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# Evaluation of *Luffa Aegyptica Mill* Powder: A Novel Superdisintegrant in Delayed Release Tablets

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## Abstract

The current research in the field of drug delivery by which pulsatile release can be achieved has been intensified. The objective of the present study was to evaluate *Luffa aegyptica mill* powder as a novel superdisintegrant in the development of pulsatile drug delivery system (PDDS). The basic design of the device consisted of a rapid release tablet core and a controlled release coat. The rapid release tablet core contained a model drug (Diclofenac sodium) and *Luffa aegyptica mill* powder and controlled release effect was achieved with a combination of coating material (PVP K-30 & HPMC K4M). A $3^2$ full factorial design was employed for the optimization of developed formulation. The developed formulations showed uniform appearance, average weight, drug content and adequate hardness. The increase in lag time was observed with an increase in HPMC concentration and decreased concentration of a superdisintegrant. Further comparison of *Luffa aegyptica mill* powder in the concentration suggested in the optimized formulation with pharmaceutically acceptable superdisintegrant in same concentration showed equivalent drug release behavior. It can be concluded from the outcome of the present research that *Luffa aegyptica mill* powder, a natural superdisintegrant, can prove to be best alternative to the existing superdisintegrants.

**Keywords:** *Luffa aegyptica mill*; Pulsatile drug delivery system (PDDS); Press Coated Pulsatile Tablet (PCPT); Lag time; Rheumatoid arthritis

## Introduction

PDDS is such system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of a particular disease states. Very negligible amount of drug or no drug is permitted to be released from the device during the lag time. This method is good for the drugs that undergoes extensive first pass metabolism and even for targeted release of the drugs [1-8]. Compression coating is a technique that does not require any solvents or special equipment's for coating of the dosage form and hence coating can be done faster and even avoiding environmental hazards. In this technique a previously compressed core tablet is further coated using different polymeric barriers by multiple compressions. This system delivers the drug from the core tablet after swelling/erosion of the hydrophilic or hydrophobic barrier of the coating shell and may exhibit a pulsatile release of the drug [9-14].

Despite the increasing demand and interest in controlled release system, a significant portion of solid dosage forms require fast disintegration and immediate dissolution after administration. For years this requirement has been met using superdisintegrant. Superdisintegrant are another version of super absorbing materials with tailor-made swelling properties. These materials are not intended to absorb significant amounts of water or aqueous fluids, but intended to swell faster. They are dispersed physically within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. Swelling pressure and isotropic swelling of the particles create stress concentrated areas where a gradient of mechanical properties will exist. In fact, a mild explosion occurs at the stress-concentrated area by which the whole structure will break apart [15].

Natural materials have been gaining lot of interest in the field of drug delivery because they are readily available, cost effective, eco-friendly, capable of multitude of chemical modifications, potentially degradable and compatible due to their natural origin. *Luffa aegyptica mill* belongs to the family *Cucurbitaceae*. Its origin can be traced to tropical Asia [16]. It is climbing annual wild vine with lobed *cucumber* like leaves that are dark green in color with rough surface. The plants with yellow flowers bear fruits that are cucumber shaped but longer in size and contain fibrous sponge in which the hard black seeds are enmeshed. It is lignocellulosic materials composed of 60% cellulose, 30% hemicelluloses and 10% lignin [17]. *Alebiowu* [18] prepared a powder from the natural sponge *Luffa aegyptica mill* and studied its disintegrant activity with corn starch as the standard. The main objective of the present study was to develop, evaluate and optimize the oral PDDS where lag time will be achieved using coating with PVP-K30 & HPMC while immediate burst after lag time will be due to natural superdisintegrant obtained from *Luffa aegyptica mill.*

## Materials and Methods

The fruits of *Luffa aegyptica mill* were collected from local area of Chandwad, Maharashtra, India. Diclofenac sodium was donated by Navketan Pharma Pvt Ltd, India. Anhydrous lactose and pregelatinised starch were obtained as gift sample from Emcure Pharma Pvt Ltd, India. Crosspovidone, Sodium Starch Glycolate and Crosscarmellose sodium were gifted by FMC Biopolymer and Signet Chemical Corporation, India and Magnesium stearate and purified talc were purchased from Loba chemie Pvt Ltd, India. The Polyvinyl pyrrolidone was ex gratis from BASF, India and HPMC from Colorcon Asia Pvt Ltd, India. All other ingredients and reagents were of analytical grade and were used as received.

