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FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM USING NOVEL NATURAL SUPERDISINTEGRANT

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ABSTRACT

The present study was an attempt to develop and evaluate an oral pulsatile drug delivery system using dried mucilage of *Hibiscus Rosa sinensis linn* as a novel superdisintegrant. The rapid release tableted core contained a model drug (Diclofenac sodium) and novel superdisintegrant (*Hibiscus Rosa sinensis linn*) and controlled release effect was achieved with a combination of coating material (Eudragit S100). A 3^2 full factorial design was employed for the optimization of developed formulation considering concentration of superdisintegrant and coating ratio as independent variables with lag time and drug release as dependent variables. The developed formulations showed uniform appearance, average weight, drug content and adequate hardness. The increase in lag time was observed with an increase in Eudragit S100 concentration and decreased concentration of novel superdisintegrant. Design expert software® was used to give the solution for optimized formulation based on the evaluation of the developed formulations. Further comparison of *Hibiscus Rosa sinensis linn* in concentration suggested in the optimized formulation with pharmaceutically acceptable superdisintegrants in same concentration showed almost similar drug release behavior. It can be concluded from the outcome of the present research that dried mucilage of *Hibiscus Rosa sinensis linn*, a natural superdisintegrant, can prove to be best alternative to the existing semi-synthetic or synthetic superdisintegrant.

KEYWORDS: superdisintegrant, *Hibiscus Rosa sinensis linn*, Chronopharmaceutics.

INTRODUCTION

Oral pulsatile/delayed delivery systems are designed to elicit programmable lag phases preceding a prompt and quantitative, repeated or prolonged release of drugs. Accordingly, they draw increasing interest because of the inherent suitability for accomplishing chronotherapeutics goals, which have recently been highlighted in connection with a number of widespread chronic diseases with typical night or early morning recurrence of symptoms (e.g. bronchial asthma, cardiovascular disease, rheumatoid arthritis, early-morning awakening). In addition, time-based colonic release can be attained when pulsatile delivery systems are properly adapted to overcome unpredictable gastric emptying and provide delay phases that would approximately match the small intestinal transit time. Oral pulsatile delivery is pursued by means of a variety of release platforms, namely reservoir, capsular and osmotic devices. Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.[1] There are three types of mechanical rhythms in our body; namely, Circadian rhythm word originates from Latin word 'circa' means about and 'dies' means day, Ultradian rhythm means oscillation of shorter duration i.e. more than one cycle per 24 h and Infradian rhythm having oscillations longer than 24 h i.e. less than one cycle per day. A biological rhythm is a self-sustaining oscillation of endogenous origin. It is defined by the characteristics of period, level, amplitude and phase.[2] The human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram. the peak time of human circadian rhythms in relation to the typical synchronizer routine of most human beings-sleep in darkness from 10:30 p.m. to 6:30 a.m. and activity during the light of the day between 6:30 a.m. and 10:30 p.m.[3] PDDS is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a pre-determined off-release period, i.e. lag time. After the lag phase, pulsatile delivery systems may give rise to a prompt and quantitative, repeated or prolonged release pattern depending on their formulation characteristics.[4]

Currently key technologies in Chronopharmaceutics include:

OROS® technology, CEFORM® technology, CONTIN® technology, DIFFUCAPS® technology, CHRONOTOPIC® technology, EGALET® technology, CODAS® technology, GeoClock® technology, PORT® technology.[5]

Advantages and disadvantage of PDDS

PDDS has unique advantages over other drug delivery systems as it does not release the drug before the desired lag time, resulting in less inter- and intra-subject variability and also avoiding the risk of dose dumping, it releases drug to the right site at the right time and hence improves the bioavailability and stability, reduced adverse effects, and thus improve patient comfort and compliance. Although advantages of PDDS are many, its only disadvantage is that the rupture time cannot be always adequately manipulated as it is strongly correlated with the physicochemical properties of the polymer.[2]

MATERIALS AND METHOD

Materials

Diclofenac sodium BP was a gift sample from Aarti Drug Ltd., Boisar Thane .anhydrous lactose AR, Loba Chemie pvt Ltd. Mumbai, starch AR Eudragit AR, PVP K30 AR Loba chemie pvt Mumbai, Talc LR loba chemie pvt Ltd Mumbai, crosspovidon L100 AR research Lab Fine chem industries Mumbai, sodium starch glycollate AR research Lab fine chem Industries crosscarmellose sodium CG, Mumbai All other chemicals and reagents used in the study were of analytical grade.

