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Research Article

Design and Development of Fast Disintegrating and Fast Releasing Tablets of *Gymnema Sylvestre*

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Abstract

Gymnema sylvestre is one of the plants with potent antidiabetic and anti obesity potential. Its formulations can serve as an alternative medicine for both diabetes and obesity. Gymnema sylvestre is available as standardized extract but all herbal dry extracts, mainly due to their hygroscopic nature creates tabletting problems like increase tablet hardness and prolong disintegration time etc. So it is difficult to prepare tablets containing high doses of extracts. The aim of the study was to develop Gymnema sylvestre extract containing tablets with the disintegration time less than 5 min and more than 90% drug release in 30 minutes. Also the effect of the type and mode of addition of the disintegrants on disintegration time and hardness of the tablets with *Gymnema sylvestre* extract was studied. It was found that the fast disintegrating tablets of the Gymnema sylvestre can be prepared from wet granulation technique. Out of the various superdisintegrants used in the wet granulation technique, cross povidone was found to be the best superdisintegrant for preparing fast disintegrating tablets of Gymnema sylvestre. The mode of addition of addition of superdisintegrant also effects the disintegration and dissolution profile of the prepared tablets.

1. INTRODUCTION

Gymnema sylvestre is an herb that is most frequently prescribed by herbalists for improving glycemic control.[1] In addition; it possesses antimicrobial, antihypercholesterolemic, hepatoprotective and sweet suppressing activities.[2] *Gymnema sylvestre* targets several of the etiological factors connected with diabetes and no single oral hypoglycemic drug presently exerts such a diverse range of effects and it may be useful in the management of diabetes mellitus and obesity.[3] Leaves of the plant contain triterpene saponins belonging to oleanane and dammarene classes. Oleanane saponins are gymnemic acids and gymnemasaponins, while dammarene saponins are gymnemasides. The antidiabetic array of molecules has been identified as a group of closely related gymnemic acids after it was successfully isolated and purified from the leaves of *Gymnema sylvestre*.[4] The gymnemic acids are useful in curbing of diabetes by a many mechanisms like it increases secretion of insulin, promotes regeneration or repairing of beta cells, increases utilization of glucose, causes inhibition of glucose absorption from intestine, inhibits insulin inactivation by acting on liver cells, reduces peripheral insulin resistance and improves uptake of glucose into cells etc.[3]

Gymnema sylvestre extracts are standardized for gymnemic acid content which is (25-75%) and the recommended daily therapeutic dose of the extract, depending on gymnemic acid content, is from 300-700 mg.[5] However the drug delivery system available for administering the herbal medicine to the patient are traditional and out-of-date, resulting in reduced efficacy of the drugs.

The drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms.[6]

Herbal dry extracts, mainly due to their hygroscopic nature, usually increase tablet hardness and prolong disintegration time and this is why production of tablets containing high doses of extracts is often impossible.[7-9] Bioavailability study of the active substances from herbal preparations is still not a common requirement but tablets or capsules should be developed considering biopharmaceutical properties like dissolution rate and disintegration time. Slow or incomplete disintegration leads to a low bioavailability of the active substance. Moreover, tablets with herbal extracts are more sensitive to the environment conditions and higher humidity during storage affects their physicochemical characteristics what is easily demonstrated by disintegration time determination. The pharmacopoeial disintegration test can be a good tool to confirm appropriate composition and stability of herbal tablets in respect to their ability to provide large surface area for the following dissolution process. Generally, for uncoated tablets disintegration time (DT) longer than 15 min is unacceptable.[10-13]

Among the excipients used for the herbal tablets the choice of disintegrants and fillers is a critical step for development of products which possess short DT and are stable during storage. The aim of this work was to develop tablets which contain up to 150 mg of *Gymnema sylvestre* extract with the disintegration time less than 5 min. Also the effect of the type and mode of addition of the disintegrants on DT and hardness of the tablets will be studied.

2. MATERIALS AND METHODS

Dry extract of *Gymnema sylvestre* was obtained from Sami labs, Bangalore. The extract was standardized to contain 75% gymnemic acids. The following tablet excipients were used: Microcrystalline cellulose (Avicel PH 101), Crospovidone (Kollidon CL), Cross-linked sodium carmellose (acdi-Sol), Sodium starch glycolate type A (Primojel), Colloidal silicon dioxide (Aerosil;), Talc, and magnesium stearate.