### Isolation and physicochemical characterization of *Luffa aegyptica mill*

The fresh fruits of *Luffa aegyptica mill* were collected and washed with water to remove the dirt, and dust. The epicarp of fruits was scraped by using scraper and sponge of fruits was isolated. The isolated sponge was shade dried at ambient temperature till its color changed from green to light brown. After shade drying it was dried in a hot air oven at 50 °C, powdered and passed through a sieve no.80 and stored in the desiccator for further use [18]. Dried powder was then tested for loss on dying, swelling index and flow properties like bulk density, tapped density, compressibility index, angle of repose and Hausner's ratio as per procedure explained in Pharmacopeias and literature [19-22].

### Formulation of Compression Coated Pulsatile Tablet

**Formulation of core tablet of Diclofenac sodium:** The core tablets were prepared by direct compression. Diclofenac sodium was chosen as a model drug as it is used in the treatment of rheumatoid arthritis, a disease that follows circadian rhythm. Initially tablet excipients were blended for 20 min in a polybag followed by the addition of magnesium stearate (0.8 %w/w) and purified talc (0.8 %w/w). The powder mixture was then blended for 5 min. Core tablets weighing 100 mg were compressed using 6mm punch on a rotary tablet machine (Rimek, Karnavati Eng Ltd., India).

**Preparation of Polymer Blends and compression coating of prepared core tablet:** PVP K-30/HPMC polymer blends were prepared using the solvent evaporation method. PVP K- 30 was dissolved in distilled water (5 %w/w), while HPMC (2 %w/w) was immersed in water to swell while complete dissolution was achieved with gentle heating at 60 °C. The two solutions were mixed at different amounts under sonication. Blends with concentrations 50/50, 60/40 and 70/30 were prepared and solvent was allowed to evaporate at room temperature to obtain dry material as a cake. For the complete drying of the blends, the cake was heated in an oven for 24 h at 80 °C [23-24]. The core tablets were then compression coated with different weight ratios of PVP K-30 and HPMC polymer mixture. Half of the polymer blend from actual amount required for coating was weighed and transferred in to 10mm die of a rotary tablet machine. Next, the core tablet (100 mg) was placed at the center on the polymer bed and remaining half of polymer blend was added in to the die and compressed using a rotary tablet machine.

### Experimental Design

A number of preliminary experiments were conducted to determine the formulation parameters that affect the physicochemical properties of compression coated pulsatile tablet. Design expert software® (trial version 8.0.1; State-Ease Inc., Minneapolis, MN, USA) was used for optimization of the formulation. A $3^2$ full factorial design was employed, where, the amount of superdisintegrant in the core tablet ($X_1$, %w/w of core tablet) and coating material ratio i.e. PVP/HPMC ($X_2$, %w/w of coating) were selected as the independent variables while lag time ($Y_1$, minutes) and the amount of the drug released in 450 minutes ($Y_2$, percent) were chosen as the dependent variables [25]. Table 1 summarizes these factors with corresponding levels and the responses studied whereas experimental formulations based on factorial designs are depicted in Table 2.

