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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF AMLODIPINE BESYLATE BY USING *HIBISCUS ROSA – SINENSIS* MUCILAGE AND MODIFIED GUM KARAYA

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ABSTRACT

In the present study, natural gums (*Hibiscus rosa – sinensis* mucilage and Modified gum karaya) was investigated as superdisintegrants for use in fast dissolving tablet formulations containing amlodipine besylate. Fast dissolving tablets of amlodipine besylate was formulated using different concentrations (2, 4, 6, 8, 10) of natural superdisintegrant viz; *Hibiscus Rosa – sinensis* mucilage and modified gum karaya. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study. The formulated tablets had good appearance and better drug release properties. The best formulation of *Hibiscus rosa – sinensis* mucilage (FHR5) and modified gum karaya (FMGK5) shows shorter disintegration time and shows 100% release is selected as optimized formulation. Hence, the present study revealed that this natural superdisintegrants (*Hibiscus rosa – sinensis* mucilage and modified gum karaya) showed better disintegrating property than the most widely used synthetic superdisintegrants. Studies showed that naturally obtained polymers are more beneficial without any side effects. Optimized formulation was subjected to stability studies as per ICH guidelines and it insignificant change in hardness, disintegration time and in vitro drug release.

INTRODUCTION: Amlodipine belongs to a class of medications called calcium channel blockers. These medications block the transport of calcium into the smooth muscle cells lining the coronary arteries and other arteries of the body. Since calcium is important in muscle contraction, blocking calcium transport relaxes artery muscles and dilates coronary arteries and other arteries of the body. By relaxing coronary arteries, amlodipine is useful in preventing chest pain (angina) resulting from coronary artery spasm. Relaxing the muscles lining the arteries of the rest of the body lowers the blood pressure, which reduces the burden on the heart as it pumps blood to the body. Reducing heart burden lessens the heart muscle's demand for oxygen, and further helps to prevent angina in patients with coronary artery disease. The usual initial antihypertensive oral dose of Amlodipine besylate tablets is 5 mg once daily with a maximum dose of 10 mg once daily.

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Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine besylate tablets to other antihypertensive therapy [1-2].

Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology. Fast dissolving formulation is popular as Novel Drug Delivery Systems because they are easy to administer and lead to better patient compliance. Paediatric and geriatric patient have difficulty in swallowing the conventional dosage forms these dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing.

Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. The advantages of fast dissolving dosage forms are increasingly being recognized in both industry and academia. The fast disintegrating tablets prepared by direct compression method, in general, are based on the action established by natural and synthetic superdisintegrants [3-6].

Plant products serve as an alternative to synthetic products because of local accessibility, environment friendly nature and lower prices compared to imported synthetic products. Majority of investigations on natural polymers in drug delivery systems are centered on polysaccharides and proteins. Number of natural, synthetic and semi synthetic polymer materials is used in the various drug delivery systems. Recent trend towards the use of vegetable and non-toxic products demands the replacement of synthetic additives with natural one. The natural materials like gums, mucilages have been extensively used in the field of drug delivery for their easy availability and no side effects [7].

In this study, natural substances like *Hibiscus rosa – sinensis* mucilage and modified gum karaya were used as superdisintegrants in the formulation of amlodipine besylate fast dissolving tablets.

MATERIALS AND METHODS:

Materials: Amlodipine besylate was received as a gift sample from ORCHID PHARMACEUTICALS. *Hibiscus rosa – sinensis* mucilage was obtained from local market. Mannitol, Magnesium stearate, Talc was obtained from S.D. FINE chemicals, Mumbai.

Methods:

Extraction of mucilage from *Hibiscus rosa - sinensis*: The fresh leaves of *Hibiscus rosa - sinensis* Linn. were collected, washed with water to remove dirt and debris, and dried. The powdered leaves were soaked in water for 5 6 h, boiled for 30 min, and kept aside for 1 h for complete release of the mucilage into water . The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature < 50^{o}C, collected, dried powdered, passed through a sieve (number 80) , and stored for further use in desiccators [8].