2.1 Preparation of tablets

Tablets of *Gymnema sylvestre* were prepared by a wet granulation process using different superdisintegrants such as crosscarmellose sodium (CCS), sodium starch glycollate (SSG) and crosspovidone (CP) to evaluate the role of different disintegrants in different percentages. Isopropyl alcohol was used as the granulating fluid.

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Various combinations of two different disintegrants were also evaluated.

The disintegrant can be incorporated in the blend before granulation, referred to as intragranular addition (IG), or after granulation, referred to as extragranular addition (EG), or it can be distributed both intra and extragranularly. The mode of addition of the best disintegrant on the disintegration of tablets containing 150 mg of the drug was evaluated by incorporating the disintegrants extragranularly (EG), intragranularly (IG) or distributing them equally (IG and EG).The composition of different batches is shown in Table 1 and 2.

Excipients were mixed with extract and appropriate amount of in IPA was added to form a wet mass. The moist mass was passed through a 0.8 mm sieve and the resulting granules were dried at 40°C. The agglomerates were eliminated by forcing the dried granules through 0.8 mm sieve. Magnesium stearate (0.5%) and Colloidal silicon dioxide (1%) were also added as a lubricant and glidant, respectively.

Table 1: Composition of different batches of wet granulated tablets of GS extract with different superdisintegrants and their combinations

S. No	Formulation Ingredients	FCP1	FCP2	FSSG1	FSSG2	FCCS1	FCCS2	FCOM1	FCOM2	FCOM3
1	GS extract %	50	50	50	50	50	50	50	50	50
2	MCC %	38.5	33.5	38.5	33.5	38.5	33.5	33.5	33.5	33.5
3	CP %	10	15	-	-	-	-	7.5	-	7.5
4	SSG %	-	-	10	15	-	-	7.5	7.5	-
5	CCS%	-	-	-	-	10	15	-	7.5	7.5
6	Colloidal silicon dioxide%	1	1	1	1	1	1	1	1	1
7	Magnesium stearate %	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total tablet weight		300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg

Table 2: Composition of different batches of wet granulated tablets of GS extract with intragranular and extragranular superdisintegrants

S. No.	Formulation Ingredient	FCRP1-IG	FCRP1-EG	FCRP1-IG&EG	FCRP2-IG	FCRP2-EG	FCRP2-IG&EG
1	GS extract %	50	50	50	50	50	50
2	MCC %	38.5	38.5	38.5	38.5	38.5	38.5
3	CP %	10(IG)	10(EG)	10(50%IG + 50%EG)	15(IG)	15(EG)	15(50%IG + 50%EG)
6	Colloidal silicon dioxide%	1	1	1	1	1	1
7	Magnesium stearate %	0.5	0.5	0.5	0.5	0.5	0.5
	Total tablet weight	300mg	300mg	300mg	300mg	300mg	300mg

The granules were evaluated for the angle of repose, bulk density and Compressibility Index. The properties of prepared granules of different batches are shown in Table -3.

2.1.1 Bulk density, tapped density and Carr's index

Ten grams of granules were introduced into a clean, dry 100 ml measuring cylinder and the volume was recorded. The cylinder was then tapped 25 times from a constant height and the tapped volume was read. The bulk density and tapped density were calculated as the ratio of the granules mass and the respective volumes. Carr's index (I) was calculated using the equation:

$$I = Dt - Db / Dt \times 100$$

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

2.1.2 Angle of repose

The fixed funnel method was employed for determining the angle of repose. The granules were poured carefully until the apex of the conical pile just touches the tip of the stem of the funnel. The angle of repose was calculated using the equation:

$$\tan \alpha = H/R$$

Where H is the height of the pile and R is the radius of the base of the conical pile.

Table 3: Properties of different batches of granules for tablets of *Gymnema sylvestre* extract.

