: In vitro dissolution Kinetics of diltiazem hydrochloride from Rice bran wax matrix formulations.**

| Formulations | Zeroorder $K_z$ ($r^2$) | First-order $K_f$ ($r^2$) | Higuchi $K_h$ ($r^2$) | Peppas $K_p$ ($r^2$) | *Peppas Diffusion exponent n* | *Peppas Kinetic Constant* K |
|---|---|---|---|---|---|---|
| **RBWI** | 7.10 (0.9999) | 0.18 (0.9012) | 21.64 (0.9869) | 7.4 (0.9995) | 0.9370 | 17.40 |
| **RBWH** | 7.6 (0.9999) | 0.27 (0.9005) | 22.54 (0.9751) | 7.53 (0.9996) | 0.9998 | 7.53 |
| **RBWG** | 8.01 (0.9999) | 0.38 (0.9040) | 23.83 (0.9849) | 7.92 (0.9996) | 0.9746 | 9.22 |
| **RBWF** | 8.55 (0.9999) | 0.47 (0.8781) | 24.01 (0.9759) | 8.11 (0.9998) | 0.9746 | 9.22 |
| **RBWE** | 9.22 (0.9999) | 0.37 (0.8504) | 24.63 (0.9821) | 8.66 (0.9998) | 0.9746 | 9.22 |
| **RBWD** | 9.25 (0.9999) | 0.28 (0.8434) | 24.59 (0.9859) | 8.69 (0.9996) | 0.9996 | 8.97 |
| **RBWC** | 9.26 (0.9999) | 0.19 (0.8928) | 24.62 (0.9852) | 8.89 (0.9996) | 0.9996 | 8.97 |
| **RBWB** | 9.43 (0.9999) | 0.20 (0.8689) | 24.35 (0.9780) | 9.33 (0.9959) | 0.9898 | 8.54 |
| **RBWA** | 10.65 (0.9999) | 0.23 (0.8491) | 26.32 (0.9790) | 11.52 (0.9937) | 0.9951 | 9.33 |

**Note:** Zero-order release rate constant ($K_z$), First-order release rate constant ($K_f$), Higuchi release rate Constant ($K_p$), and $r^2$ is respective regression coefficient.

**Table VII: In vitro dissolution kinetics of diltiazem hydrochloride three-layered matrix tablets**

| Formulations | Zero-order $K_z$ ($r^2$) | First-order $K_f$ ($r^2$) | Higuchi $K_h$ ($r^2$) | Peppas $K_p$ ($r^2$) | *Peppas Diffusion exponent n* | *Peppas Kinetic Constant* K |
|---|---|---|---|---|---|---|
| PRBW A | 11.20 (0.9955) | 0.2 (0.9993) | 30.25 (0.9939) | 30.11 (0.9911) | 0.4994 | 29.68 |
| PRBW B | 15.28 (0.9914) | 0.4 (0.9632) | 37.90 (0.9927) | 53.25 (0.9884) | 0.28 | 52.25 |
| PRBW C | 28.82 (0.9349) | 0.3 (0.9998) | 51.89 (0.9863) | 40.55 (0.9996) | 0.7 | 74.47 |
| PRBW D | 42.17 (0.9626) | 0.6 (0.9999) | 60.15 (0.9993) | 42.05 (0.9636) | 0.75 | 89.34 |

**Note:** Zero-order release rate constant ($K_z$), First-order release rate constant ($K_f$), Higuchi release rate constant ($K_p$), and $r^2$ is respective regression coefficient.

**Fig. 3 Mean (± S. D.) Percent of Diltiazem hydrochloride released from hydrophilic composition (n=3) containing 49% (with lactose), 49 (with MCC) % and 62 (without lactose and MCC) % of sterculia foetida gum in the dissolution study.**

