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Research Article

COMPARATIVE EVALUATION OF NATURAL AND SYNTHETIC SUPERDISINTEGRANT FOR PROMOTING NIMESULIDE DISSOLUTION FOR FAST DISSOLVING TECHNOLOGY

KALPESH K. MEHTA[1*], HETUL H. PATEL[2], NITIN D. PATEL[1], CHINTAN N. VORA[1], N. J. PATEL[1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva-382711, Mehsana, Gujarat, India, [2] Shree Swaminarayan Pharmacy College, Kevadia colony, Narmada, Gujarat.
Email: kk30180@yahoo.com, nd121185@rediffmail.com

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ABSTRACT

The purpose of this research was to develop fast dissolving tablets of Nimesulide containing natural *Lepidium sativum* (family: Cruciferae) known as asaliyo and widely used as herbal medicine and pharmaceutical excipient as disintegrating agent. The mucilage was extracted from seeds of *Lepidium sativum* and was used to develop the fast dissolving tablet of Nimesulide. The extracted mucilage was characterized for Weight loss on drying, Particle size, pH of solution, Swelling ratio, Bulk and tapped density, Compressibility index, Viscosity and Angle of repose. The disintegration property of extracted mucilage in FDTs was compared with widely used superdisintegrants like Sodium starch glycolate (SSG), Kyron T314, Ac Di Sol. The prepared FDTs were evaluated for Uniformity of weight, Hardness, Tablet thickness, Percentage friability, Wetting time, *In-vitro* disintegration time and *In-vitro* dissolution. From the study, it was concluded that higher dissolution of tablet could be obtained when mucilage concentration is 10% and also the mannitol concentration was 10%. Promising batch (M5) exhibited better drug dissolution (79.9%) after 30 min than the other tablets. The disintegration and mean dissolution time for batch M_5 was 17 sec and 5.27 sec respectively is better than other tablet prepared from other synthetic disintegrating agent.

Keywords: *Lepidium sativum,* Nimesulide, Kyron T314, FDT

INTRODUCTION

Now a days fast dissolving technology has a nice applicability in case of patient care. Because this type of formulation can disintegrate within few seconds and release their active ingredient very fast and onset of action can be achieved in few minutes. Mostly superdisintegrants are added to the formulations to break up the tablet into small particle that can rapidly dissolve. Many synthetic substances like Sodium Starch Glycolate, Ac-di-Sol, Crossprovidone, and Kyron T314 have been used as a disintegrating agent in the tablet formulation.[1] Mucilage and gums have been used since ancient times for their medicinal uses. In the modern era also they are widely used in the pharmaceutical industries as thickeners, water retention agents, emulsion stabilizers, suspending agents, binders and film formers. Apart from its use in finished medicines, newer uses have been found in the preparation of cosmetics, textiles, and paint paper. Mucilage of natural origin is preferred over synthetic and semisynthetic agent because they are cheaper, abundantly available, nontoxic and nonirritating in nature. *Lepidium sativum* (family: Cruciferae) is known as asaliyo and is widely used as herbal medicine in India. It is widely available in market and has very low cost. Parts used are leaves, root, oil, seeds etc. Seeds contain higher amount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E and F and two new monomeric imidazole alkaloids semilepidinoside A and B. Mucilage of *Lepidium sativum* has various characteristic like binding, disintegrating, gelling etc.[2] Hence in the present study, a method is developed to isolate the mucilage from seeds and its use to develop the fast dissolving tablet. The disintegration property of FDTs was compared with widely used superdisintegrants like Sodium starch glycolate (SSG), Kyron T314, Ac Di Sol. Nimesulide, chemically 4'-nitro-2'-phenoxy methane sulfonanilide, is a weakly acidic nonsteroidal anti-inflammatory drug falls under BCS class II drug , is selected as a model drug as it is widely used in the treatment of the management of a variety of painful and inflammatory conditions like post operative pain, primary dysmenorrhea and painful osteoarthritis. It shows high anti-inflammatory, antipyretic, and analgesic activities in addition to low toxicity, a moderate incidence of gastric side effects, and a high therapeutic index.[3-10]

MATERIALS

Nimesulide (4'-nitro-2'-phenoxy methane sulfonanilide) was gifted from Texas Laboratories Mehsana, Gujarat. Ac-di-sol and SSG were supplied by Lincoln Pharmaceutical Ltd, Ahmedabad. *Lepidium sativum* seed was obtained from local market Mehsana. All other ingredients were used of analytical grade.