Formulation code	Angle of repose (o)	Bulk Density gm/cm^3	Tap density gm/cm^3	Carr's Index
FCP1	32.45±1.09	0.413±0.01	0.487±0.016	15.195±0.12
FCP2	33.49±1.67	0.410±0.009	0.461±0.022	11.062±0.34
FSSG1	28.45±2.11	0.371±0.05	0.453±0.031	18.65±0.78
FSSG2	29.34±1.45	0.382±0.017	0.476±0.033	19.76±0.69
FCCS1	30.96±2.16	0.501±0.028	0.648±0.01	22.976±1.09
FCCS2	31.913±1.78	0.414±0.017	0.494±0.021	16.981±0.98
FCOM1	31.45±1.56	0.411±0.016	0.498±0.021	17.45±1.67
FCOM2	27.46±1.65	0.412±0.014	0.502±0.023	18.54±1.97
FCOM3	29.726±2.06	0.449±0.013	0.531±0.012	15.442±1.04
FCP1-EG	33.56±0.98	0.415±0.021	0.512±0.043	19.76±1.04
FCP1-IG&EG	32.67±0.76	0.434±0.032	0.523±0.045	17.56±1.08
FCP2-EG	34.67±1.54	0.408±0.04	0.485±0.038	15.76±1.43
FCP2-IG&EG	34.54±1.96	0.406±0.026	0.471±0.046	13.65±0.56

2.1.3 Compression of Tablets

The granules were compressed into tablets of 300 mg using 10 mm round flat punches on 10-station rotary tablet machine (Clit). For comparison, tablets containing neither fillers nor disintegrants were prepared by direct compression of the extract and magnesium stearate powder mixture. The properties of prepared tablets of different batches are shown in Table -4.

2.2 Evaluation of tablets

The prepared tablets were evaluated for the following parameters:

2.2.1 Thickness

The thickness of the tablets was determined using a vernier calliper. Five tablets from each batch were used, and average values were calculated.

2.2.2 Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, and the test was performed according to the official method.

2.2.3 Hardness
Six tablets randomly selected from each batch were used for the test. Monsanto hardness tester was employed.

2.2.4 Friability
For each formulation, the friability of 10 tablets was determined using the Roche friabilator.

2.2.5 Disintegration time
The disintegration time (DT) of tablets was determined according to IP using a disintegration tester. Six tablets randomly selected from each batch were used for the test. The disintegration medium was distilled water maintained at 37±0.5.

2.2.6 Wetting Time
The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

2.2.7 *In Vitro* drug Release
The in vitro dissolution studies were carried out using USP apparatus type II at 75 rpm. The dissolution medium consisted of phosphate buffer pH 1.2 (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals (2 min, 5 min, 10 min, 15 min, 20 min and 30 minutes.) was measured by the developed HPLC method. To quantify gymnemic acid in the samples, the total gymnemic acids were converted to DAGA. This conversion was done by saponification of the procured extract using potassium hydroxide in methanol and the HPLC was carried out.[14] The release studies were conducted in triplicate. The mean values were plotted versus time and shown in table 5.

2.2.8 Drug content
The quantity of total gymnemic acid present in the formulations was determined by the developed HPLC method.

Table 4: Properties of different batches of tablets of *Gymnema sylvestre* extract.

S. No.	Formulation code	Thickness (mm)	Weight variation (192.5-207.5 mg (IPlimits±7.5%) (n = 20)	Drug Content %	Hardness Kg/cm^2 (n = 6)	Friability (%)	Disintegration time (minutes) (n = 6)	Wetting Time (minutes) (n = 6)
1	FCRP1	5.2	197±4.6	97.26	4.7±0.72	0.42	2.6±0.27	2.2±0.67
2	FCRP2	5.4	199±3.6	96.13	3.9±0.91	0.51	1.0±0.17	0.9±0.1
3	FSSG1	5.3	197±4.8	99.67	5.1±0.88	0.73	3.5±0.15	3.1±0.13
4	FSSG2	5.2	202±3.5	95.78	4.7±0.72	0.30	3.2±0.34	3.0±0.39
5	FCCS1	5.2	198± 3.6	98.28	5.2±0.62	0.88	4.1±0.25	3.9±0.75
6	FCCS2	5.4	200±5.8	102.45	5.6±0.81	0.98	3.4±0.29	3.1±0.21
7	FCOM1	5.4	199±4.8	97.45	4.5±0.77	0.32	2.4±0.54	2.0±0.29
8	FCOM2	5.3	201± 3.7	98.34	5.1±0.86	0.53	3.9±0.23	3.7±0.28
9	FCOM3	5.4	196±1.8	100.34	5.3±0.54	0.77	2.5±0.19	2.3±0.49
10	FCRP1-EG	5.2	202±3.5	98.43	5.1±0.86	0.82	1.4±0.31	1.2±0.37
11	FCRP1-IG&EG	5.3	204± 1.7	99.97	4.8±0.73	0.51	1.9±0.27	1.6±0.26
12	FCRP2-EG	5.4	203±1.7	98.34	4.9±0.43	0.93	0.33±0.17	0.2±0.13
13	FCRP2-IG&EG	5.3	197±4.8	97.80	4.7±0.89	0.83	0.5±0.27	0.2±0.16

