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Studies in Development and Evaluation of Sennoside Formulations

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A large number of Chinese and Japanese medicinal plants have been widely studied and data generated to provide scientific basis to the traditional claims. In majority of herbal formulations, preformulations and post formulation studies are lacking. Hence, an attempt is made to develop *senna* formulations using crude powder, standardized extract and calcium sennosides. *Senna* powder tablets were prepared by wet granulation method. Different binders and diluents affected the % compressibility and hardness of the formulations. Polyvinyl pyrrolidone and cocrystallized lactose-microcrystalline cellulose showed improved tablet characteristics. *Senna* powder contains mucilage, which slows the disintegration of the tablet. Cross-linked polyvinyl pyrrolidone improved disintegration time of *senna* power tablets. To improve the bioavailability, incorporate more amounts of actives and to reduce the dosage size, tablets of *senna* extract and calcium sennosides were prepared. Sennosides content was analyzed using HPLC method. Formulation parameters and dissolution study results of *senna* powder tablet were compared with tablet containing *senna* extract calcium sennosides. Calcium sennosides and *senna* extract tablet showed better dissolution than *senna* powder tablet.

The growth of the herbal medicines and food supplements has been very impressive and quite phenomenal. The share of Indian Herbal Medicinal Plants in the world market is very unimpressive. This may be due to a number of lapses like; the active compounds responsible for the proposed activity are not properly identified, there is no uniformity in the process of manufacture, no SOPs are available for production and validation of formulations and important one is the formulation part, which is almost untouched. It is necessary to evaluate preformulation and post formulation aspects of these herbal dosage formulations.

Senna is known as an anthraquinone laxative which is used to treat constipation and for bowel evacuation before radiological procedures[1,2]. The active anthraquinone are liberated into the colon from the glycoside by colonic bacteria and an effect usually occurs 6–12 h after administration[3,4]. They stimulate and increase the peristaltic movements of the colon by local action upon intestinal wall[5]. For the treatment of constipation, *senna* is usually administered as tablets, granules or syrup. In UK, usual adult dose is the equivalent of 15–30 mg of total sennosides given as a single dose at bedtime[6]. Dried powder of *senna* leaves was used for the present investigation.

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MATERIALS AND METHODS

Senna (Cassia angustifolia, Family: Leguminaceae*)* plants were cultivated in the pharmacognosy garden of the college and mature leaves were harvested. Ca-sennosides (20% w/w) was gifted by Dishman Pharmaceuticals, Ahmedabad. Other materials used in the study such as lactose, dicalcium phosphate (DCP), microcrystalline cellulose (MCC), cocrystallised lactose-MCC, magnesium stearate, talc, starch and polyvinyl pyrrolidone (PVP) were of pharmaceutical grade and used as received. Na-2-hydroxy isobutyrate, acetonitril were of HPLC grade. Double dis-

tilled water was used throughout the study. HPLC grade water was used for analysis.

Dried *senna* leaves were powdered to 60#. *Senna* powder was extracted with 70% hydroalcohol by cold maceration for 4 d and filtered. The extract was concentrated on a water bath. Sennosides in *senna* powder (SP), *senna* extracts (SE) and Ca- sennosides (CS) were analyzed by high performance liquid chromatography (HPLC) method[7].

Formulations of *senna* powder:

Senna powder was blended with diluents like, lactose/DCP/MCC/Co-crystallized lactose-MCC in the ratio of 1:0.5. Granules were prepared using PVP (3, 5, 7 and 10 %) in isopropyl alcohol or starch paste (5, 7, and 10 %). Granules were evaluated for compressibility, friability and flowability. Best binder and diluent fitting into criteria were selected for further studies. *Senna* powder contains mucilage and disintegration of the tablets is the major formulation problem. Cross linked PVP was used as disintegrating agent in 2, 3, 4, 5 and 6% concentration. The effect of intra and extra granuler addition of disintegrating agent was studied. Granules were lubricated with 1% magnesium stearate and 2% talc. Granules were compressed using high-speed multipunch tablet press with oblong shaped punches. The tablets had an average weight of 800 mg. The average crushing strength was 4.8 kgf and friability was 0.52%. The composition of the formulations is shown in Table 1.

Formulation of *senna* extract:

Tablets of SE were prepared by wet granulation method. Since the extract is semi-solid, less amount of binder would be necessary to prepare tablets. Formulations of SE were prepared using non-aqueous binder (3%PVP). The effect of diluents like lactose/DCP/MCC/co-crystallized lactose-MCC was studied. Granules and tablets were evaluated for compressibility parameters and friability. Dried starch powder was added as a disintegrating agent. The composition of various batches of SE is presented in Table 2.