METHODS

Methodology for extraction of mucilage *Lepidium sativum*[11]

The seeds of *Lepidium sativum* contain the mucilage around the outer layer. The major problem in isolation of mucilage is that it swells but does not separate from the seeds. Because of this, general methods of separation of mucilage are not applicable to separate the seed mucilage and hence, different procedures were tried for the separation of mucilage.

Method A

In first method (method A) the seeds (100 g) were boiled with distilled water (1 litre) for 15 minute and the mass was filtered through Buckner funnel without filter paper. The retained residues were boiled with distilled water (0.5 litre) for 15 minute and the combined liquid was passed through eight folds of muslin cloth. The mucilage was precipitated from the filtrate by adding ethanol. The precipitated mucilage was dried in an oven at 45^{0}C till it was completely dried. The powder was passed through 80 # mesh sieve and weighed to calculate the yield.

Method B

In the second method (method B) the seeds (100 g) were soaked for 12 hour in distilled water (1litre) and then added to a blender to separate mucilage from seeds. After blending for 15 minute the mass was passed through eight folds of muslin cloth. The mucilage was precipitated from the filtrate by adding 1 liter of acetone. The powder was passed through 80 # mesh sieve and weighed to calculate the yield after drying at 45^{0}C for 6 h.

Method C

In third method (method C) the seeds (100 g) were soaked for 12 hour in distilled water (1litre) and crushed in blender for 15 minute. The dispersion was boiled for 30 minutes and the mass was passed through eight folds of muslin cloth. The mucilage was precipitated from the filtrate by adding acetone. The powder was passed through 80 # mesh sieve and weighed to calculate the yield after drying at 45 ^{o}C for 6 hour.

Characterization of mucilage[2]

Chemical characterization of *Lepidium sativum* mucilage

The presence of mucilage in extracted material was confirmed using Molisch's test and by treatment with ruthenium red.

Physicochemical characterization of *Lepidium sativum* mucilage

Weight loss on drying: Weight loss on drying was determined for an appropriate quantity of mucilage at 105 °C for 2 hour and percentage loss of moisture on drying was calculated using the formula.

LOD (%) = (Weight of water in sample/Weight of dry sample) ×100

Particle size: The particle size of the dried-powder mucilage was determined by the microscopic method, and the study was carried out in triplicate.

pH of solution: The pH of the 0.5% solution was measured with a pH meter.

Charring: A few milligrams of dried mucilage were placed in a melting-point apparatus. The temperature was taken and recorded when the material started to char.

Swelling ratio: The study was carried out using a 100 ml stoppered graduated cylinder. The initial bulk volume of 1 gm of dried mucilage was recorded. Water was added in sufficient quantity to yield 100 ml of a uniform dispersion. The sediment volume of the swollen mass was measured after 24 hour, stored at room temperature. The swelling ratio was calculated by taking the ratio of the swollen volume to the initial bulk volume.

Bulk and tapped density: A Preweighted, presieved quantity of dried mucilage was poured into a graduated cylinder, and the volume recorded. The cylinder was tapped until the powder-bed volume reached a minimum value, and the tapped volume was recorded. The bulk and tapped densities were calculated.

Bulk density = Mass/Bulk volume;

Tapped density = Mass/Tapped volume

Compressibility Index: Compressibility index gives the important property of granules. It is also known as Carr's index. It can be calculated by following equation: It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below: [19]

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Viscosity: Rheological studies of dried mucilage were carried out using varying concentrations (0.1–0.5% w/v) prepared in distilled water. The viscosities were measured using a Brookfield viscometer.