Table 5: In Vitro Dissolution Parameters in pH 5.5 Phosphate Buffer

Formulation Code	D_{5MIN}	D_{10MIN}	D_{15MIN}	D_{20MIN}	D_{30MIN}
FCP1-+IG	37.23±1.4	57.45±2.4	72.08±3.7	87.14±3.6	95.06±4.23
FCP1-EG	18.70±1.43	37.2±2.61	49.08±3.65	57.45±3.12	81.12±3.65
FCP1-IG&EG	27.56±2.67	45.34±1.98	67.6±3.76	84.23±2.13	90.04±4.04
FCP2-IG	48.65±2.7	67.54±2.8	85.4±2.98	92.21±3.5	96.86±3.21
FCP2-EG	21.54±2.5	39.45±2.12	68.71±3.76	71.45±3.06	85.65±3.35
FCP2-IG&EG	32.9±1.56	51.19±3.54	74.02±3.54	89.55±2.85	92.05±2.05

D is cumulative percent drug released in, 5 min, 10 min, 15 min, 20 min and 30minutes. (n =6)

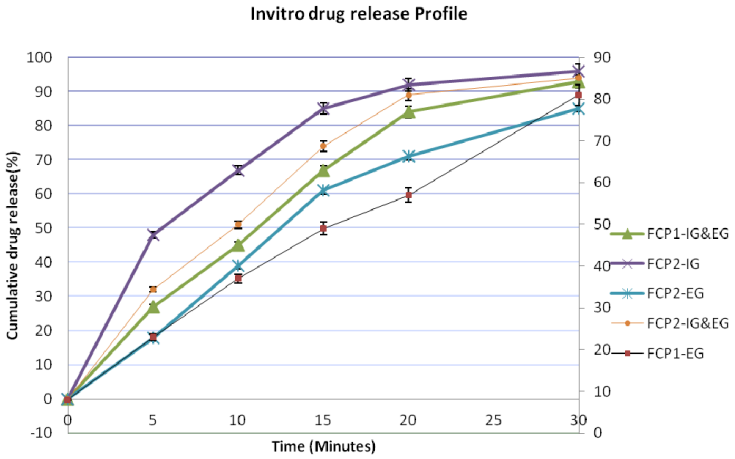

Figure 1: *In vitro* cumulative percent drug release in 1.2 pH phosphate buffer

2.3 Stability studies

In order to determine the change in *in-vitro* release profile on storage, stability study were performed for the best formulation (FCRP2-IG&EG) 40°C ± 2°C / 75% ± 5% RH. Samples were withdrawn at regular intervals during the study of 60 days. Formulations were evaluated for weight gain, drug content, in-vitro drug release, hardness, wetting time and disintegration time.

Table 6: Physical Characteristics of the optimized batch during stability studies at Temperature (40°C±2°C / 75% RH±5%) (n =6)

Physical Parameter	0 days	15 Days	30 Days	60 Days
Weight (mg)	197±4.8	197±3.4	196±3.1	196±3.9
Percent drug content (%)	97.80	97.68	96.56	96.51
Hardness (Kg/cm2)	4.7±0.89	4.6±0.82	4.8±0.82	4.7±0.34
Disintegration time (sec)	30±3.7	34±2.6	35±3.2	35±4.4
Wetting time (sec)	15±2.7	18±1.2	19±2.5	20±3.8
Drug release % after 30min	92.05±2.05	93.54 ±2.53	91.95±3.15	91.07±2.85

3. RESULTS AND DISCUSSION

Dried plant extracts are often used as therapeutically active material in the manufacture of tablets. They are quite often very fine, poorly compressible, and very hygroscopic powders. Additionally, tablets containing a high amount of dried extract show prolonged disintegration times; therefore, the release of the active constituents is affected.