### Physiochemical Characterization of Core and Compression Coated Tablet

The core and compression coated tablets were evaluated for various tablet formulation parameters like hardness, friability, weight uniformity, disintegration and drug content. The hardness of tablets (n=6) were determined using Tablet strength tester (Monsanto, 13-1). The friability (%) of the tablets was determined using a USP-I friabilator (EF 1W; Electrolab), and weight uniformity of tablet was done as per pharmacopeial guidelines. Disintegration time of the core tablet was determined using a disintegration tester (ED-2L; Electrolab) and drug content of the tablet was assayed in triplicate using validated method employing UV-Spectrophotometer (Jasco, V-630) [22].

| Factors (Independent variables) | Levels | | | Responses (Dependent variables) |
|---|---|---|---|---|
| | (-1) | (0) | (+1) | |
| Amount of superdisintegrant (%) | 10 | 12 | 14 | $Y_1$ (Lag time of 360 minutes) |
| Ratio of coating material i.e. PVP/HPMC blend | (70:30) | (60:40) | (50:50) | $Y_2$ (Drug release in 450 minutes) |

**Table 1:** Experimental Design (factor selected and responses measured)

| Ingredients (mg/tab) | C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 |
|---|---|---|---|---|---|---|---|---|---|
| Diclofenac sodium | 50 | 5 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Pregelatinised starch | 19 | 1 | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| Anhydrous lactose | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| *Luffa aegyptica mill* powder (%w/w) | 10 | 1 | 10 | 12 | 12 | 12 | 14 | 14 | 14 |
| Magnesium stearate | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Talc | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Coating (%w/w) | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |
| Total wt. (mg/tab) | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

**Table 2:** Formulation table for Diclofenac sodium compression coated tablet

### *In Vitro* Drug Release Study

The dissolution studies were performed with the help of USP apparatus II (Electrolab, Mumbai, India, model TDT-08L) and stirring rate was set at 100rpm. Initially dissolution medium was 900 ml of 0.1N HCL maintained at 37 ± 0.5 °C for 2 hours which was then replaced by 900 ml of phosphate buffer pH 6.8. At appropriate time intervals sample were withdrawn from dissolution vessel and analyzed using UV Spectrophotometer (Jasco, V-630, Japan) at 276 nm [22]. An equal volume of fresh prewarmed dissolution medium was added after withdrawing each sample to maintain the sink condition. The amount of drug released was then determined with the help of calibration curve and the cumulative percentage of drug released was calculated.

### Optimization of the Formulation and Comparative Studies

The dissolution data obtained for experimental batches prepared as per $3^2$ factorial design was put up to the software and giving the desired objective formulations were screened. Optimized formulation as suggested by Design Expert® software was then formulated and its efficiency was compared with the formulation developed using equivalent concentration of pharmaceutically accepted superdisintegrant like sodium starch glycolate (SSG), crosscarmellose sodium and crosspovidone [26].

### Stability Study

The stability of optimized formulations was carried out according to ICH guidelines. The formulations were stored at accelerated (40 ± 2 °C /75 ± 5% RH) test conditions in stability chamber (Remi, CHM-6S) for three month. At the end of each month, tablets were tested for drug content and percent drug released [27].

## Results and Discussion

The objective of the present work was to evaluate natural superdisintegrant in the development of PDDS. The pulsatile system described herein consists of two different components, the central rapid release core tablet made up of drug, superdisintegrant and other directly compressible excipients and external barrier layer consisting of PVP K30 and HPMC K4M. Central core consists of natural superdisintegrant, intended to give burst release of drug once lag time is over. The PDDS was developed using compression coating technique which is one of the simplest coating methods and has been applied for many drugs to develop the site and/or time controlled release preparation. This technique has many advantages such as short processing time and limited steps, no use of solvents, low labor and energy requirement.

### Characterization of Novel Superdisintegrant Powder

Novel superdisintegrant powder was initially characterized for various preformulation properties such as loss on drying, swelling index, flow properties, compressibility index and Hausner's ratio. From the results of physicochemical characterization study (Table 3) it is cleared that the dried powder has a good flow properties and swelling index, which is a sign to indicate the suitability of the said material as a superdisintegrant as well as for a direct compression [19-22].

| Parameters | Results |
|---|---|
| Loss on drying (%) | 0.1122±0.01004 |
| Swelling index (ml) | 2.66±0.2886 |
| Bulk density (g/ml) | 0.5503±0.00866 |
| Tapped density (g/ml) | 0.6455±0.02080 |
| Compressibility index (%) | 14.43±1.8840 |
| Hausner's ratio | 1.17±0.0264 |
| Angle of repose (˚) | 36.13±0.2020 |