Preparation of modified gum karaya: Powdered gum was taken in a porcelain bowl and subjected of heating using sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling property similar to GK, but viscosity was decreased as a function of temperature and time period of heating. However, it was observed that GK samples were charred, when heated at 140^{o}C. In the preparation of modified form of GK, no further change in viscosity of GK was observed by heating it at 120^{o}C for more than 2h. Hence, these conditions of heating at 120^{o}C for 2h were selected to prepare modified form of GK. The prepared modified form of GK was finally re-sieved (100 mesh) and stored in airtight container at 25^{o}C [9].

Standard calibration curve: Solutions ranging from 2 to 10µg/ml were prepared in 0.1N Hcl buffer (pH 1.2 fluid). Absorbance was measured for each solution at λ_{max} of 361 nm, using Schimadzu UV spectrophotometer.

Drug-excipient compatibility study by IR spectroscopy: The physico-chemical compatibility between Amlodipine besylate and the excipients used in the research was tested by IR spectroscopy using Perkin Fourier Transform Infrared Spectrophotometer.

The samples were scanned under diffuse reflectance mold and graph was plotted by KBr pellet technique. The spectra were recorded in the wave number region between 4400cm^{-1} to 400cm^{-1}. The individual spectra obtained for Amlodipine besylate, excipients were compared with the spectra of the physical mixture of Amlodipine besylate and excipients.

Preparation of Fast Dissolving Tablets of Amlodipine Besylate: Fast dissolving tablets of amlodipine besylate was prepared by direct compression method. The drug and excipients were passed through sieve no.80 to ensure better mixing, natural superdisintegrants *Hibiscus rosa – sinensis* mucilage and Modified gum karaya were used in different proportions. The powders were compressed into tablets on tablet punching machine using 9mm punch and weight of the tablet is 200mg (**Table 1**).

TABLE 1: COMPOSITION OF AMLODIPINE BESYLATE FAST DISSOLVING TABLETS

S. No.	Ingredients (mg)	FHR1	FHR2	FHR3	FHR4	FHR5	FMGK1	FMGK2	FMGK3	FMGK4	FMGK5
1	Amlodipine besylate	10	10	10	10	10	10	10	10	10	10
2	*Hibiscus rosa – sinensis* mucilage	2	4	6	8	10	_	_	_	_	_
3	Modified gum karaya	_	_	_	_	_	2	4	6	8	10
4	MCC	100	100	100	100	100	100	100	100	100	100
5	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Talc	2	2	2	2	2	2	2	2	2	2
7	Mannitol	84.5	82.5	80.5	78.5	76.5	84.5	82.5	80.5	78.5	76.5

EVALUATION:

A. Precompression Parameters:

1. **Angle of Repose (θ):** The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\tan(\theta) = h / r$; $\theta = \tan^{-1}(h / r)$

Where, θ is the angle of repose, h is the height in cms, r is the radius in cms.

2. **Bulk Density (Db):** It is the ratio of total mass of powder to the bulk volume of powder. It will be measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight will be noted.This initial volume is called the bulk volume. From this the bulk density will be calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder.

3. **Tapped Density (D_t):** It is the ratio of total mass of the powder to the tapped volume of the powder. Volume will be measured by tapping the powder for 750 times and the tapped volume will be noted, if the difference between these two volumes is less than 2%. If it is more than 2%, tapping will be continued for 1250 times and tapped volume will be noted. Tapping will be continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$Dt = M / Vt$$

Where, M is the mass of powder, Vt is the tapped volume of the powder.

Powder Flow Properties: The flow properties were determined by;

1. **Carr's index (or) % compressibility:** It indicates powder flow properties. It is expressed in percentage and is given by.

$$\mathbf{I = Dt – Db / Dt \times 100}$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

2. **Hausner's Ratio:** Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = Dt / Db$$

Where, Dt is the tapped density, Db is the bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

B. Postcompression parameters:

1. **Thickness:** Thickness will be measured by using Vernier callipers.