Angle of Repose: The fixed funnel and free-standing cone methods employ a funnel that is secured with its tip at given height, H, which was kept 2 cm, above graph paper that is placed on a flat horizontal surface. With r, being the radius of base of conical pile,

$$\tan \theta = h / r$$

Differential scanning calorimetry (DSC) studies: DSC study was carried out using DSC-TA60 instrument (M/s Shimadzu, Japan) to check the compatibility of ingredients. DSC thermograms of pure drug (Nimesulide), Mucilage (*Lepidium sativum)* were individually taken for their identical endothermic reaction. Finally physical mixture of all above ingredients was scanned for DSC.

Fourier transforms infrared (FTIR) spectral studies: Fourier transform infrared (FTIR) spectral data were taken on a Shimadzu (model FTIR-8300) instrument to find out chemical stability of the excipients. FTIR spectra of pure drug, mucilage and mixture were obtained. All the samples were crushed with potassium bromide to get pellets at 1 ton/cm^2. Spectral scanning was done in the range between 4000-400 cm^{-1}.

Preparation of fast dissolving nimesulide tablets[12]

Different fast dissolving tablet formulations were prepared by direct compression method.

All the powders were passed through 80 # sieve to decrease the particle size. Required quantity of drug and excipients mixed thoroughly. The blend was compressed using Rotary Tablet Machine-12 Station. Each tablet contained 100 mg of Nimesulide and other pharmaceutical ingredients.

Formulation for optimization of mannitol as a solubilizing agent

Composition for optimization of mannitol as a solubilizing agent for fast dissolving formulation is shown in Table 1.

Formulation of preliminary trial batches to check the activity of mucilage as disintegrating agent[13]

Composition of preliminary trials batches to check the activity of mucilage as disintegrating agent is shown in Table 2.

Optimization of mucilage concentrations as dissolution and disintegration enhancing agent

Composition for optimization of mucilage as a disintegrating agent for fast dissolving formulation is shown in Table 3.

Formulation for comparison of mucilage with SSG and Ac-di-sol super disintegrants

Comparison of mucilage with SSG and Ac-di-Sol as a disintegrating agent for fast dissolving formulation is shown in Table 4.

Table 1: Formulation for optimization of mannitol as a solubilizing agent

	PM0	PM1	PM2	PM3	PM4
Drug	100	100	100	100	100
MCC	129.5	117	104.5	92	79.5
Mannitol (%)	0	5	10	15	20
SSG (%)	5	5	5	5	5
Mg Stearate	3	3	3	3	3
Talc	5	5	5	5	5
Total Weight	250	250	250	250	250

*All quantity in mg.

Table 2: Two trial batches to check the activity of mucilage as disintegrating agent

	PM	PS
Drug	100	100
MCC	107	107
Mannitol	25	25
Mucilage	5%	-
SSG	-	5%
Mg Stearate	3	3
Talc	5	5
Total Wt.	250	250

* All Quantity in mg

Table 3: Optimization of mucilage concentration as dissolution and disintegration time enhancing agent

	M1	M2	M3	M4	M5	M6	M7
Drug	100	100	100	100	100	100	100
MCC	112	108	104	100	96	92	88
Mannitol	25	25	25	25	25	25	25
Mucilage (%)	2	4	6	8	10	12	14
Mg Stearate	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5
Total Weight	250	250	250	250	250	250	250

* All Quantity in mg

Table 4: Comparison of mucilage with SSG and Ac-di-Sol as a disintegrating agent

Formulation	M(Mucilage)	S(SSG)	A(Ac-di-sol)
Nimesulide	100	100	100
MCC	96	107	108
Mannitol	25	25	25
Mucilage	10%	-	-
SSG	-	5%	-
Ac-di-Sol	-	-	4%
Mg Stearate	3	3	3
Talc	5	5	5
Total Weight	250	250	250

* All Quantity in mg

Evaluation of physical parameter of prepared mucilage FDT of Nimesulide[14]

Prepared tablets were evaluated for certain physical properties like uniformity of weight, hardness, friability and dissolution study.