Note: Mean of 6 ± SD

**Table 3:** Physical characteristics of natural superdisintegrant powder

## Formulation and Evaluation of Pulsatile Compression Coated Tablet

Tablets were evaluated for hardness, disintegration, friability, drug content and uniformity of weight. The core tablet and different batches of compression coated formulation exhibited optimum hardness and friability of less than 1.0% (Table 4). The disintegration time for the core tablets was found to be less than one minutes. Rapid disintegration is desirable to get a rapid release after the completion of the desired lag time. The core tablet was formulated in such a way that it should release more than 90% drug within 90 minutes after making contact with the dissolution medium. The PVP/HPMC blend was selected as a coating material to maintain lag time of about 6 hours.

| Batch | Weight variation[a] (mg) | Hardness[b] (Kg/cm$^2$) | Friability[c] (%) | Drug content[d] (%) |
|---|---|---|---|---|
| **C1** | 40 | 3.33±0.48 | 0.76±0.12 | 99.9±0.91 |
| **C2** | 40 | 3.58±0.52 | 0.55±0.21 | 99.9±0.75 |
| **C3** | 40 | 3.83±0.12 | 0.64±0.18 | 99.4±0.48 |
| **C4** | 40 | 3.83±0.21 | 0.35±0.05 | 99.1±0.68 |
| **C5** | 40 | 3.91±0.38 | 0.43±0.17 | 98.9±0.63 |
| **C6** | 40 | 3.91±0.19 | 0.56±0.21 | 98.5±0.59 |
| **C7** | 40 | 4.00±0.31 | 0.45±0.11 | 98.7±0.42 |
| **C8** | 40 | 3.75±0.20 | 0.57±0.18 | 98.5±0.82 |
| **C9** | 40 | 3.85±0.32 | 0.51±0.09 | 98.8±0.75 |

**(Notes: [a]Test performed on 20 tablets; [b]Mean of 6±SD; [c]Test performed on number of tablet weighing not less than 4 gm; [d]Mean of 3±SD.)**

**Table 4:** Physicochemical characterization of C1-C9 batches

## *In vitro* drug release study

The combination of PVP K-30 and HPMC K4M is commonly used for preparation of press coated tablets for the adjustment of the drug release time. The coating layer was composed of PVP/HPMC blends at different compositions, acting as a stimulus responsible layer. PVP is a water-soluble tertiary amide and a strong Lewis Base and HPMC is a barely water-soluble polymer carrier with the ability to swell on contact with aqueous solutions, creating a hydrocolloid gel mass on the external surface. This mass gradually dissolves during time. Therefore, from such a system, the release of the active ingredient is expected to be controlled by the dissolution rate of the polymer gel. Main disadvantage of pulsatile release formulation is that they require a long residence time in the gastrointestinal track. One of the basic mechanisms to extend this time period is the use of bioadhesive polymers. HPMC K4M is well known as one of the most effective mucoadhesive polymers and hence was chosen for combining with PVP K-30 [23,24]. These blends were found miscible in the entire composition range, ensured by the interactions taking place between hydroxyl groups of HPMC and carbonyl groups of PVP. The miscibility of the system enhances the mucoadhesive properties of the blend, compared with those of pure HPMC, which is desired for such applications. The enhancement was attributed to the higher rate of wetting and flexibility of the new matrices due to the faster dissolution of the PVP macromolecules.