Formulation of calcium sennosides:

Tablets of CS were prepared by wet granulation method. Formulations of CS were prepared using non-aqueous binder (3%PVP). The effect of diluents like, lactose/DCP/MCC/Co-crystallized lactose-MCC was studied. Granules were evaluated for compressibility parameters and friability. Dried starch powder was added as a disintegrating agent. The composition of various batches of CS is presented in Table 3.

Evaluation of sennosides tablets:

The tablets of SP, SE extract and CS prepared by wet granulation and direct compression were evaluated for preformulation and post formulation parameters. Angle of Repose, Carr's Index, Hausners' Ratio, crushing strength, friability and disintegration time were measured as per standard methods[8,9]. The results are shown in Tables 1-3.

HPLC analysis of sennosides:

The quantitative determination of sennosides was performed by high performance liquid chromatography (HPLC) using Pump (L-7110, Merck Hitachi), STR ODS II column (150x46). The mobile phase used was a mixture of Na-2-hydroxy isobutyrate buffer (pH 3.8) and acetonitrile in ratio of 6:1 (v/v). The filtered mobile phase was pumped at a flow rate of 1 ml/min. The column temperature was maintained

TABLE 1: FORMULATION AND CHARACTERISTICS OF SENNA POWDER TABLETS

Ingredients/ Batches	A1	A2	A3	A4	A5	A6	A7
Senna powder (mg)	300	300	300	300	300	300	300
Cross PVP (%)	2§	3§	4§	5§	6§	4¶	6¶
Lactose-MCC (mg)	167.56	163.56	159.56	155.56	151.56	159.56	151.56
Carr's Index	11.21	14.44	13.04	14.22	21.70	14.54	24.13
Hausners Ratio	1.12	1.16	1.15	1.16	1.27	1.16	1.31
Angle of Repose	32.82	32.01	32.41	32.20	33.27	31.64	31.26
Hardness (kgf)	5.3	5.2	4.6	5.4	5.1	5.3	5.4
Disintegration Time (min)	>50	>50	>50	34	14	11	10
Friability (%)	0.43	0.39	0.41	0.31	0.20	0.24	0.31

MCC is Microcrystalline cellulose and PVP is polyvinyl pyrrolidone. §=100% intragranular, ¶= 50% intragranular and 50% extragranular.

TABLE 2: FORMULATION AND CHARACTERISTICS OF SENNA EXTRACT TABLET

Ingredient/ Batches	E1	E2	E3	E4
Senna extract (mg)	300	100	100	100
DCP (mg)	276	-	-	-
Lactose (mg)	-	276	-	-
MCC (mg)	-	-	276	-
Lactose-MCC (mg)	-	-	-	276
Carr's Index	6.83	10.35	3.88	7.07
Hausners' Ratio	1.06	1.11	1.04	1.07
Angle of Repose	34.63	31.12	32.24	31.1
Hardness (kgf)	5.2	5.0	5.4	5.2
Disintegration Time (min)	16	13	9	11
Friability (%)	0.29	0.12	0.11	0.23

MCC is Microcrystalline cellulose and PVP is polyvinyl pyrrolidone. DCP is di-calcium phosphate

at 40°. The eluent was detected by UV detector at 270 nm.

***In vitro* dissolution study of sennosides tablets:**

Formulations containing different forms of senna were subjected to in-vitro dissolution study in USPXXIV dissolution apparatus Type II at 37±0.5° and at 100 rpm for 120 min using distilled water as a dissolution medium[10]. Samples were withdrawn at the end of specified time and analysed. Percent release of sennosides from each formulation was analysed as per HPLC method. Total content of actives from senna was also recorded from the same batches and release of sennosides from formulations having SP, SE and CS were compared (Table 4).

RESULTS AND DISCUSSION

The dianthrone glycosides, sennosides A and B are of medicinal interest because of their strong laxative properties[11]. All official pharmacopoeias suggest the measurement of sennosides B as a total sennosides present in *senna*. Hence, all raw materials, SP, SE and CS were estimated for total sennoside content. The sennoside contents of SP, SE and CS were found to be 1.46 %, 10.60% and 18.46%, respectively. Since, sennosides were estimated as a major constituent for *senna*, all the formulations were analyzed by HPLC method for sennosides content. In vitro release of drug from each formulation was also estimated.