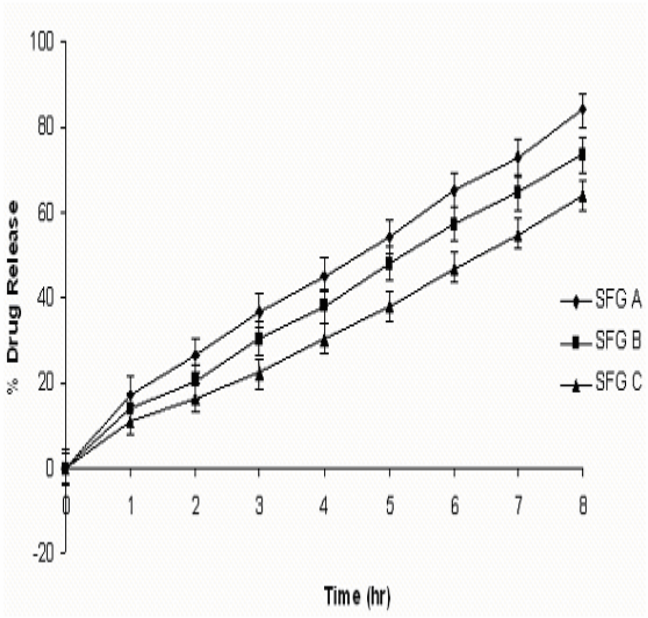


**Fig. 4 Texture profile showing probe displacement resistance for tablet containing sterculia foetida gum with lactose**

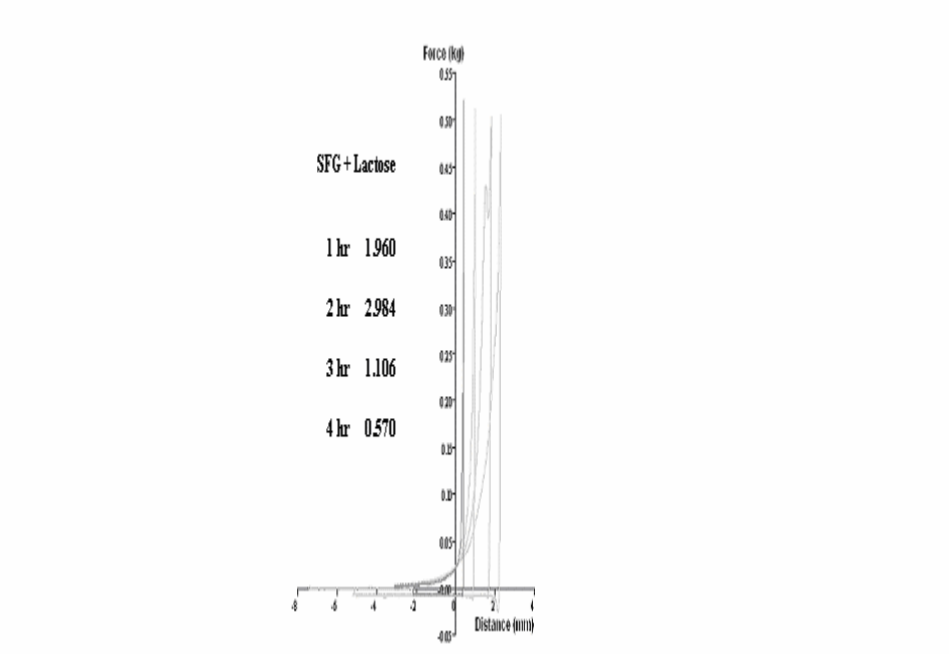



**Fig. 5 Mean (± S. D.) Percent of Diltiazem hydrochloride released from hydrophobic composition (n=3) containing 10%(PRBW A), 18% (PRBW B), 38% (PRBW C) and 58% (PRBW D) of rice bran wax in the dissolution study.**

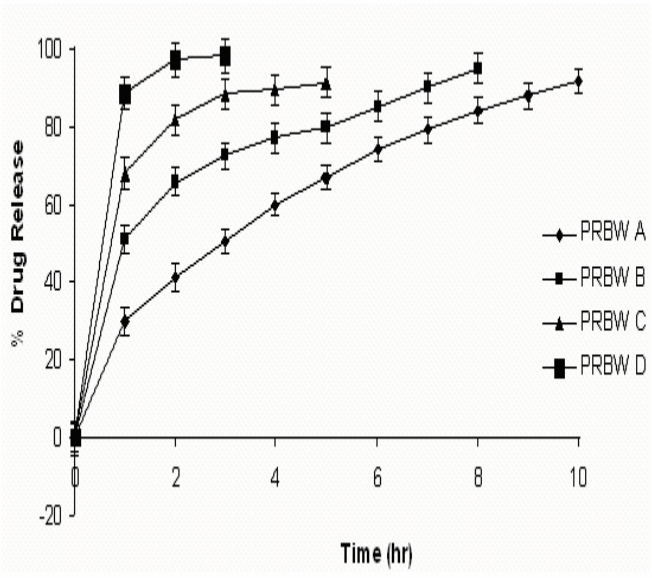


**Fig. 6 Mean (± S. D.) percent of Diltiazem hydrochloride released from three layer matrix tablets (n=3) containing 40 mg of hydrophilic composition as a release retardant layer on either side of core containing 75% (RBW A), 85% (RBW B) and 98% (RBW C) of sterculia foetida gum in the dissolution study.**