The *in vitro* drug release study carried out using USP dissolution apparatus II shows that less or no percent drug released observed during first 2 h, which could be attributed to the low solubility of drug in the acidic milieu as well as integrity of the PVP/HPMC coating, which does not allow the diffusion of drug (Figure 1). Upon exposure of the press coated tablets to the dissolution medium it was observed that the coating layer disintegrates first, followed by the immediate release of drug from the active core [23,24]. *In vitro* drug release study reveals that, as the proportion of novel superdisintegrant in tablet increased from 10 to 14 %w/w, there was a remarkable change in the release rate of the drug from the developed formulation. It was observed that when coating barrier comes in contact with dissolution media it gradually erode up to a limited thickness. After that rupture of the shell is observed under the pressure applied by the swelling of the tablet core. Rupture always develop on the sides of the tablet as the initial thickness of the coating layer in these points is lower than on the top and bottom surface of the tablet. After the lag time, rapid release of the drug takes place within 90 minute due to the burst effect given by the superdisintegrant. Result also revealed that as the amount of HPMC increases, lag time also increases. A direct relation was found from optimization study between amount of *Luffa aegyptica* in core tablet and amount of HPMC in controlled release layer with the *in vitro* lag time (Figure 2, 3) [18,23,24].

The responses observed for $Y_1$ (Lag time, minutes) and for $Y_2$ (Cumulative percentage drug release in 450 minutes) for all the nine experimental runs have been depicted in Table 5. On feeding this data into design expert software® and suggesting the required criteria, one desirable solution was obtained. The optimized batch (Table 6) suggested by design expert software® contained 12.30 %w/w of superdisintegrant and 62.50:37.50 of PVP K-30 and HPMC K4M ratio of coating materials will exhibit lag time of 6 hours and more than 90% drug release within 450 minutes after lag time.