Methodology

Isolation of natural superdisintegrant:

Hibiscus is a genus of flowering plants in the mallow family, Malvaceae.[6] The fresh leaves of *Hibiscus Rosa Sinensis Linn* were collected and washed with water to remove the dirt, and dust particles. The leaves were dried at ambient 40^0C in hot air oven and then macerated in water for 5-6 hrs. boiled for 30min and kept aside for 1hr to allow complete release of mucilage in water. Mucilage was extracted using muslin cloth to remove mark and Acetone was added to precipitate the mucilage. Then mucilage was separated and dried in oven at less than 50^0C then passed through #80 sieve and stored at room temperature.[7]

Development of Prototype formulation

Prior to development of preliminary trials of core tablets, initially 5 prototype formulation (F1-F5) were prepared to study effect of novel superdisintegrant concentration on disintegration time. **Table no.1** summarizes the composition for batches F1-F5. These prototype formulations were evaluated for hardness, friability, weight variations and disintegration time.

Prototype Formulation

Table 1: Composition for prototype formulation F1-F5

Ingredients/ Batch No. (mg/tab)	F1	F2	F3	F4	F5
Diclofenac Sodium	50	50	50	50	50
PVP K30	8	8	8	8	8
Anhydrous lactose	38	35	29	29	34
Test substance	2	5	6	6	8
Magnesium stearate	1	1	1	1	1
Talc	1	1	1	1	1
Micro-crystalline cellulose	--	--	5	--	--
Starch	--	--	--	5	--
Total	100	100	100	100	100

Formulation of Core Tablets

Granules used were prepared by wet granulation technique. Drug, superdisintegrant were passed from seive no. 80 and then 5% solution of pvp k-30 was added as binder to the mixture and then wet mass was obtained and passed through seive no. 16 and then Magnesium stearate and talc were added. The granules prepared were dried at 50˚C. The powder mixture was then blended for 5 min. Core tablets (diameter 6 mm, hardness 3-6 kg/cm^2, average tablet weight 100 mg) were compressed using a rotatory tableting machine (Rimek, Karnavati Eng. Ltd). The core tablet should be formulated in such a way that it release maximum drug after lag time. The core tablets were prepared by varying concentration of novel superdisintegrant, microcrystalline cellulose and starch to study the effect of these agents on drug release from core tablet. Based on the results of trial batches F1-F5 further trial batches were prepared which are summarized in **Table no 2.**

Formulation of press coated tablets

The combination of PVP K30 and novel superdisintegrant is commonly used for preparation of press coated tablets for the adjustment of the drug release time. The coating layer was composed of Eudragit S100 at different compositions, acting as a stimulus responsible layer. This polymer do not allow the drug release in acidic Ph due to presence of carbonyl anionic group. The enhancement was attributed to the higher rate of wetting and flexibility of the new matrices due to the slower dissolution of the PVP macromolecules. Upon exposure of the prepared tablets to the release medium it was found that the coating layer disintegrates first, followed by the immediate release of drug from the active core.

Table 2: Composition of trial batches(V1-V3)

Ingredients/ Batch No. (mg/tab)	V1	V2	V3
Diclofenac Sodium	50	50	50
PVP K30	8	8	8
Anhydrous lactose	34	29	29
Test substance	6	6	6
Magnesium stearate	1	1	1
Talc	1	1	1
Micro-crystalline cellulose	--	5	---
Starch	--	---	5
Coating Ratio	300	300	300
Total	400	400	400

Optimization of Formulation

A 3^2 randomized full factorial design was used in this study. In this design two factors were evaluated, each at 3 levels. The amount of novel superdisintegrant i.e. *dried mucilage of Hibscus Rosa Sinensis Linn* and coating ratio (Eudragit S100) were selected as independent variables and the lag time ($6_{1/2hrs}$) and drug release after lag time were selected as dependent variables. The dependent and independent variables and used levels are summarized in **Table no 3**. The nine optimization batches (C1-C9) were prepared in 3^2 full factorial designs as per **Table no 4**.