2. **Hardness:** The hardness of tablet will be measured by Monsanto hardness tester. The hardness is measured in terms of kg/cm^2.

3. **Drug content:** Twenty tablets were powdered, and 10 mg equivalent weight of Amlodipine besylate in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 0.1N Hcl buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 361 nm.

4. **Uniformity of Weight:** Twenty tablets were randomly selected from each formulation, individually weighed, the average weight and standard deviation was calculated.

5. **Friability:** Roche Friabilator was used to determine the friability. Pre weighed tablets were placed in Friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6. **Wetting Time and Water Absorption Ratio:** A piece of paper folded twice was kept in a Petri dish containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time. Test was done with the same procedure as that of wetting time. In this test initial weight of tablet was taken before placing on petri dish. After complete wetting the wetted tablet was then weighed. Water absorption ratio, R was determined using the equation:

$$R = [(Wb - Wa)/Wb] \times 100$$

Where, Wa and Wb were the weights of the tablet before and after water absorption.

7. ***In vitro* Dispersion Time:** Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37± 0.5°C. Time required for complete dispersion of tablet was measured.

8. ***In vitro* Disintegration Test:** The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no.10) was immersed in water bah a 37 ± 2^o C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacological standards, dispersible tablets must disintegrate within 3min when examined by the disintegration test for tablets.

9. ***In-vitro* Dissolution Study:** The release rate Amlodipine Besylate from fast dissolving tablets is determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test will be performed using 900 ml of pH 1.2 buffer(0.1N Hcl buffer), at 37± 0.50C and 50 rpm. A sample (5 ml) of the solution is withdrawn from the dissolution apparatus at regular intervals for 10 min. The samples are replaced with fresh dissolution medium of same quantity. The samples are filtered through a 0.45ì membrane filter. Absorbance of these solutions is measured at 361 nm using a Shimadzu UV/Vis double beam spectrophotometer. Cumulative percentage of drug release is calculated using an Equation obtained from a standard curve [10-12].

10. **Stability Studies:** The stability study of the tablets will be carried out according to ICH guidelines by storing tablets in stability chamber at 25±20°C / 60±5% RH and 40±20°C/75±5% RH for 3 months. The effects of temperature and time on the physical characteristics of the tablet are evaluated for assessing the stability of the prepared formulations. The different parameters that are to be studied are disintegration time, hardness, friability, drug content and dissolution rate [13].

RESULTS AND DISCUSSION: Fast dissolving tablets acts as a major role to eradicate different types of circumstantial attacks of various diseases in the market. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Many patients, especially elderly find it difficult in swallowing tablets, capsules, fluids and thus do not comply with prescription, which results in high incidence of non-compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Significance of this drug delivery system includes ease administration, improved patient compliance, rapid onset of action and may offer an improved bioavailability, ideal for pediatric and geriatric patients and rapid onset of action.

Fast dissolving tablets of amlodipine besylate were prepared by adding natural superdisintegrating agents i.e. *Hibiscus rosa – sinensis* mucilage and Modified gum karaya.

IR spectra of Amlodipine besylate and its physical mixture with formulation excipients were determined using FT-IR. And found, there is no interaction between the drug and excipients (**Fig. 1, 2, 3**).