TABLE 3: FORMULATION AND CHARACTERISTICS OF CALCIUM SENNOSIDES TABLETS

Ingredient / Batches	C1	C2	C3	C4
Calcium sennosides (mg)	300	100	100	100
Lactose (mg)	276	-	-	-
MCC (mg)	-	276	-	-
Lactose-MCC (mg)	-	-	276	-
DCP (mg)	-	-	-	276
Carr's Index	6.39	9.44	12.47	10.68
Hausners' Ratio	1.37	1.26	1.20	1.30
Angle of repose	38.07	43.84	29.32	31.02
Hardness (kgf)	4.2	5.3	4.8	4.5
Disintegration Time (min)	13	09	11	14
Friability(%)	0.48	0.14	0.19	0.39

MCC is Microcrystalline Cellulose and PVP is Polyvinyl Pyrrolidone. DCP is Di-calcium Phosphate

Tablets of SP were prepared using wet granulation method. Diluents like lactose/DCP/MCC/Co-crystallized lactose-MCC. The selection of diluent was made on the basis of derived properties of granules like, angle of repose, Carr's Index, Hausners' Ratio. The results revealed that Co-crystallized lactose-MCC give the lowest Carr's index and angle of repose (Table 1). Thus it can be concluded that co-crystallised lactose MCC gives better compressibility and flow properties as compared to other diluents. Another study was conducted to see the effect of binders on tablet characteristics. Alcoholic PVP (3, 5, 7 and 10 %) and starch paste (5, 7 and 10%) were used for the study. Starch paste did not give satisfactory results. Tablets had very high friability and

TABLE 4: COMPARISON OF PERCENT SENNOSIDES RELEASED FROM FORMULATION CONTAINING SENNA POWDER, SENNA EXTRACT AND CALCIUM SENNOSIDES

Formulations	Total sennosides content in tablet*	Percent sennosides released from tablet*
A6	81.1±0.78	47.1±0.25
E4	95.1±0.55	77.4±0.88
C4	100±1.01	96.6±1.09

*Mean±SEM of three values.

low crushing strength. When 5% of PVP was used it showed better tablet characteristics (Table 1).

Senna powder contains mucilage, which forms stiff gel around the tablet when placed in aqueous medium. This delays the disintegration time. Cross-linked PVP was used as a super-disintegrating agent in the formulations. The effect of intragranular and extra granular addition of super disintegrant was also studied (Table 1). Only extra granular addition of the super disintegrant did not show much effect on disintegration time of the tablets. But 50% extra granular and 50% intra granular addition gives satisfactory results at low concentration of disintegrating agent. Batch A6 was selected for *in vitro* dissolution study.

Sennosides content in SE and CS is high, fewer tablets would be needed to fulfill the dosage requirements. The manufacturing problem associated with senna powder like, high friability, low compressibility and disintegration time could also be resolved by use of SE and CS.

Tablets of SE and CS were prepared by wet granulation method. The selection of diluents and formulation parameters were same as that of SP. In SE formulations, Batch E4 containing Co-crystallized lactose-MCC also showed better compressibility and flow properties. Less amount and relatively cheaper diluents are employed in batch E4. Because of stickiness of SE, all the batches showed good crushing strength at low concentration of binder compared to SP formulation. As SE does not contain any mucilage, only 7% of anhydrous starch powder was required as a disintegrating agent. Batch E4 was selected for *in vitro* dissolution study (Table 2). In CS formulations also Batch C4 containing Co-crystallized lactose-MCC showed better tablet characteristics. Hence, it was selected for *in vitro* dissolution study.

Tablets of SP, SE and CS were subjected to *in vitro* dissolution testing using USP type II apparatus. Results shown in Table 4 reveal that the formulations containing SP show less percentage release compared to formulations containing SE and CS. Hence, from the overall study it is revealed that CS definitely has better advantage with regard to formulation feasibility, elegance and dissolution.

Our previous studies have dwelt upon crucial preformulation and post formulation aspects of *Triphala*[12]. In continuation of our work on herbal formulations attempts have been made to give sufficient and reliable inputs for formulating *Senna*. In conclusion, co-crystallised lactose-MCC and alcoholic PVP proved to be best diluent and binder respectively. Tablets of *Senna* powder showed high friability compared to tablets of *Senna* extract and Calcium sennosides. In the dissolution study also CS tablets exhibited better performance. The proposed formulation has certain distinct advantages such as concentrated actives, compact tablet form, ease of handling and administration, etc. Number of other Ayurvedic formulations are under active investigation to generate similar data.

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