Table No 3

Factors (Independent variables)	Levels			Responses (Dependent variables)
	(-1)	(0)	(+1)	
Amount of superdisintegrant (%)	6	7.5	9	Lag time of 6.5 hr.
Ratio of coating material (%w/w) i.e Eudragit S100	200	250	300	Drug release after lag time

Table 4: Composition of optimization batches C1-C9

Ingredients (mg/tab)	C1	C2	C3	C4	C5	C6	C7	C8	C9
Diclofenac sodium	50	50	50	50	50	50	50	50	50
PVP K30	5	5	5	5	5	5	5	5	5
Anhydrous lactose	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Test substance	6	7.5	9	6	7.5	9	6	7.5	9
Starch	5	5	5	5	5	5	5	5	5
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Coating ratio (%w/w)	200	200	200	250	250	250	300	300	300
Total wt.	300	300	300	350	350	350	400	400	400

Evaluation of Diclofenac Sodium Press Coated Pulsatile Release Tablets

The tablet where evaluated for weight variation, friability as per IP.[8]

Drug Content

Twenty tablets were weighed individually and powdered in pestle mortar and an amount equivalent to 50 mg of Diclofenac Sodium was extracted with 10 ml of methanol and sonicated for 10 min. The solution was filtered through a watman filter paper and the content of Diclofenac Sodium in the solution was determined by measuring absorbance at 276 nm after suitable dilution.[9]

***In vitro* release study**

The dissolution studies were performed according to the USP apparatus II (Electrolab, model TDT-08L, Mumbai, India) using 900 ml of 0.1N HCL maintained at 37± 0.5^0C stirred at 50 rpm for 2 h. Then the same tablets were removed and placed in 900 ml of phosphate buffer P^H 6.8 and 7.4 as dissolution media maintained at 37± 0.5^0C. At appropriate time intervals dissolution sample were withdrawn and analyzed using UV Spectrophotometer at 276 nm. 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. **Table no.5** summarizes specifications of *In vitro* dissolution study.

Table no 5: Specifications of *In vitro* dissolution studies

Sr. No.	Specifications	
1	**Apparatus**	USP dissolution apparatus II
2	**Speed**	50rpm
3	**Volume of media**	900 ml (P^H 1.2) for first 2 h, 900 ml (P^H 6.8, 7.4)
4	**Media used**	P^H 1.2 buffer, P^H 6.8 and 7.4 Phosphate buffer
5	**Stirrer**	Paddle
6	**Replacement volume**	5 ml
7	**Temperature**	37 $\pm$ 0.5^0C

Comparative Study

Optimized formulation as suggested by Design Expert® software was selected for further comparative study with pharmaceutically accepted superdisintegrants namely, sodium starch glycolate (SSG) and crosscarmellose sodium **Table 6** depicts the composition of the batches selected for comparative studies.

Table 6: Composition of comparative batches J1-J3

Ingredients (mg/tab)	J1 *(Hibiscus Rosa Sinensis linn)*	J2 (CCS)	J3 (SSG)
Diclofenac sodium	50	50	50
PVP K30	5	5	5
Anhydrous lactose	q.s.	q.s.	q.s.
Superdisintegrant	7	7	7
Starch	5	5	5
Magnesium stearate	1	1	1
Talc	1	1	1
Coating ratio	300	300	300
Total wt. (mg)	400	400	400

RESULTS AND DISCUSSION

Characterization novel superdisintegrant powder

Novel superdisintegrant was characterized for their physical properties such as weight loss on drying, swelling index and flow properties like density, compressibility index, angle of repose and Hausner's ratio. Which is shown in **Table 7**. It is clear from result that the dried powder has a good flow properties and swelling index which is a sign to indicate the suitability of the material for a direct compression.