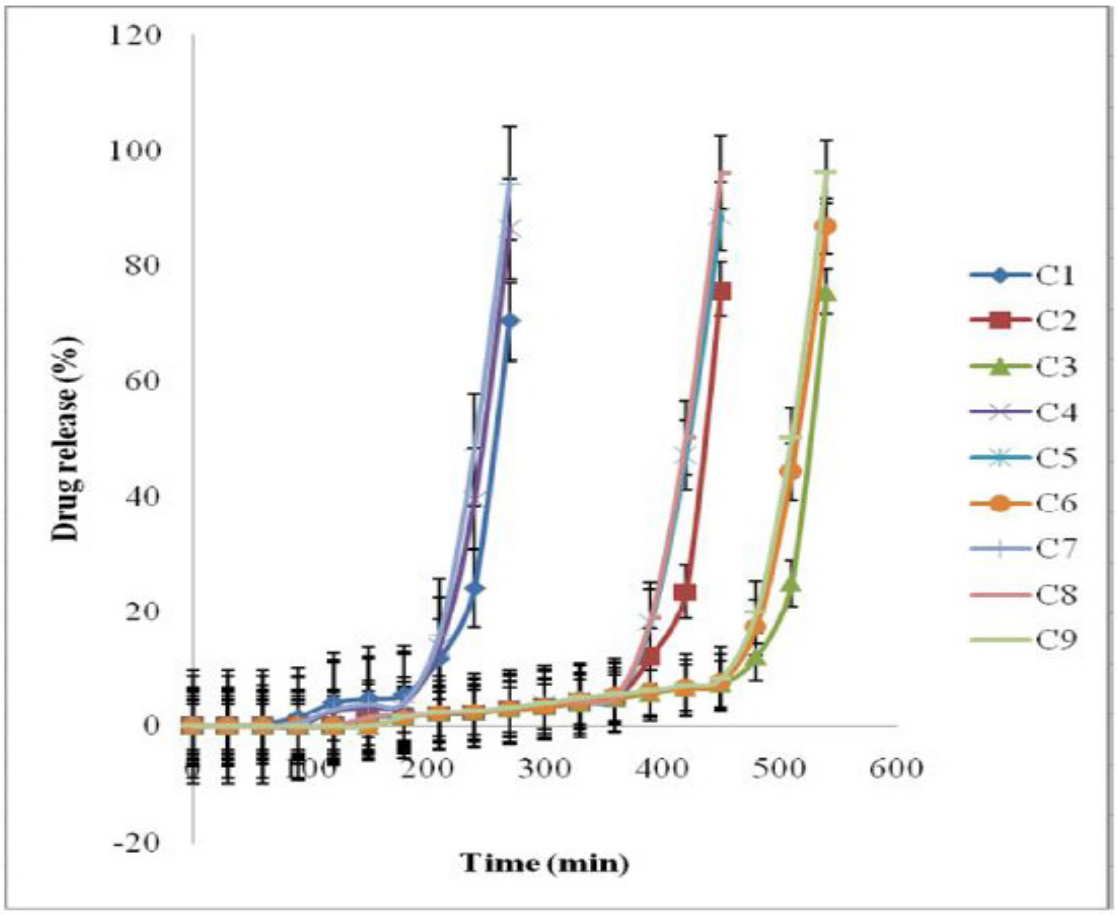


**Figure 1:** Dissolution Profile of C1-C9 formulations **(n=3)**

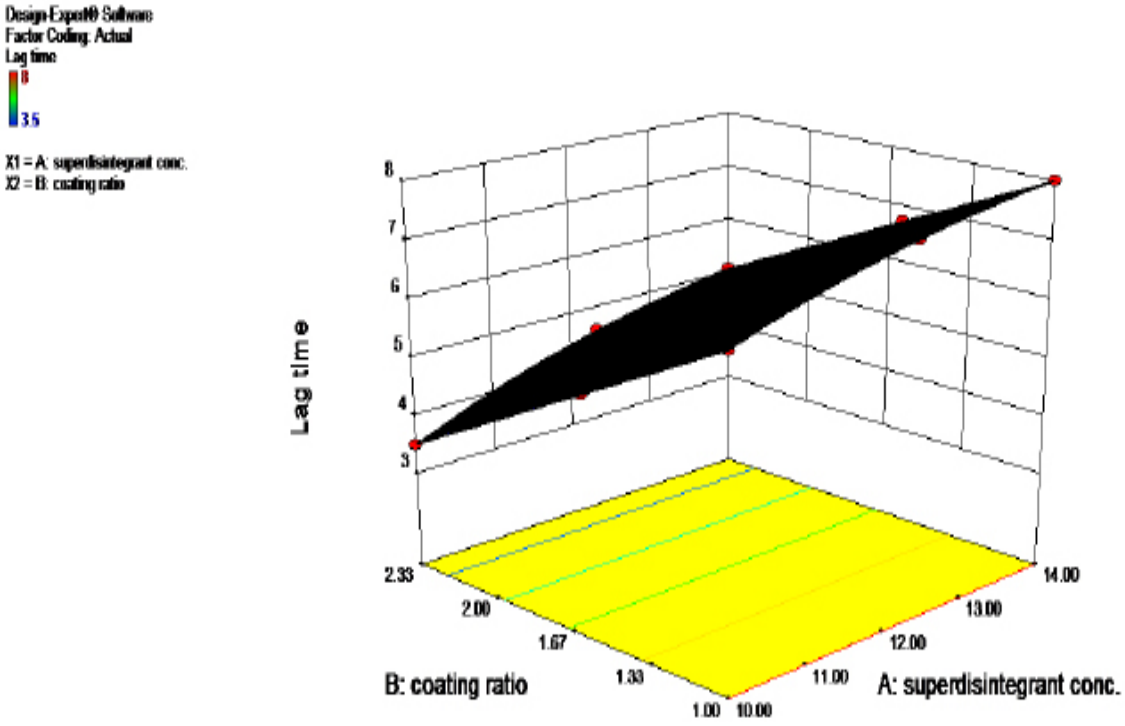


**Figure 2:** 3D response curve for lag time ($Y_1$)

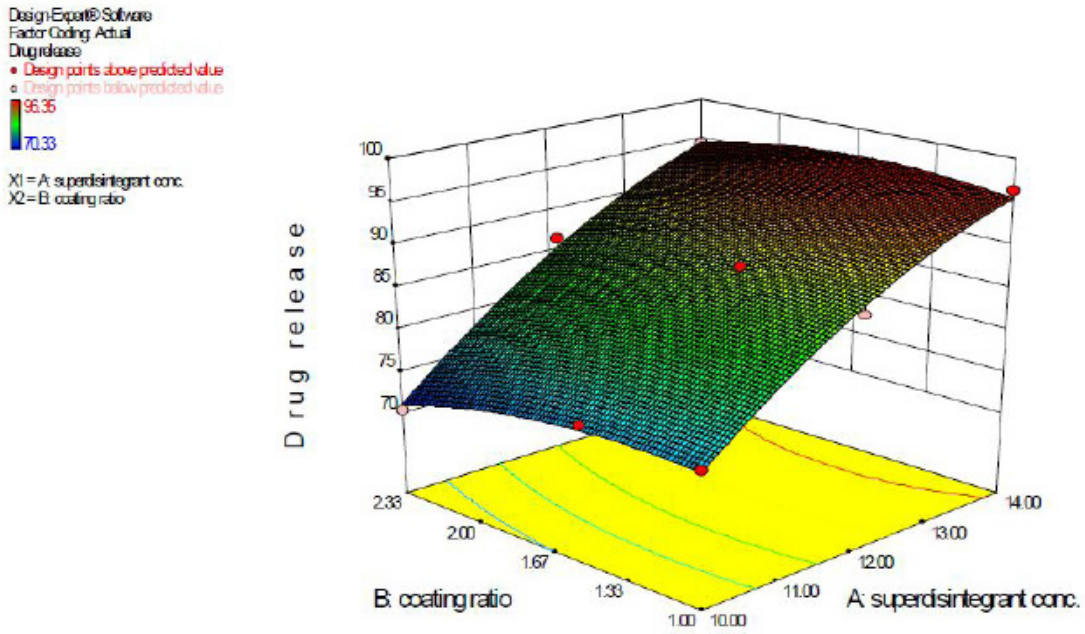


**Figure 3:** 3D response curve for drug released after lag time ($Y_2$)

| Batch | $Y_1$ (Lag time, minutes)[n] | $Y_2$ (Drug released in 450 min, %)[n] |
|---|---|---|
| **C1** | 3.5±0.53 | 70.33±5.35 |
| **C2** | 6.5±1.56 | 75.83±4.04 |
| **C3** | 8±2.49 | 76.46±1.04 |
| **C4** | 3.5±1.06 | 86.42±3.79 |
| **C5** | 6.5±1.35 | 88.70±3.59 |
| **C6** | 8±2.87 | 86.86±0.00 |
| **C7** | 3.5±1.07 | 94.29±2.35 |
| **C8** | 6.5±0.46 | 96.16±4.98 |
| **C9** | 8±0.01 | 96.35±6.25 |

**Note: n=3± SD**

**Table 5:** Result data of responses for C1-C9 batches

| | |
|---|---|
| Superdisintegrant conc.(%w/w) | 12.30 |
| coating ratio (% w/w) | 62.50:37.50 |
| Q6 (lag time in min.) | 6.00 |
| Q7.5 (Drug release in %) | 90.00 |
| Desirability | 1.000 |

**Table 6:** Solution for optimized batch

## Comparative Study

Batch J1, J2, J3 & J4 contains *Luffa aegyptica*; cross carmellose sodium, crosspovidone and SSG as superdisintegrant respectively and evaluated for *in vitro* dissolution study. The dissolution data (Figure 4) of batches J1-J4 revealed that, batch J1 containing *Luffa aegyptica* shows same drug release when compared with batch J2, J3 and J4, which indicated that *Luffa aegyptica* can be used as novel superdisintegrant in development of pulsatile drug delivery system [26].

## Stability Study

The optimized final batch was further kept for stability studies as per ICH guidelines. Samples were withdrawn every 30 days after initial day 0 analysis and were analyzed for *in-vitro* dissolution profiles and drug content similar to the developmental batches and results of this study revealed insignificant changes in both the evaluated parameters (Table 7). From the stability studies, it was clear that the tablets were stable after three months.