Uniformity of weight[15]

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1 mg by using Sartorious balance (BT 124 S). Weight control is based on a sample of 20 tablets. Determinations were made in triplicate.

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-5 kg/cm^2 is considered adequate for mechanical stability. Determinations were made in triplicate.

Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

$$\% \ \textit{Friability} = \frac{W_0 - W}{W_0} \times 100$$

***In-vitro* disintegration test[16]**

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electrolab, Mumbai, India) distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Wetting time[17]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm^2 diameter were placed in a petridish with a 10 cm^2 diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, was added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time.

***In-vitro* dissolution profile of prepared Nimesulide FDT[18]**

The release rate Nimesulide from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method).

The dissolution test was performed using 900 ml of phosphate buffer (pH 7.4) at 37^{0}C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 2, 5, 10, 15, 20, 25 and 30 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µm membrane filter. Absorbance of these solutions was measured at 392 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULT AND DISCUSSION

Characterization of mucilage

Chemical characterization of *Lepidium sativum* mucilage

The presence of mucilage in extracted material was confirmed using Molisch's test and by treatment with ruthenium red. Both tests were positive for the presence of mucilage.

Physiochemical characterization of *Lepidium sativum* mucilage

The results of other investigations (percentage yield, particle size, pH of solution, loss on drying) are shown in Table 5.

Table 5: Physicochemical property of dried mucilage *Lepidium sativum*

Percentage yield	22%
pH	6.2
Particle size	189.57 µm

Loss on drying

The weight loss on drying indicates the amount of moisture present in the material available to interact with other material. For dried mucilage, the loss on drying was 17.53%.

Swelling ratio

The swelling ratio of mucilage, determined in distilled water was 3.7. There was a significant change in swelling by the end of the

study, which indicated that the mucilage had excellent swelling properties.

Viscosity

The viscosity of the extracted dried mucilage was 8.05cps for 0.5 % solution. It can be concluded that mucilage has a viscosity of such type that is suitable for fast dissolving drug delivery.

Flow property

The flow properties and compressibility of the dried mucilage, including bulk and tapped density, Carr's index, the Hausner's ratio, and the Angle of repose are shown in Table 7. It can be concluded that the dried mucilage has a good flow properties which is suitable for a direct-compression formulation.

DSC study

DSC curves obtained for pure Nimesulide, Mucilage (*Lepidium sativum)*, Nimesulide + mucilage is shown in figure 1. Pure powdered Nimesulide showed a melting endotherm at 152.95°C. DSC thermo grams of physical mixture of drug and excipients showed the melting peak of the drug at 152.15°C. Presence of all peaks indicates that all ingredients were compatible.

The FTIR a study was carried out for the drug, mucilage (*Lepidium sativum),* and mixture of both drug and mucilage. IR spectrum for the pure drug, mucilage and mixture are indicated in Figures 2. The peaks of all the functional groups lie within the limit. From the IR studies it was found that there was no interaction of the functional groups of drug with the mucilage in case of fast dissolving tablet of nimesulide.

Table 6: Rheological data of dried mucilage *Lepidium sativum*

Concentration	Viscosity
0.1%	1.95 cps
0.2%	2.85 cps
0.3%	3.35 cps
0.4%	6.15 cps
0.5%	8.05 cps

Table 7: Flow properties of dried mucilage *Lepidium sativum*

Bulk density (g/ml)	0.37
Tapped density (g/ml)	0.62
Carr's index (%)	40.32
Hausner's ratio	1.67
Angle of repose (⁰)	36.14