Table 7: Characteristics of novel superdisintegrant mucilage

Parameters	Results
Loss on drying (%)	1.3±0.0104
Swelling Index (ml)	2.1±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

IR spectrum of the *Hibiscus Rosa Sinensis*

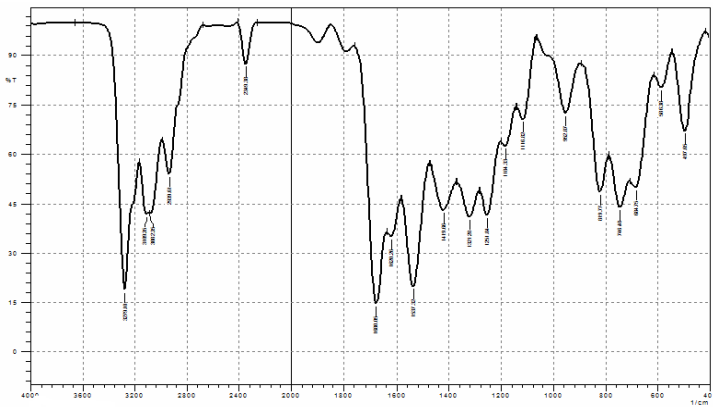

Fig.1: IR spectrum of the *Hibiscus Rosa Sinensis*

Peak(cm^{-1})	Chemical group
3363	O-H
2924	C-H
1024	C-H

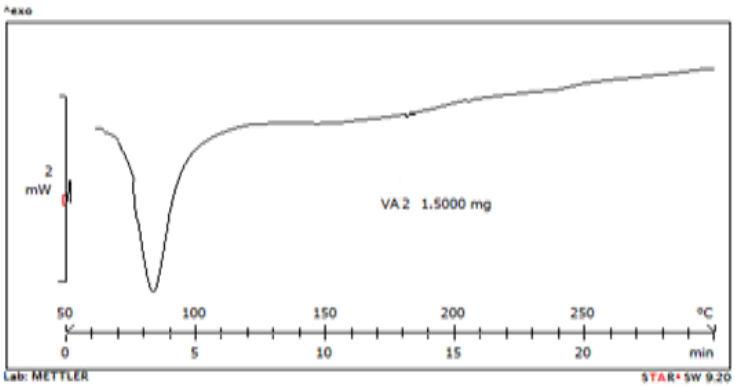

Fig. 2: DSC spectrum of the *Hibiscus Rosa Sinensis Linn*

Drug-Excipients Compatibility Study

The result of DSC spectra of drug and novel superdisintegrant shows no interference in peak, which indicate that there was no major incompatibility between drug and novel superdisintegrant.

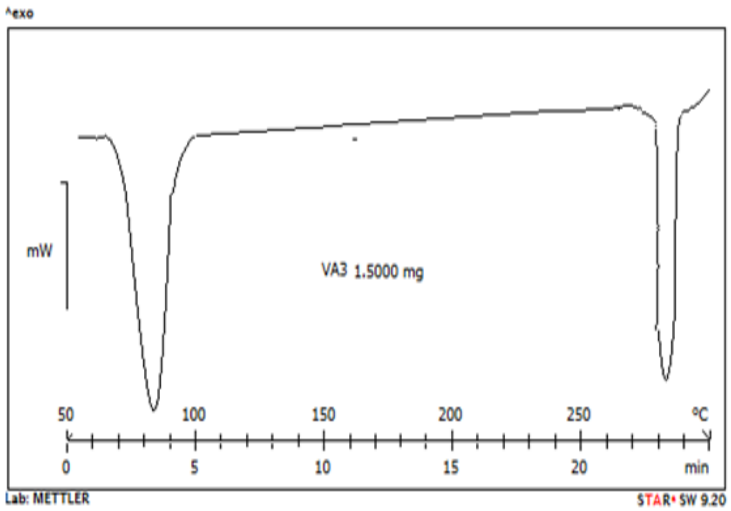

Fig. 3: Combine DSC spectrum for drug and superdisintegrant

Evaluation

Pre-compression Parameters

- **For Granules used for compression**

Granules where characterized for their physical properties such as density, compressibility and Hausner's ratio. Results are shown below,

Table 8: Pre-compression parameters of granules used for compression

Parameters	Granules
Bulk density(g/ml)	0.5360
Tapped density (g/ml)	0.6455
Compressibility index (%)	16.83
Hausner's ratio	1.20
Angle of repose	33.23

Formulation of press coated tablet

- **Developmental of prototype formulation**

In order to decide the proper formulation, initially 5 prototype formulation (F1-F5) were carried out to study effect of novel superdisintegrant concentration on disintegration time. In case of batches F1-F5, it was found that as concentration of superdisintegrant increases the disintegration time was found to be decreases and vice-versa. This gave the preliminary information of minimum concentration of superdisintegrant required for further studies. **Table no. 9** summarized the evaluation parameter for prototype formulation F1-F5.