GS dry extract is a slightly compressible substance which can be tabletted practically without other excipients. Tablets containing 300 mg of the extract and magnesium stearate (0.5 %) were produced, however, they were very hard, and were disintegrating slowly dissolving in about 4-5 hrs by surface dissolution**.** A good compressibility of the extract is most probably caused by its water content which is between 2-3%w/w.

Some alternatives have been proposed to minimize these problems and producing immediate release tablets or fast disintegrating tablets which are the solid unit dosage forms/entities containing medicinal substances which disintegrate or dissolve rapidly within a few seconds or minutes. Out of the various technologies available to develop fast dispersible tablets the, superdisintegrant addition, was selected. The wet granulation technology was used for tablet formulation as the physical properties of the extract batches usually are not reproducible, which can affect flowability of the powder during tabletting and cause serious problems in uniformity of the final product. Hence it was tried to prepare fast disintegrating tablets by granulation technique with different types and concentration of superdintegrants.

The Microcrystalline cellulose was selected as the filler because the solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. The granulation was done by isopropyl alcohol. The combination of different disintegrants was also tried.

From the initial formulation studies it was found that the tablet mass was very sticky so the binder was avoided in the formulations. The colloidal silicon dioxide is added in 1% concentration to reduce the friability of the tablets because it enhances the adherent properties of other ingredients.

The granules were evaluated for the angle of repose, bulk density, tapped density and Car's index. All the parameters were in good compressibility range. The tablets were compressed and evaluated for various tablet properties viz thickness, hardness, friability, weight variation and disintegration time.

The hardness of tablets was between 3-6 Kg/cm^2. The least disintegration time was found to be with batch no. FCP2 containing 15% of cross povidone which was 60 seconds and the hardness of the same tablet was 4.5 Kg/cm^2. The tablet disintegrated by bursting. The disintegration time for all the batches prepared by granulation technique was between 60 seconds to 8 minutes. It was found that the cross povidone is a better superdisintegrant for formulation fast disintegrating tablets of *Gymnema sylvestre* and it is giving very good disintegration at 15% concentration. The combination of superdisintegrants is also not as effective as 15% cross povidone.

Further the disintegrant can be incorporated in the blend before granulation, referred to as intragranular addition (IG), or after granulation, referred to as extragranular addition (EG), or it can be distributed both intra and extragranularly referred to as IG&EG. The disintegration time of batches FCP2-IG, FCP2- EG and FCP2-IG&EG containing crosspovidone 15% were found to be 60 seconds, 20 seconds and 30 seconds. The dissolution study was performed for batches FCP1-IG, FCP1- EG and FCP1-IG&EG all containing 15% of cross povidone. The dissolution curves are shown in graph 1. From the dissolution profile it is evident that the dissolution from the tablets containing intragranular superdisintegrant if faster and more (96% in 30 minutes) as compared to extragranular superdisintegrant (85% in 30 minutes) but its disintegration time is also more (60 seconds) as compared to (20 seconds) EG-superdisintegrant. Hence a combination of IG and EG superdisintegrant(15% cross povidone) will be taken in the optimized formulations giving disintegration in 30 seconds and 92% drug release in 30 minutes.

The results of stability studies indicated that the optimized formulations was stable, and did not show any significant difference in drug content, disintegration time and dissolution rate after a study period of two months.

4. CONCLUSION

It can be concluded that the immediate release tablets of the *Gymnema sylvestre* can be prepared from wet granulation technique. Out of the various superdisintegrants used in the wet granulation technique, cross povidone was found to be the best superdisintegrant for preparing fast disintegrating tablets of *Gymnema sylvestre*. The mode of addition of addition of superdisintegrant also effects the disintegration and dissolution profile of the prepared tablets. And the combination of inter-granular and extra-granular superdisintegrant addition gives the fast disintegration and dissolution of the tablet.

5. ABBREVIATIONS

DT: Disintegration time
EG: Extragranularly
IG: Intragranularly

6. ACKNOWLEDGEMENT

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7. CONFLICT OF INTEREST: Nil

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