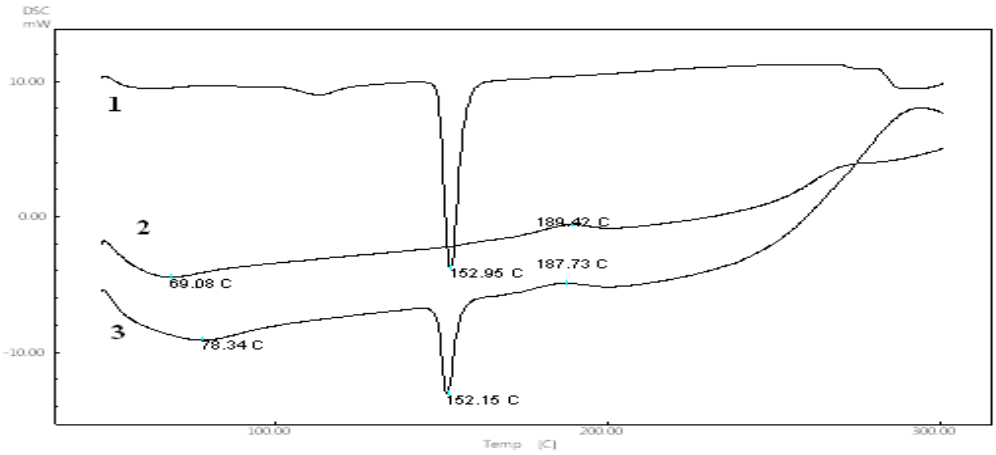

Fig 1: DSC Spectra of Nimesulide (1), Mucilage (2), Nimesulide + Mucilage (3)

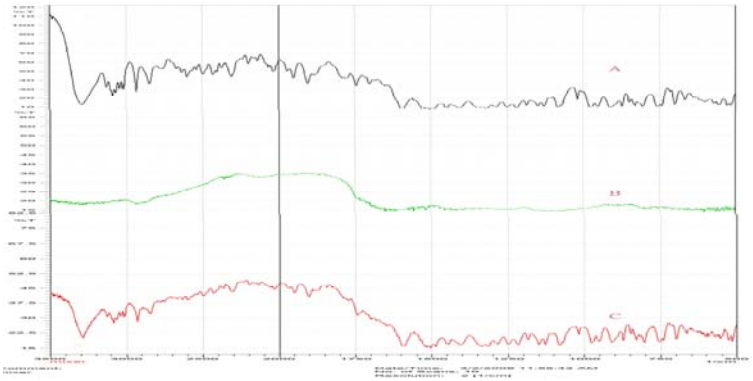

Fig 2: FTIR Spectra of Nimesulide (A), Mucilage (B), Nimesulide + Mucilage (C)

Characterization of prepared tablet

Optimization of mannitol as a solubilize agent

In preliminary study, different batches were prepared as per the composition given in Table 1. Different other evaluation parameters were also studied. Considering release profile, batches PM0- PM4 shows drug release with slight variations. From all batches, it was

found that Batch PM2 gives desirable fast release action. Moreover, hardness, disintegration time of tablet were found 4±0.2 kg/Cm², 42 sec, it gives 65.22% release of drug with in 30 minute (Figure 3). Therefore, the mannitol concentration 10% was selected for further work.

Table 8: Evaluation parameters of Nimesulide fast dissolving tablet

Batch code	Hardness (n=5) kg/cm²	DT time (Sec)	Wetting time (Sec)	%Friability	Weight Variation
PM_0	4.36 ± 1.20	47	51	0.42	248 ± 2.50
PM_1	4.09 ± 0.89	44	48	0.51	251 ± 2.00
PM_2	4.00 ± 0.55	42	50	0.35	249 ± 2.74
PM_3	4.51 ± 0.89	40	47	0.40	249 ± 2.15
PM_4	4.46 ± 1.20	37	41	0.42	253 ± 2.54