Table 9: Evaluation parameters for prototype formulation F1-F5

Parameters	F1	F2	F3	F4	F5
Tablet weight(mg)	101.06±10	99.74±10	101.17±10	100.6±10	100.35±10
Hardness(kg/cm^2)	3.5±0.2886	3.2±0.4812	3.6±0.2876	3.8±0.2776	3.4±0.2638
Friability (%)	0.3364	0.4812	0.3471	0.2986	0.3087
Disintegration Time (Min.)	9.14±0.57	8.04±0.79	7.34±0.27	7.54±0.34	5.43±0.13

- **Development of Press coated Tablet**

From the drug release profile for batches V1-V2 it was concluded that as the concentration of Eudragit S100 increases lag time was found to be increased. Among the batch V1-V3, batch V3 showed pulsatile drug release with desirable lag time, hence batch V3 was selected for further design of formulation to obtained 8 hrs lag time and pulse release after lag time. Hence batch V3 was selected for factorial design studies to optimize effects of variables on formulation. There after further studies with full 3^2 factorial studies were carried out and based on there studied. **Table no.10** shows *In vitro* Drug Release of press coated tablets.

Table no 10: % Drug release of Trial Batches V1-V3

Time(min)	V1	V2	V3
0	0	0	0
60	0	0	0
120	2.80	0	0
180	4.20	1.87	1.50
240	39.46	2.43	2.52
300	---	4.01	3.55
360	---	5.04	5.41
390	---	18.00	6.25
420	---	47.10	6.81
450	---	47.10	7.75
480	---	---	9.26
510	---	---	44.22
540	---	---	96.16

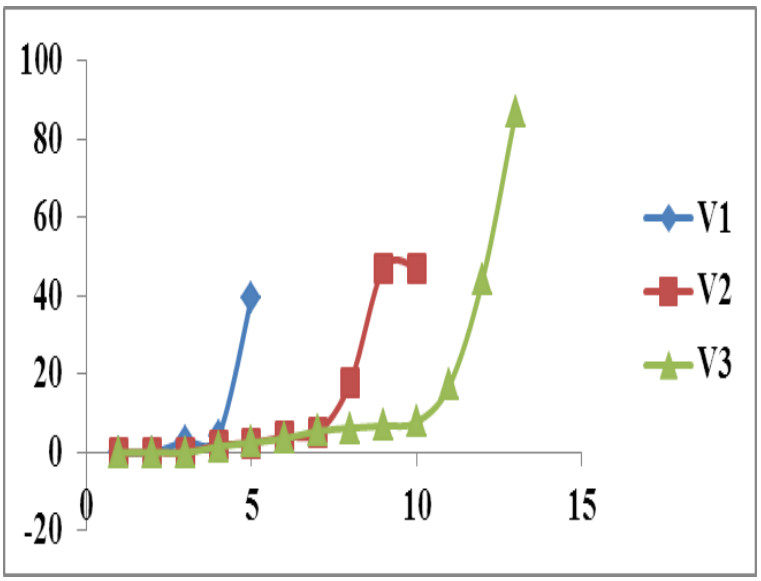

Fig. 4: Dissolution profile of Batches V1-V3

Optimization of Formulation is based on the factorial design evaluation parameter for batch C1-C2.