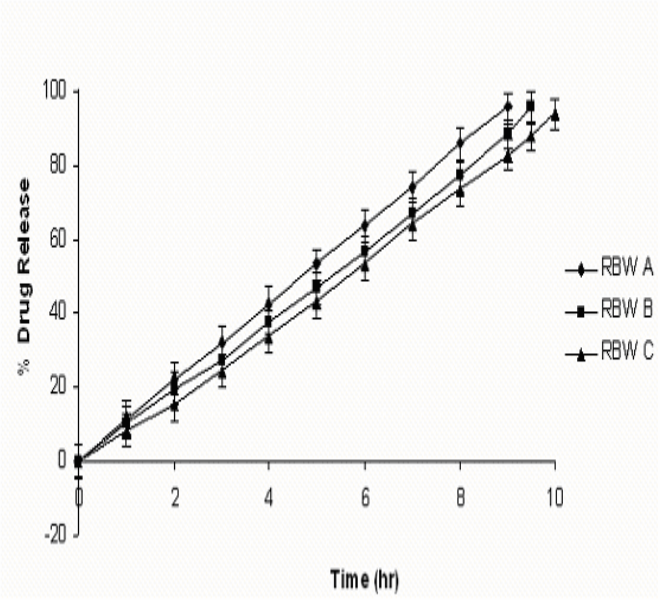



**Fig. 7 Mean (± S. D.) percent of Diltiazem hydrochloride released from three layer matrix tablets (n=3) containing 80 mg of hydrophilic composition as a release retardant layer on either side of core containing 75% (RBW D), 85% (RBW E) and 98% (RBW F) of strculia foetida gum in the dissolution study.**

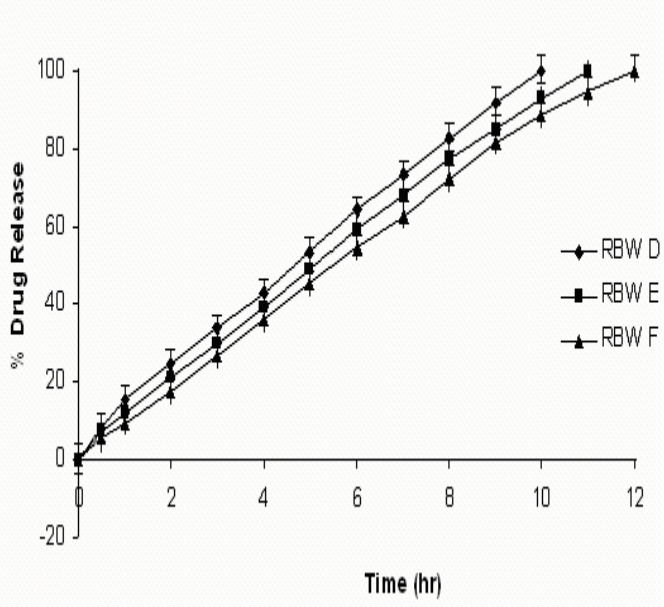


**Fig. 8 Mean (± S. D.) percent of Diltiazem hydrochloride released from three layer matrix tablets (n=3) containing 120 mg of hydrophilic composition as a release retardant layer on either side of core containing 75% (RBW A), 85% (RBW B) and 98% (RBW C) of sterculia foetida gum in the dissolution study.**