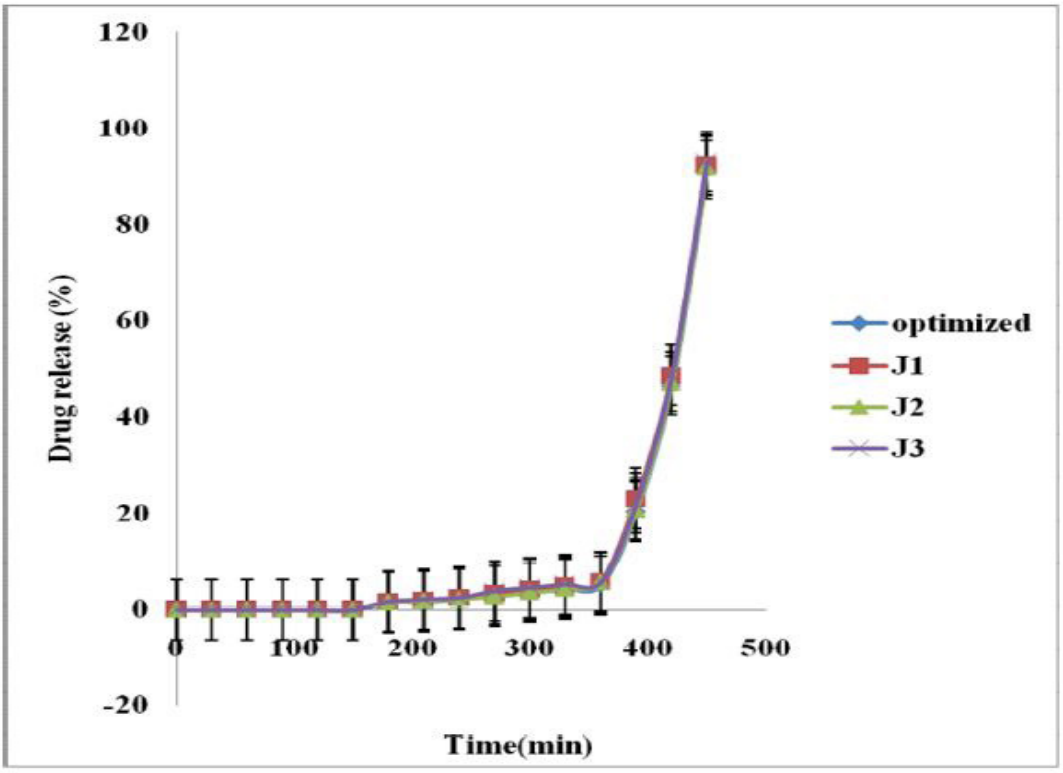


**Figure 4:** Dissolution Profile for comparative batches **(n=3)**

| Parameter | Batch No. 01 | | | | Batch No. 02 | | | | Batch No. 03 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 0 | Day 30 | Day 60 | Day 90 | Day 0 | Day 30 | Day 60 | Day 90 | Day 0 | Day 30 | Day 60 | Day 90 |
| **Drug content (%)** | 99.80 | 97.83 | 96.93 | 95.82 | 98.81 | 98.69 | 97.87 | 96.93 | 98.92 | 97.12 | 96.89 | 95.12 |
| **Drug release (%)** | 93.83 | 91.90 | 90.12 | 90.02 | 94.29 | 93.86 | 92.82 | 91.22 | 94.10 | 93.18 | 92.12 | 92.01 |

**Table 7:** Accelerated Stability Study Data

## Conclusion

The outcome of the present study indicated that natural superdisintegrant like *Luffa aegyptica mill* powder exhibits excellent disintegration property. The increase in lag time was observed with an increase in HPMC concentration and decreased concentration of novel superdisintegrant. The comparison of *Luffa aegyptica mill* as a novel superdisintegrant with pharmaceutically acceptable superdisintegrant for *in vitro* drug release study shows almost similar results and thus *Luffa aegyptica mill* can be used in development of pulsatile dosage form. As primary ingredients are cheap, biocompatible, biodegradable and easy to manufacture, they can be used as superdisintegrant in place of currently marketed synthetic super disintegrating agents.

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