Table 11: Evaluation parameters of batch C1-C9

Parameters	C1	C2	C3	C4	C5	C6	C7	C8	C9
Weight variation (mg)	400.1	398.7	399.8	398.8	401.2	398.9	398.5	400.2	398.1
Hardness (Kg/cm^2)	3.33	3.58	3.83	3.83	3.91	3.91	4	3.75	3.83
Friability (%)	0.766	0.559	0.641	0.358	0.432	0.565	0.450	0.572	0.518
Drug content (%)	99.94	99.92	99.45	99.18	98.96	98.51	98.77	98.51	98.82

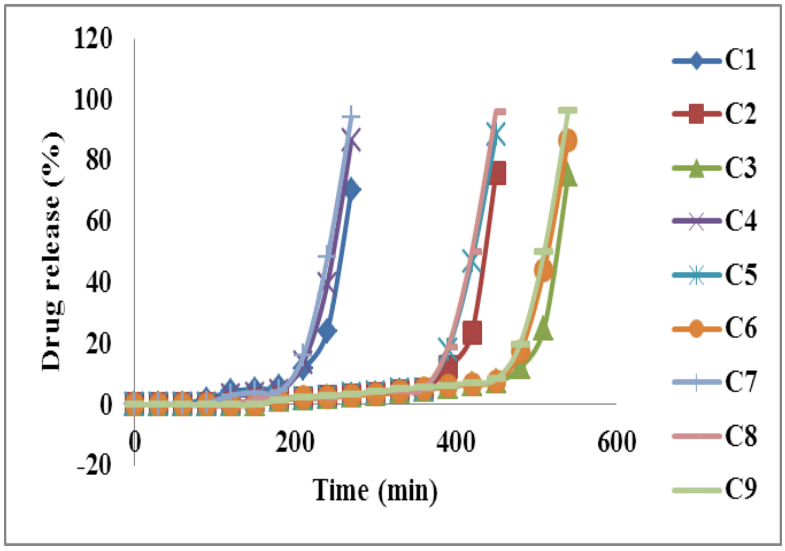

Fig. 4: Dissolution profile of Batches C1-C9

● ***In vitro*** **Drug Release Study**

Table 12: % Drug release of batches C1-C9

Time (min)	Cumulative % drug release								
	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
60	0.26	0	0	0	0	0	0	0	0
120	2.29	0	0	2.80	0	0	3.08	0	0
180	4.69	0.87	1.55	4.20	1.87	1.50	4.29	2.24	1.65
240	24.0	2.34	2.49	39.46	2.43	2.52	48.11	2.71	2.80
300	52.33	3.46	3.55	---	4.01	3.55	---	4.23	4.20
360	77.42	4.95	4.95	---	5.04	5.81	---	5.32	5.69
390	---	12.13	5.88	---	18.00	6.25	---	18.72	6.35
420	---	23.41	6.81	---	47.10	6.81	---	50.13	7.19
450	---	75.83	7.47	---	88.70	7.75	---	96.16	8.40
480	---	---	8.10	---	---	8.26	---	---	9.87
510	---	---	24.97	---	---	44.21	---	---	50.09
540	---	---	75.46	---	---	86.86	---	---	96.35

Solution for optimized batch

Ingredients (mg/tab)	Optimized batch
Diclofenac Sodium	50
PVP K30	5
Anhydrous lactose	q.s.
Test substance	7
Starch	5
Magnesium stearate	1
Talc	1
Coating Ratio (Eudragit S100)	300
Total wt. (mg)	400

Composition of opitimized batch

Sr. No.	Superdisintegrant conc. (mg)	coating ratio (mg)	$Q_{7.5}$ (Lag time)	Q_{CDR} (%CDR)	Desirability
1	7	300	7.5	90.00	1.000

Comparative Studies

From above studies, optimized final batch containing 7% of *Hibiscus Rosa Sinensis Linn* and coating material 300mg was selected for further comparative study with pharmaceutically accepted superdisintegrant namely sodium starch glycolate and cross carmellose sodium.

Evaluation of comparative batches J1-J3

Drug Release Study

The dissolution data of batches J1-J3 revealed that, batch J1 i.e. optimized batch containing *Hibiscus Rosa Sinensis Linn* shows same drug release when compared with batch J2 and J3. Which indicate that *Hibiscus Rosa Sinensis Linn* can be use as novel superdisintegrant in development of pulsatile drug delivery system. **Table no. 13** summarized percent drug release of comparative batches J1-J3. Dissolution profile of the batches J1-J3 shown in **figure 5.**

Table 13. % Drug release of the batches J1-J3

Time (min)	J1	J2	J3
0	0	0	0
60	0	0	0
120	0	0	0
180	1.59	1.60	1.65
240	2.15	2.40	2.46
300	3.55	4.20	4.57
360	5.04	5.97	5.70
390	28.42	30.10	32.14
420	46.54	48.69	48.78
450	91.32	92.38	93.01
480	9.02	9.12	9.14
510	46.54	48.69	47.29
540	91.32	92.38	92.02