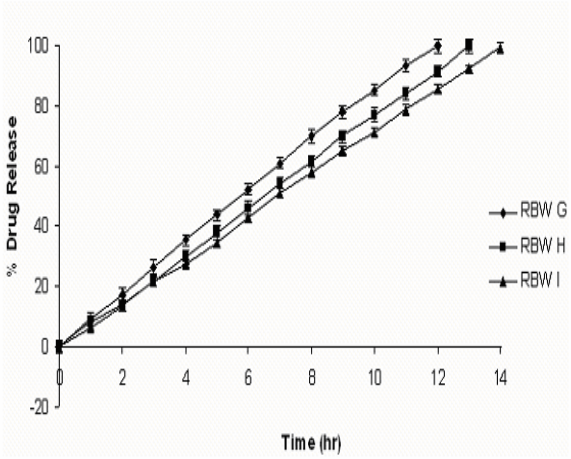
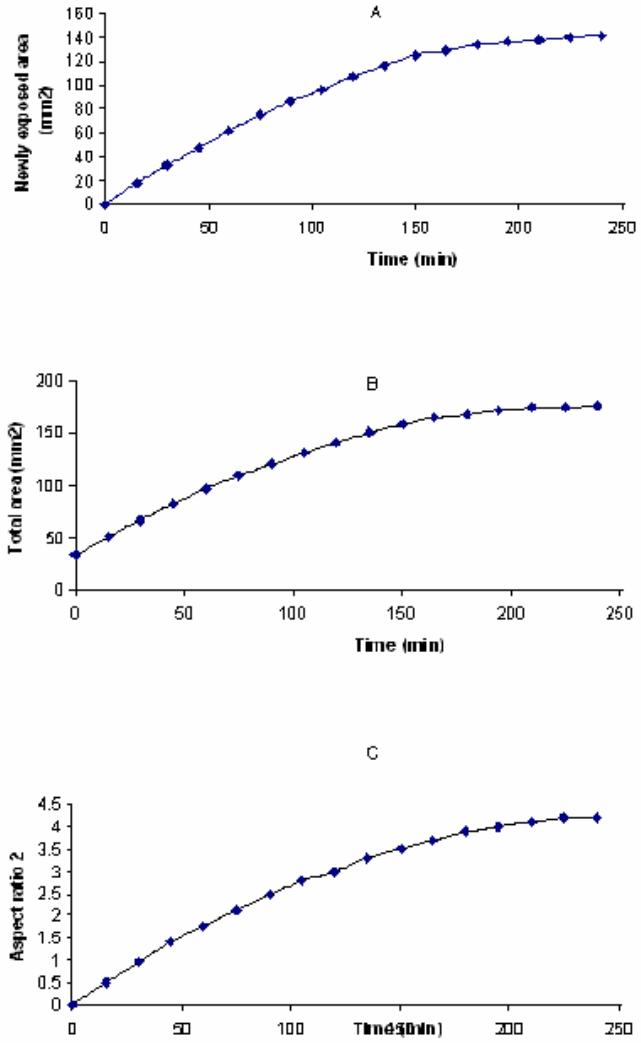



**Fig. 9 Profile of exposed surface area of drug loaded core in three layered tablet (batch RBW H).**



## Conclusion

It was possible to successfully formulate oral modified release tablets of Diltiazem Hydrochloride lasting for more than 12 hours.

Based on the results obtained, it can be concluded that the formulation (RBW G, RBW H and RBW I containing 120mg of 75%, 85% and 98% of Sterculia foetida gum respectively as hydrophilic barrier layer and 250 mg of Rice bran wax as hydrophobic layer, compressed to produce three layered tablets of Diltiazem Hydrochloride with the hardness of 6 $kg/cm^2$, gave a significant drug release for 12, 13 and 14 hour respectively which was close to zero order.

It was concluded that first-order release profile obtained from Rice bran wax matrix tablets (core), required the ratio of SFG: lactose (75:23%, 85:13%, 98:00%) for suitably converting the respective nonlinear profiles in to linear release profile more than 12 hr.

The new concept of real time texture probing or texture analysis (TA) was utilized to understand the swelling and erosion front movements of sterculia foetida gum matrices. The TA information could be well linked with other behaviors including dissolution. The newly exposed surface area, total area and aspect ratio 2 opened a new window on how drug would be released from three layered tablets with respect to surface erosion of top and bottom layer as the time proceed.

Novel recommendations have been given in the selection of polymers. RBW have been successfully utilized for middle hydrophobic layer in association with a natural gum i.e. SFG for erodible upper and lower layer in the three layered tablet construction.

The three layered designs recommended might be applicable to other soluble drugs. The whole work of getting an insight and development of multilayered solid units to modify the release profile in favor of a formulator would be of immense use for the therapeutic molecules having diverse physico-chemical properties.

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