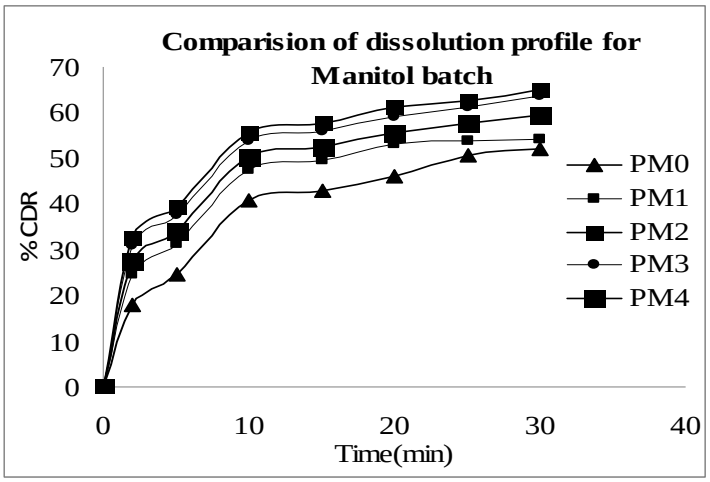

Fig 3: Drug release profiles of different mannitol batches

Preliminary trails batches to check the activity of mucilage as disintegrating agent

In present investigation attempt was made to prepare Fast Dissolving tablet formulation of Nimesulide using mucilage as a disintegrating agent in one batch and in another batch SSG batch tablets were prepared by direct compression method. In preliminary study, different batches were prepared as per the composition given in Table 2. From the obtain result, it was found that 5 % mucilage batch gives desirable fast release action compared to 5% SSG (Figure 4).

Optimization of mucilage concentration as a super disintegrating agent

In preliminary study, different batches were prepared as per the composition given in Table 3. All the batches were evaluated for *in-vitro* dissolution study (Figure 5) and other evaluation parameters (Table 9). From all batches, it was found that Batch M5 (Table 3) gives desirable fast release action. Moreover, hardness, disintegration time of tablet were found 4±0.2 kg/cm², 17 sec, it gives 79.90% release of drug with in 30 minute. Therefore, the mucilage concentration 10% was selected for further work.

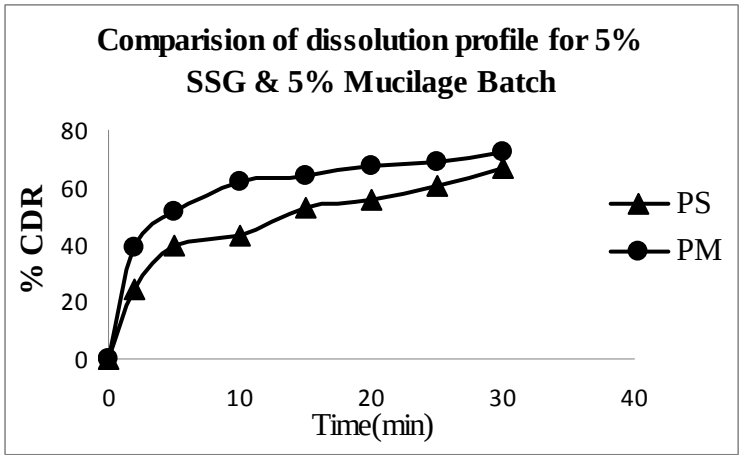

Fig 4: Comparative cumulative drug release profile for mucilage and SSG

Table 9: Evaluation parameters of Nimesulide fast dissolving tablet using mucilage

Batch code	Hardness (n=5) kg/cm²	DT time (Sec)	Wetting time (Sec)	%Friability (n=10)	Weight Variation (n=20)
M1	4.06 ± 1.17	37	40	0.43	249 ± 2.48
M2	4.11 ± 0.78	34	37	0.46	250 ± 1.00
M3	4.02 ± 0.49	31	35	0.45	251 ± 1.64
M4	4.14 ± 0.75	24	27	0.43	249 ± 1.15
M5	4.00 ± 0.20	17	19	0.47	250 ± 1.45
M6	4.23 ± 1.08	16	21	0.44	249 ± 1.89
M7	4.12± 1.15	16	22	0.47	249 ± 1.40