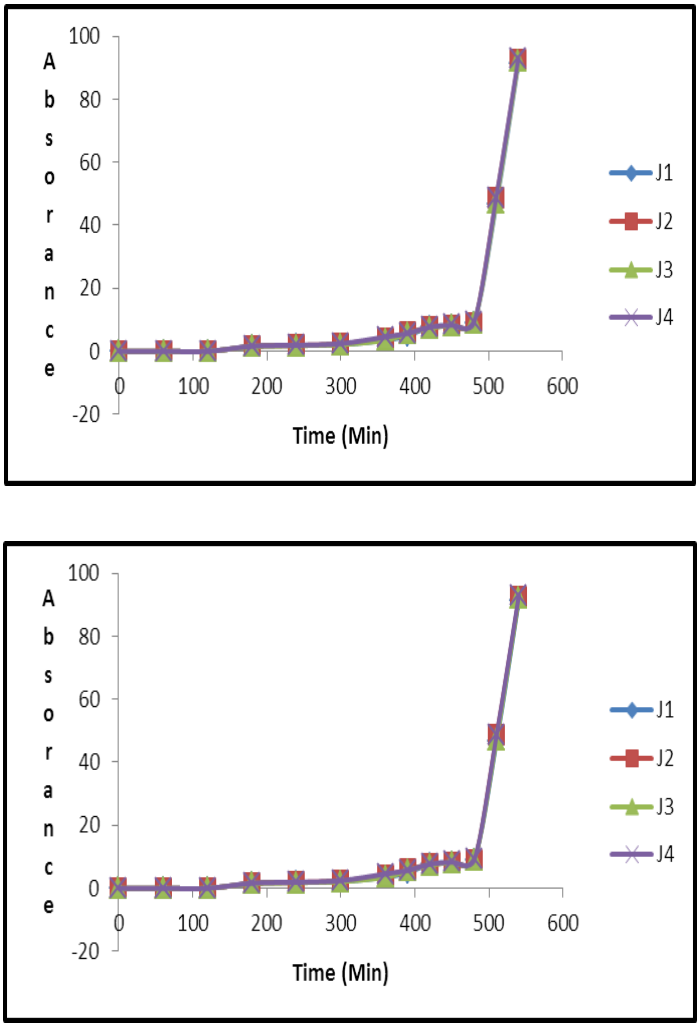

Fig 5. Dissolution profile of the batches J1-J3

Stability Studies

Therefore, from above studies optimized final batch was selected for further stability consideration. Hence this batch was repeated and repeated batch was kept for stability studies as per ICH guidelines in Glass vial packing. Samples were withdrawn according to the sampling plan after 1 month. Accelerated stability studies were analyzed for in-vitro dissolution profiles. From the stability studies of the optimized batches it was found that the tablets remained stable even after exposing to high temperature and moisture conditions. The dissolution profile of drug from the tablets was found to decrease to some extent after stability. The dissolution profiles for 3 month stability are given as below:

Table 14: Evaluation parameters for stability batches

Para.	Batch No. 01				Batch No. 02				Batch No. 03			
	In.	1	2	3	In.	1	2	3	In.	1	2	3
Drug content (%)	99.8	98.9	98.3	97.8	98.8	98.6	97.8	97.2	98.9	98.1	97.8	97.1
Drug release (%)	93.8	92.9	92.1	92.0	94.2	93.8	93.4	92.7	94.1	93.8	93.1	92.9

CONCLUSION

The outcome of the present study indicated that natural superdisintegrant like *Hibiscus Rosa Sinensis Linn* mucilage exhibits excellent disintegrating property. The increase in lag time was observed with an increase in Eudragit S100 concentration and decreased concentration of novel superdisintegrant. The comparison of *Hibiscus Rosa Sinensis Linn* as a novel superdisintegrant with pharmaceutically acceptable superdisintegrants for *in vitro* drug release study shows almost similar results and thus *Hibiscus Rosa Sinensis Linn* 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 superdisintegrating agents.

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