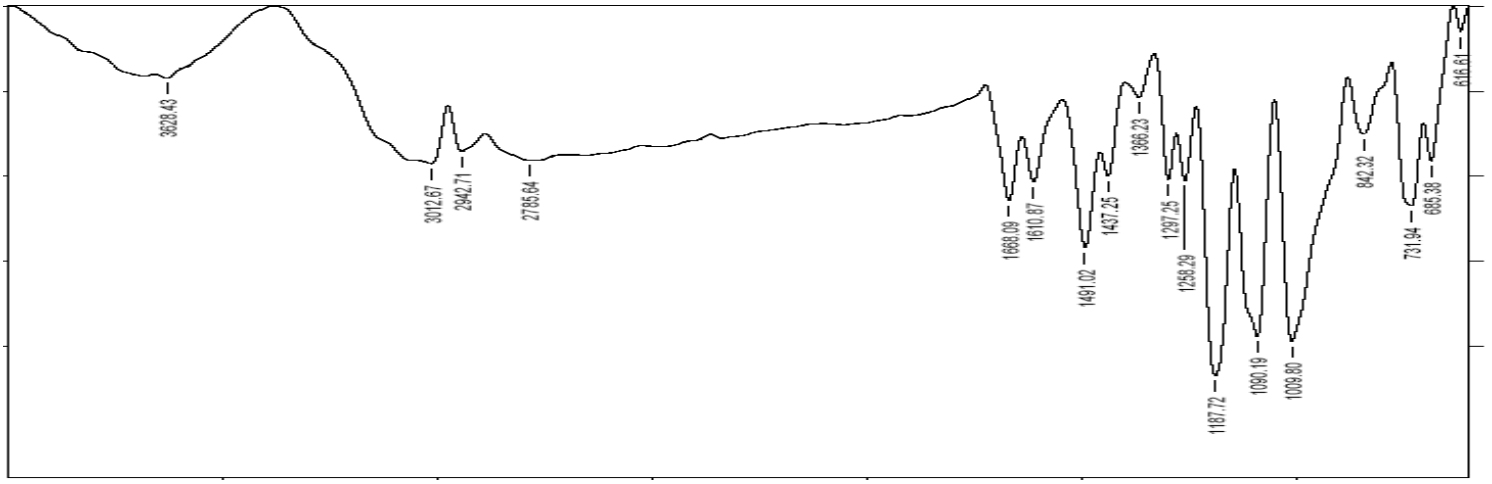

FIG 1: IR SPECTRUM OF AMLODIPINE BESYLATE

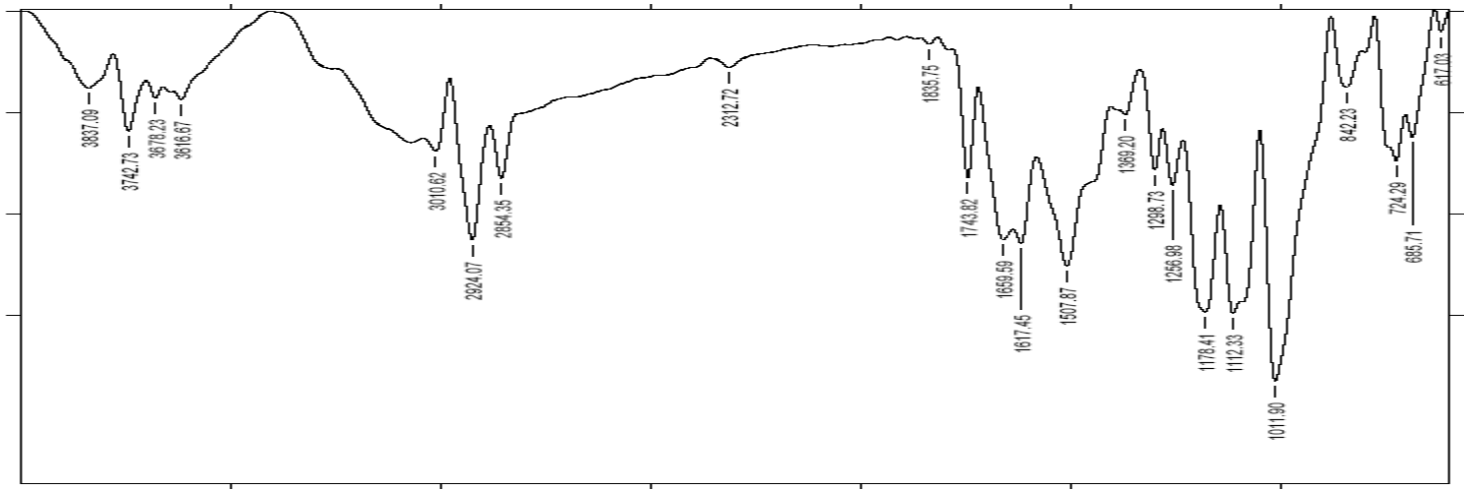

FIG 2: IR SPECTRUM OF DRUG + *HIBISCUS ROSA – SINENSIS* MUCILAGE

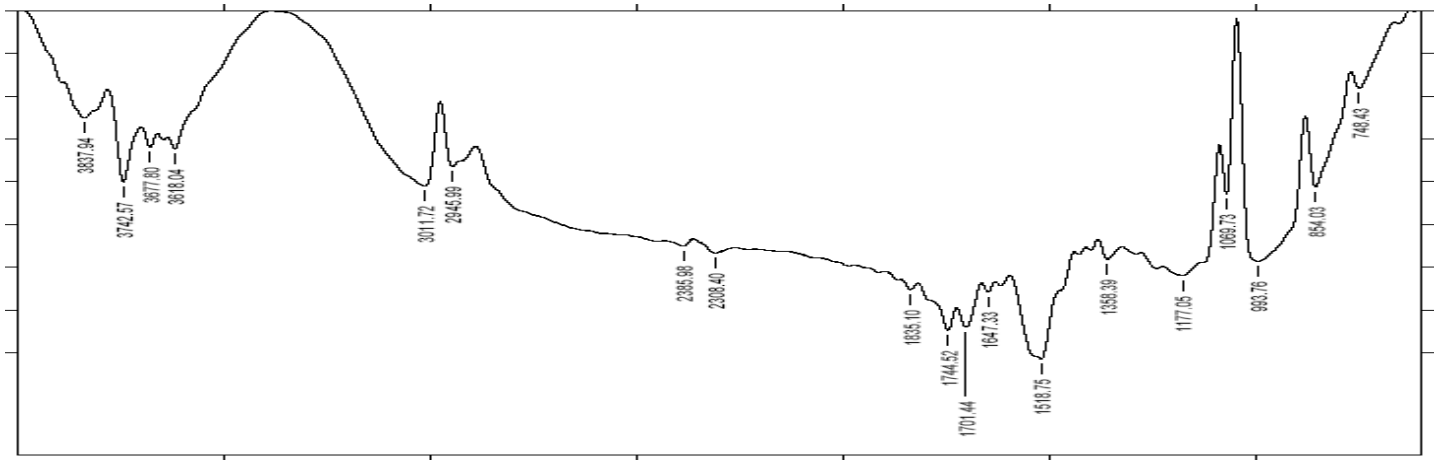

FIG 3: IR SPECTRUM OF DRUG + MODIFIED GUM KARAYA

The pre-compression parameters of all the formulations were depicted in the **table 2**. The angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio shows good flowability in almost all the formulations resulting suitable for the preparation of Fast dissolving tablets.

The prepared tablets were evaluated for different parameters and results were depicted below.