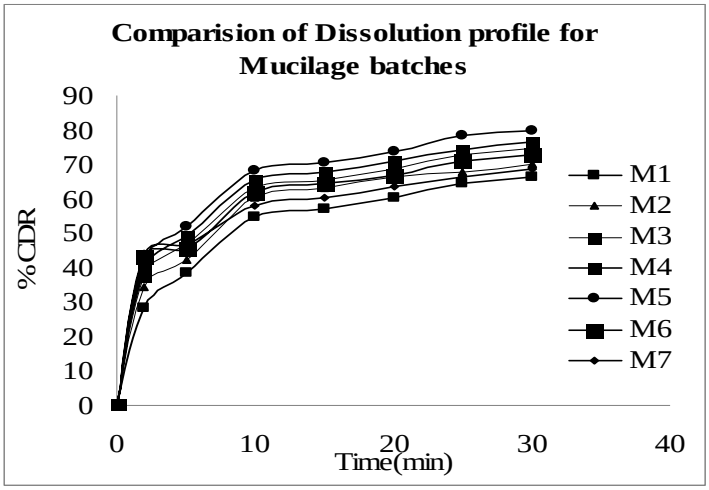

Fig 5: Comparative cumulative drug release profile for different mucilage batches

Table 10: Evaluation parameters of Nimesulide fast dissolving tablet using Mucilage, SSG, and Ac-di-Sol Batches

Batch code	Hardness (n=5) kg/cm²	DT time (Sec)	Wetting time (Sec)	%Friability (n=10)	Weight Variation (n=20)
M(Mucilage)	4.00 ± 0.20	17	19	0.39	252±1.45
S(SSG)	4.81 ± 0.78	39	42	0.45	249±1.75
A(Ac-di-sol)	4.20 ± 0.49	36	39	0.37	250±1.54

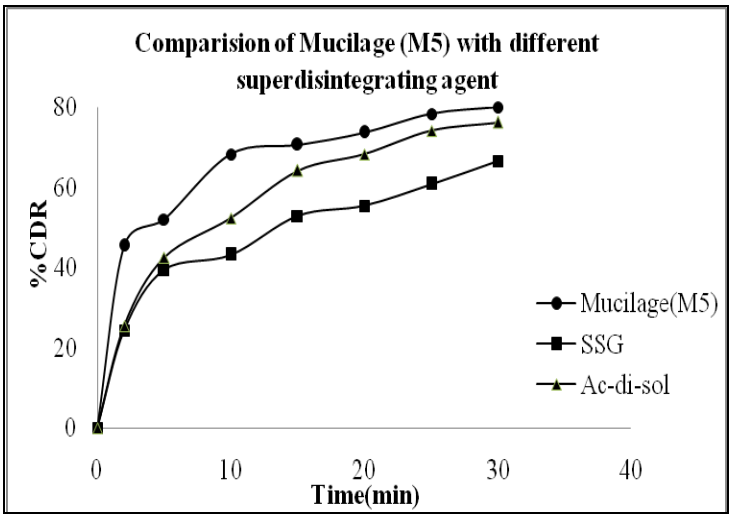

Fig 6: Comparison of cumulative drug release profile of mucilage with different super disintegrating agents

Formulation for comparison of mucilage with SSG and Ac-di-Sol super disintegrants

Different batches were prepared as per the composition given in Table 4. All the batches were evaluated for *in-vitro* dissolution study (Figure 6) and other evaluation parameters (Table 10). From all batches, it was found that Batch M (Figure 6 and Table 10) gives desirable fast release action, DT time and Wetting time.

CONCLUSION

In the all above formulation mucilage was incorporated as a disintegrating agent to reduce the disintegration time and mannitol was incorporated to increase the solubility of mucilage. Based on result, it was concluded that higher dissolution of tablet could be obtained when mucilage concentration is 10% and also the mannitol concentration was 10%. Promising batch (M5) exhibited better drug dissolution (79.9%) after 30 min than the other tablets. The disintegration and mean dissolution time for batch M (mucilage) was 17 seconds and 5.27 seconds respectively, is better than other tablet prepared from other synthetic disintegrating agent. From the obtain result, it was found that mucilage batch gives desirable fast release action as compare to Ac-di-Sol and SSG.

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