TABLE 2: EVALUATION PARAMETERS OF AMLODIPINE BESYLATE FAST DISSOLVING TABLETS

FORMULATION CODE / PARAMETERS	FHR1	FHR2	FHR3	FHR4	FHR5	FMGK1	FMGK2	FMGK3	FMGK4	FMGK5
Angle of Repose (θ)	26°52′	25°65′	23°54′	24°41′	24°52′	30° 60′	28°60′	27°10′	26°30′	24°30′
Carr's index %	15.87±0.65	15.08±0.65	14.82±0.58	14.59±0.66	13.98±0.55	15.54±0.24	15.08±0.65	14.28±0.89	13.64±0.94	13.46±0.82
Thickness (mm)	2.83±0.55	2.92±0.24	2.81±0.32	2.9±0.33	3.01±0.85	2.83±0.55	2.94±0.24	2.99±0.63	3.0±0.66	3.2±0.98
Hardness (kg/cm^2)	2.8±0.22	3.42±0.55	3.51±0.51	3.1±0.69	3.0± 0.25	2.7±0.32	3.2±0.33	3.3±0.65	3.28±0.69	3.3±0.58
Drug content (%)	99.61±0.45	99.54±0.55	101.31±0.25	99.79±0.58	99.82±0.54	99.44±0.06	99.31±0.41	99.48±0.52	100.11±0.44	99.82±0.21
Weight variation (mg)	200±0.65	199±0.55	201±0.58	200±0.69	199±0.28	199±0.65	201±0.69	199±0.44	199±0.32	201±0.54
Friability (%)	0.22±0.12	0.42±0.25	0.48±0.58	0.52±0.36	0.58±0.64	0.69 ± 0.02	0.72±0.03	0.76±0.09	0.78±0.12	0.83±0.09
Wetting time (sec)	42	38	31	28	26	29	24	20	18	15
Water absorption ratio (%)	79	82	88	91	93	74	79	86	92	94
In vitro dispersion time (min)	2.1	2	2.1	1.8	1	4.3	3.9	3.2	3	3
In vitro disintegration test (sec)	120	122	124	55	48	25	20	18	15	12

Thickness of the formulations FHR1 to FHR5 varied from 2.81±0.32 to 3.01±0.85 mm while of formulations FMGK1 to FMGK5 showed from 2.83±0.55 to 3.2±0.98 mm respectively. The hardness was uniformly maintained and it was found to be within 2.7±0.32 to 3.51±0.51kg/cm^2. Percent friability was less than 1% in the entire formulations and the values obtained lies within 0.22±0.12 to 0.83 ± 0.09 and found within the range only. The percentage weight variation for all the formulations are tabulated in **Table 2**. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5%. The percentage drug content of all the tablets was found to be between 99.31±0.41 to 101.31±0.25, which was within the acceptable limits.

Tablets from each batch show immediate disintegration. Disintegration time decreases with increase in concentration of the disintegrants. Disintegration time was given in **table 2**. The rapid disintegration was seen in the formulation FHR5 containing *Hibiscus rosa – sinensis* mucilage as superdisintegrating agent. This is due to the rapid uptake of water from the medium, swelling and burst effect. Formulation FMGK5 of Modified gum karaya also shows rapid disintegration**.** As the concentration increases, the disintegration time decreases profoundly.

The wetting time was rapid in all the formulations. Wetting is closely related to inner structure of tablets. This may be due to ability of swelling and also capacity of absorption of water. The results were depicted in the **table 2**. The water absorption ratio that is the uptaking of water was very fast and which that ratio found higher.

Dissolution profile of the formulations FHR1, FHR2, FHR3, FHR4, FHR5 and formulations FMGK1, FMGK 2, FMGK 3, FMGK 4, and FMGK 5 is shown in **Figure 4 & 5**. As the concentration of the polymer increased there was decrease in the disintegration time and increase in dissolution of drug. 90% of the drug was released from the all the formulations within 15 minutes.

From drug release, it was observed that increase in concentration of superdisintegrant increases the drug release. Therefore formulation FHR5 and FMGK5 was selected as the optimized formulation as it showed good release, good wetting property and good precompression and good post compression results. From the values obtained, it is proved that all the formulations FHR1 to FHR5 and FMGK1 to FMGK5 dissolution (release) of the drugs follows first order.

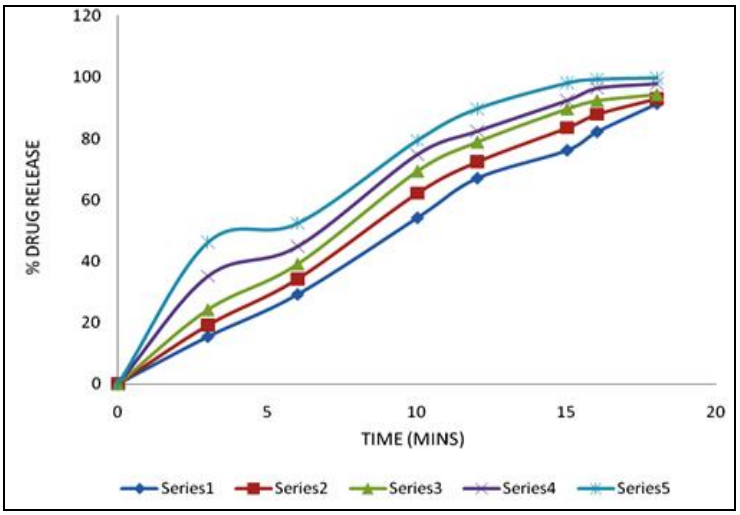

FIG. 4: DISSOLUTION PROFILE OF H R FORMULATION

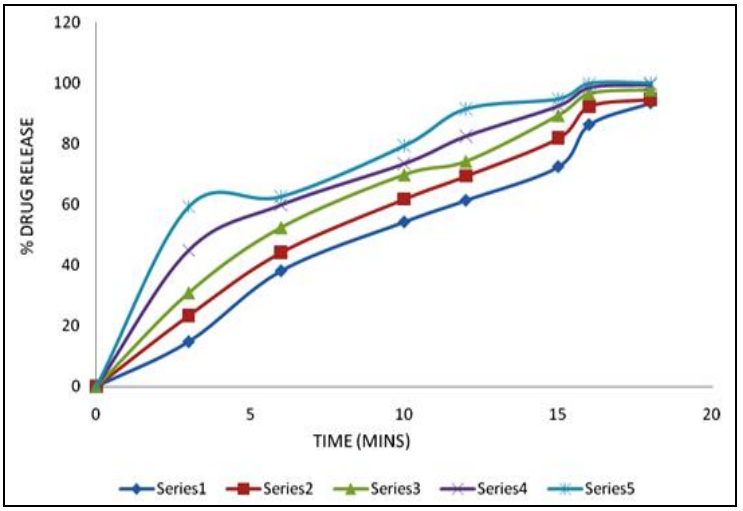

FIG. 5: DISSOLUTION PROFILE OF MGK FORMULATION

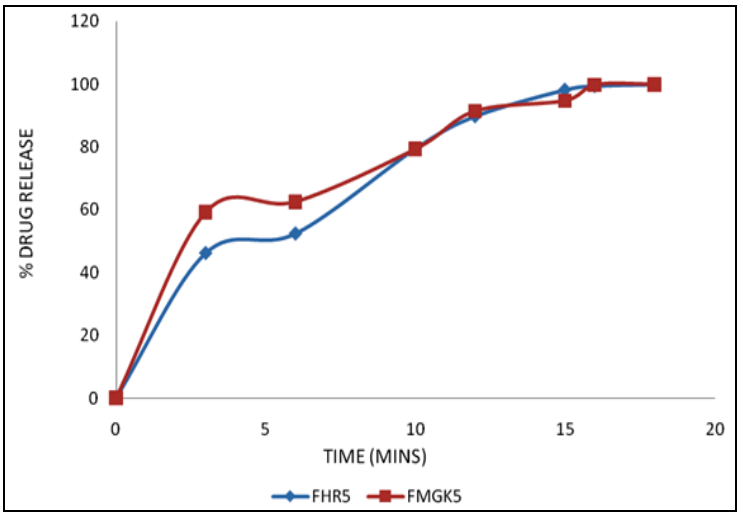

FIG. 6: DISSOLUTION PROFILE OF OPTIMIZED FORMULATIONS

S.NO.	CODE	ABBREVIATION
1	HR	*Hibiscus Rosa – sinensis*
2	MGK	Modified gum karaya

The optimized formulations FHR5 and FMGK5 were kept for accelerated stability and monitored for appearance, hardness, friability, drug content, in vitro dispersion time, wetting time and dissolution profile study and found to stable for all the different parameters (**Fig. 6**).

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